

## PHASE I TRIAL DESIGN

### Continual Reassessment Method A Modification

The primary objective of phase I studies is to determine the maximum tolerated dose (MTD) which produces a specific level of toxicity. The designs described below can be utilized when MTD needs to be determined in patients, not in healthy volunteers.

**Traditional designs:** decision rule-based, "1-in-3" designs. In these designs, patients (typically in groups of three or more) are treated at gradually increasing doses of the drug until a percentage of these patients display dose limiting toxicity.

**Continual Reassessment Method (CRM):** In papers published in 1990 and 1992, O'Quigley et al introduced an alternative method which promised to eliminate or at least alleviate the problems inherent with the "1-in-3" designs.

The Continual Reassessment Method (CRM) is based entirely on a bayesian decision framework that combines bayesian statistics with decision making. With the bayesian approach, a one-parameter model is defined to estimate the dose toxicity curve taking into account a *prior* distribution, which defines the amount of information regarding the curve, which is currently available. As information accumulates, the model is continually updated *posteriorly* and decisions are made on the *posterior* distribution. As a result, no data is lost and there is the assurance that the decision to increase or decrease the dose level is consistently reassessed, as more information becomes available.

### One-Parameter Model

The one-parameter model suggested by O'Quigley was defined as:

$$f(x, a) = \left[ \frac{\tanh(x) + 1}{2} \right]^a$$

where  $x$  was the scaled dose level of the drug and  $a$  was the unknown parameter characterizing the dose response curve. The *prior* is representative of all information that is known about the dose toxicity curve *prior* to commencement of the study. O'Quigley has indicated that the exponential model, i.e.  $f(a) = \exp(-a)$ , where  $a > 0$ , is sufficiently *vague* to prevent undue bias from entering the estimation process when initial information is limited.

### Two-Parameter Model

The one-parameter model proves to be adequate in the most situations, i.e. when the dose response curve displays the typical "s-shape". However, in some cases where the dose response curve deviates from this shape (for example, when toxicity increases at a slower rate, so that the true toxicity curve is more horizontal), the one-parameter model may be inappropriate.

The model, which we propose, is defined as :

$$f(x, R, a) = \left[ \frac{\tanh(xR) + 1}{2} \right]^a$$

where  $x$  and  $a$  remain as defined in the one-parameter model. The additional parameter introduced is  $R$  which is considered to be a scaling parameter for the range of the dosing interval. As  $R$  decreases, the dose response curve becomes more "horizontal" or "flat" for increases in  $a$ . Alternatively, for large values of  $R$ , the dose response curve becomes more "s-shape", typical of the expected curvilinear relationship between toxicity and dose. We define the *priors* of  $a$  and  $R$  to be  $\exp(-a)$ ,  $a > 0$  and  $\exp(-R)$ ,  $R > 0$ , respectively. Figure 1 shows examples of several dose response curves defined by the one- and two-parameter models.

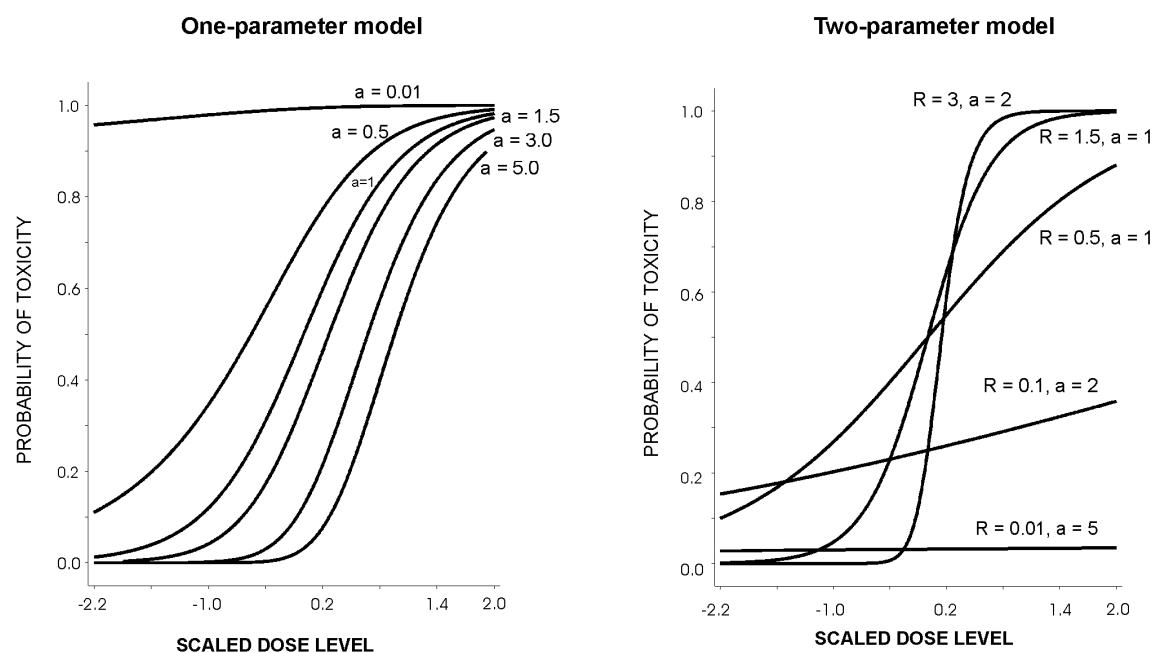


Figure 1. Illustration of the one- and two-parameter models

### Case Study

The limitation of the one-parameter model discussed earlier arose from an actual study presently being conducted.

Cancer patients were treated at combination dose levels of two drugs to determine the most efficacious combination treatment which produced dose-limiting toxicity in 33% of patients. In total, 8 dose levels, labelled  $D_1 - D_8$  ( $D_1$  being the fall back dose level) were experimented and data was collected from patients over four cycles of treatment. Dose limiting toxicity was acknowledged if certain hematological parameters showed either grade III or grade IV toxicity. The rules for dose allocation were as follows :

1. At trial commencement, a group of three (3) patients were treated at the first dose level.
2. If 2 of the 3 patients showed dose limiting toxicity, another group of patients would be exposed to the same dose.
3. If there was no toxicity, the subsequent group of patients would be treated at the next higher dose level.
4. Patients at the dose level were then assessed for dose limiting toxicity. Study procedures continued from Step 2.

### Results

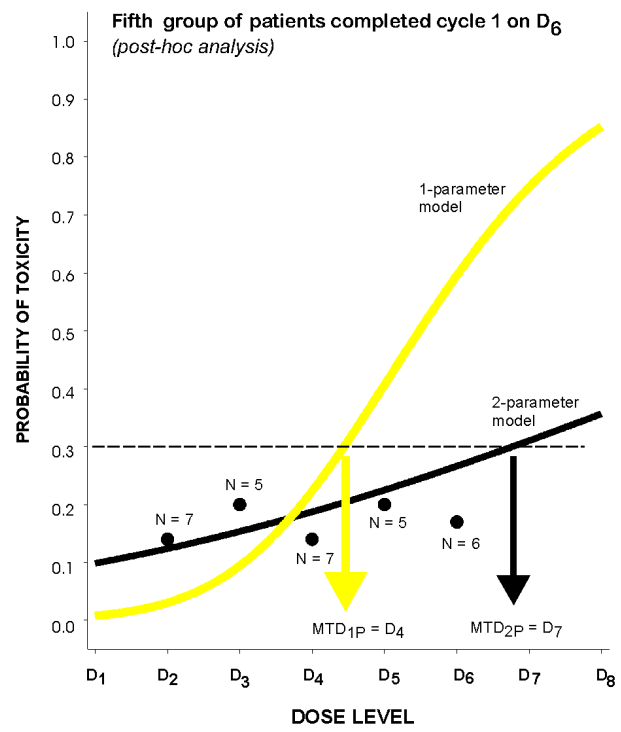
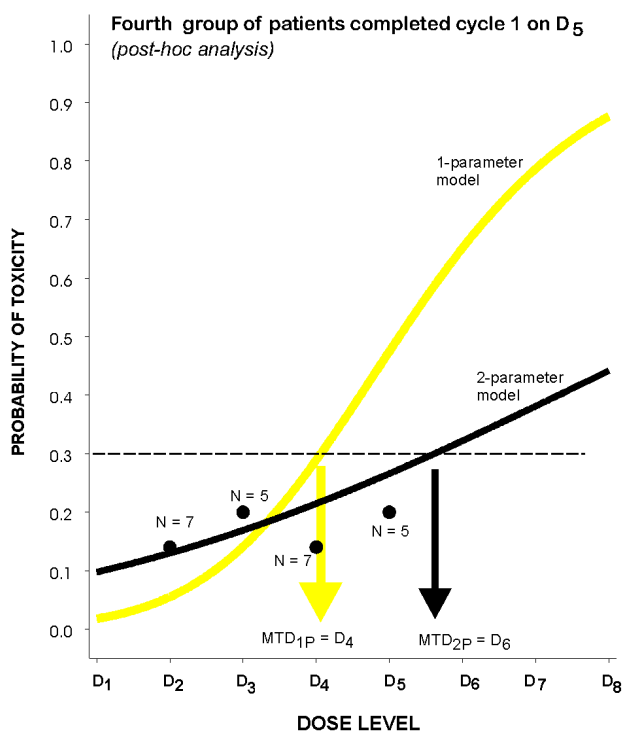
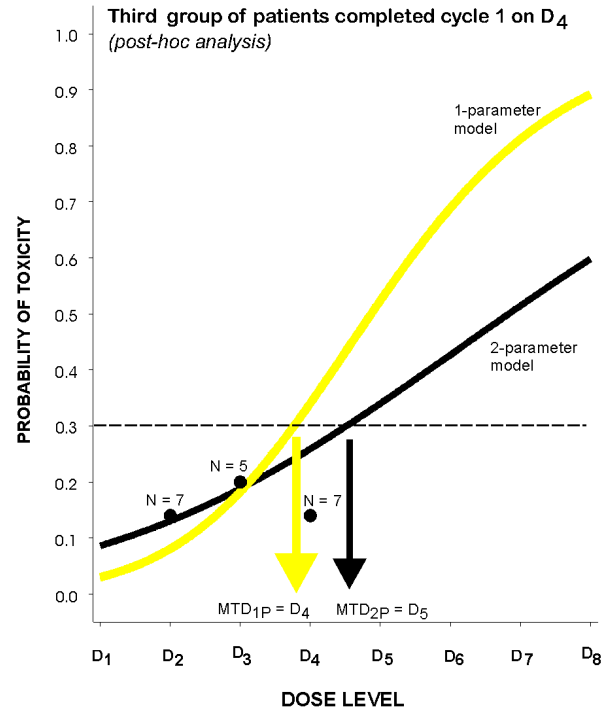
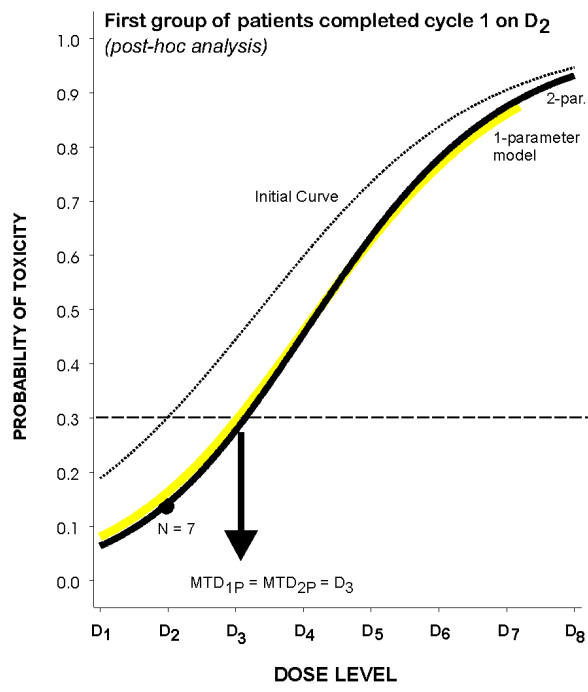
#### Analysis of Cycle 1 data: Simulation of dose-allocation by CRM

The toxicity data collected in cycle 1 and the MTD estimates at the completion of each dose level are illustrated in Figs. 2a-d.  $D_2$  being our best initial estimate of MTD, the initial curve (dotted line labelled "initial curve" on Fig. 2a) was parameterized to ensure 33% toxicity at the starting dose, and 95% toxicity at the highest dose level  $D_8$ . One of the seven patients treated at  $D_2$  showed dose-limiting toxicity. The 1- and two-parameter models produced similar fit to the data (Fig. 2a).

Significant differences between fits achieved by the two models started to manifest after the third group of patients completed cycle 1 on  $D_4$ . The one-parameter model expected a step increase in toxicity while the two-parameter model showed a closer fit to the actual data. As a result, the one-parameter model – if it were used for dose-allocation – would have recommended  $D_4$  to be repeated in the next group of patients. The two-parameter model would have allowed the study to proceed to  $D_5$  (identical to the actual clinical decision). Five patients were treated at  $D_5$  with one patient showing dose-limiting toxicity. The discrepancy between the fits and the recommended doses increased between the two models: the one-parameter model would have again "insisted" on repeating  $D_4$  while the use of the two-parameter model would have facilitated the increase of the dose to  $D_6$ . The same pattern of differences can be seen on Figs. 2c-d.

### Conclusion

The two-parameter model provides a better fit to toxicity observations and facilitates a dose-allocation scheme similar to that of current research practices.



Figures 2.a-d. Cycle 1 toxicity data and the MTD estimation provided by the 1- and 2-parameter models at 4 stages of the study