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Toxicity equivalence range design (TEQR): A practical Phase I design

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ABSTRACT

Purpose: This paper introduces the target equivalence range (TEQR) design, a frequentist implementation of the modified toxicity probability interval (mTPI) design, as a competitor to the standard 3 + 3 design (3 + 3). The 3 + 3 is the work horse design in Phase I. It is good at determining if a safe dose exits, but provides poor accuracy and precision in estimating the level of toxicity at the maximum tolerated dose (MTD). Its main competitor, the continual reassessment method (CRM) has not found a true niche in the Phase I armamentarium resulting from statistical and implementation complexities.
Methods: We describe the four competing designs (3 + 3, mTPI, CRM, and TEQR), comparing them based on i) operating characteristics from simulated trials, and ii) ease of implementation.
Results: The TEQR is better than the 3 + 3 when compared on; 1) number of times the dose at or nearest the target toxicity level was selected as the MTD, 2) number of patients assigned to dose levels at or nearest the MTD, 3) overall trial dose limiting toxicity rate and 4) accuracy and precision of estimates for the rate of toxicity at the MTD. Further it is reasonably comparable to the CRM and mTPI on 1–3.
Conclusion: The TEQR offers trial designers a competitor to the 3 + 3 for ease of implementation with better operating characteristics and the added attraction of a glimpse of activity at the MTD. The R package TEQR, freely available from the comprehensive R archive network, includes functions to calculate dose escalation guidelines and operating characteristics.
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1. Introduction

The objectives of Phase I trials; include 1) determining if a safe dose of a drug exists; and 2) identifying a dose for Phase II trials, which in the case of a cytotoxic chemotherapy drug, is the maximum tolerated dose (MTD). Based on these objectives, the main endpoint of interest is a dose limiting toxicity (DLT); *i.e.* an adverse event that requires dose reduction or termination. The MTD is the dose believed to be toxic enough to be cytotoxic to cancer cells but not so toxic that the patients are unable to comply with the treatment schedule. The MTD has been defined both as a dose determined by rules based on the number of study participants experiencing DLTs (e.g. 3 + 3 design: the MTD is defined as the highest dose in which fewer than 33% of patients experience a DLT, when at least six patients were treated at that dose) and as the dose associated with a pre-specified rate of study participants experiencing DLTs (e.g. continual reassessment method (CRM): the MTD is defined as the dose with a toxicity probability closest to a pre–specified target toxicity probability).

The 3 + 3 design is good at determining if a safe dose exits, and it remains the workhorse Phase I design in oncology with it or a variant being used in over 97% of chemotherapy trials [1,2]. The CRM [3,4] and the modified toxicity probability interval (mTPI) design [5,6] are more accurate than the 3 + 3 design in their identification of an MTD with a pre-specified DLT rate and out-perform the 3 + 3 in i) the number of times the dose at or nearest the target toxicity level was selected as the MTD and ii) number of patients assigned doses at or nearest the target. In addition, they provide a glimpse of activity, because more patients are treated at the MTD.

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The mTPI achieves a substantial simplification over the CRM by focusing on the currently enrolling dose level, generating a simple decision table that exhibits escalation decisions for review in a protocol. The drawback is that, like the CRM, it is based on Bayesian inference, involving notions of prior and posterior distributions that are typically unfamiliar to physician investigators.

The TEQR design is a frequentist implementation of the mTPI achieving similar operating characteristics, but is simpler in concept and dose escalation rules. The TEQR design recommends escalation, staying at the same dose level, or de-escalation according to whether the empirical DLT rate from the data at the current dose level is below, within, or above a target DLT equivalence range specified in the design. The additional pre-specification of an unacceptable DLT rate, a too toxic level, defines when a dose is closed to further accrual.

The remainder of this paper is divided into four sections, 1) simple descriptions of three extant designs and the new TEQR design, 2) a hypothetical example of the TEQR design, 3) comparison of statistical operating characteristics, and 4) discussion of implementation considerations and conclusions.

1.1. Simple descriptions of three extant designs and the new TEQR design

1.1.1. 3 + 3 design

In the 3 + 3 design, patients are treated in cohorts of 3 at a dose level, escalating for each subsequent cohort through a fixed set of doses, not skipping any dose levels, based on the following rules. If 0/3 patients experience a DLT, the next cohort of 3 patients is treated at the next higher dose level. If 1 of the 3 patients experiences a DLT, the next cohort of 3 patients is treated at the same dose level for a total of 6 patients. Escalation will terminate as soon as two or more patients experience a DLT at a given dose level. The MTD will be defined as the highest dose in which fewer than 33% of patients experience a DLT, when at least six patients were treated at that dose.

Table 1 presents the dose escalation rules and associated toxicity rates. These rules are only loosely based on toxicity rates, so there is no way of adjusting the design to be more or less aggressive, except by changing the dose level increments, which may not be possible for some agents. There are also inconsistencies, such as 1) escalating at a DLT rate of 0 in 3 subjects and 0.17 in 6 subjects, and 2) holding at DLT rate of 0.33 in 3 subjects yet de-escalating, never to return to that dose, at the same rate in 6 subjects. Some of the inconsistency is due to discreteness, but the 3 + 3 design lacks the option of de-escalating with the possibility of returning to a dose level, making for a greater disparity in the decisions after observing a DLT rate of 0.33.

1.1.2. CRM design

The CRM is a model-based design using Bayes theorem as its engine. Thus, the posterior distribution for the DLT rate is proportional to the model likelihood times the prior. The CRM implements a model to estimate the DLT rate as a function of Dose (e.g. DLT Rate = $\text{Dose}^{\exp(\theta)}$, where θ is a shape parameter), replacing Dose (1,2,3,4,5, and 6) with predefined toxicity levels (e.g. Prob. of toxicity = (0.05, 0.15, 0.23, 0.34, 0.51, and 0.76)). The combined model/prior information is largely a technical device that allows the DLT rate estimate at one dose to be influenced by results at other doses, but with the estimated rates being dominated by the observed data. The CRM models the DLT events as conditional Bernouli random variables, while the shape parameter follows a chosen prior distribution. This method requires the user to define i) the toxicity target level for the MTD (e.g. 0.20), ii) initial estimates of the toxicity probabilities at each dose in the dose schedule (Prob. of toxicity = (0.05, 0.15, 0.23, 0.34, 0.51, and 0.76), iii) a base model, in our case an exponential model, iv) a prior distribution for the model parameter (we chose $P(\theta) \sim \text{Normal}(0, 2)$ as a reference prior, loosely based on Thall and Lee [4] and verified by sensitivity analysis (not included), v) the total sample size, and the vi) cohort size. Further the user must run the model after each cohort's data is available to make a dose escalation/de-escalation decision. Research on the behavior of the CRM has shown that it achieves the most clinically acceptable results (lower toxicity, fewer patients on higher doses in conjunction with accurate selection of the MTD) if dose escalations are limited to one dose level and cohort size is greater than one [7], and we expect that cautious institutional review boards (IRBs) would demand some such limitations.

1.1.3. Toxicity probability interval designs

The (TPI) design [5] implements an up and down design where the decision to escalate to a higher dose, stay at the same dose, or de-escalate to a lower dose is determined by the portion of the toxicity probability scale (0–1) with the highest mass for the posterior probability of toxicity at the current dose (p_i) using a beta-binomial distribution with a beta (.005,.005) prior. The toxicity probability scale (0–1) is partitioned into { $(0, p_T - K_1\sigma_i)$, $[p_T - K_1\sigma_i, p_T + K_2\sigma_i]$, $(p_T + K_2\sigma_i, 1)$ } where p_T is the target toxicity probability, σ_i is the posterior standard deviation of p_i and K_1 and K_2 are small positive constants such that $(0 < p_T - K_1\sigma_i < p_T + K_2\sigma_i < 1)$. There are two addition rules: 1) terminate the trial if dose level 1 is too toxic and 2) if the current dose is safe but based on the data the next dose is deemed unsafe, stay at the current dose.

The mTPI design is a variant of this design in which the dose escalation guidelines are determined by the portion of the toxicity probability scale (0–1) with the highest unit probability mass, where the unit probability mass is the ratio

Table 1
Dose escalation guidelines for the 3 + 3 design (E—Escalate, S—Stay, DU—De-escalate and do not return to this dose, MTD—determine this dose to be the MTD).

		<2 DLTS at the previous dose	<2 DLTs at the previous dose	≥2 DLTs at the dose above
		Number of subjects treated at the current dose level		
Number of subjects that experience a DLT at the current dose (associated DLT rate)		3	6	6
	0	E (0.00)	–	MTD (0.00)
	1	S (0.33)	E (0.17)	MTD (0.17)
	2	DU (0.67)	DU (0.33)	DU (0.33)

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