Bayesian Clinical Trials

Dose Finding CRM

Phase I study

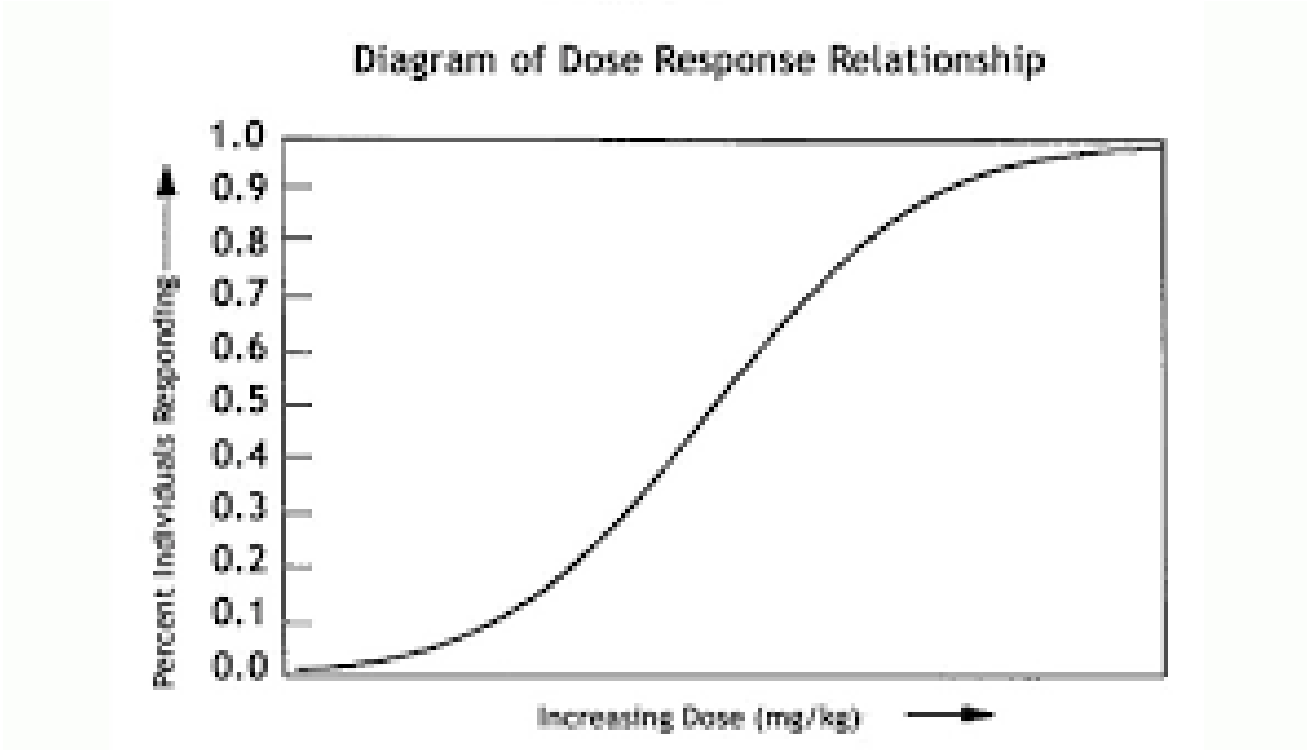
Goals:

1. Determine a safe dose for further clinical studied
2. Study pharmacokinetics of the drug

Toxicity Dose-Response Curve

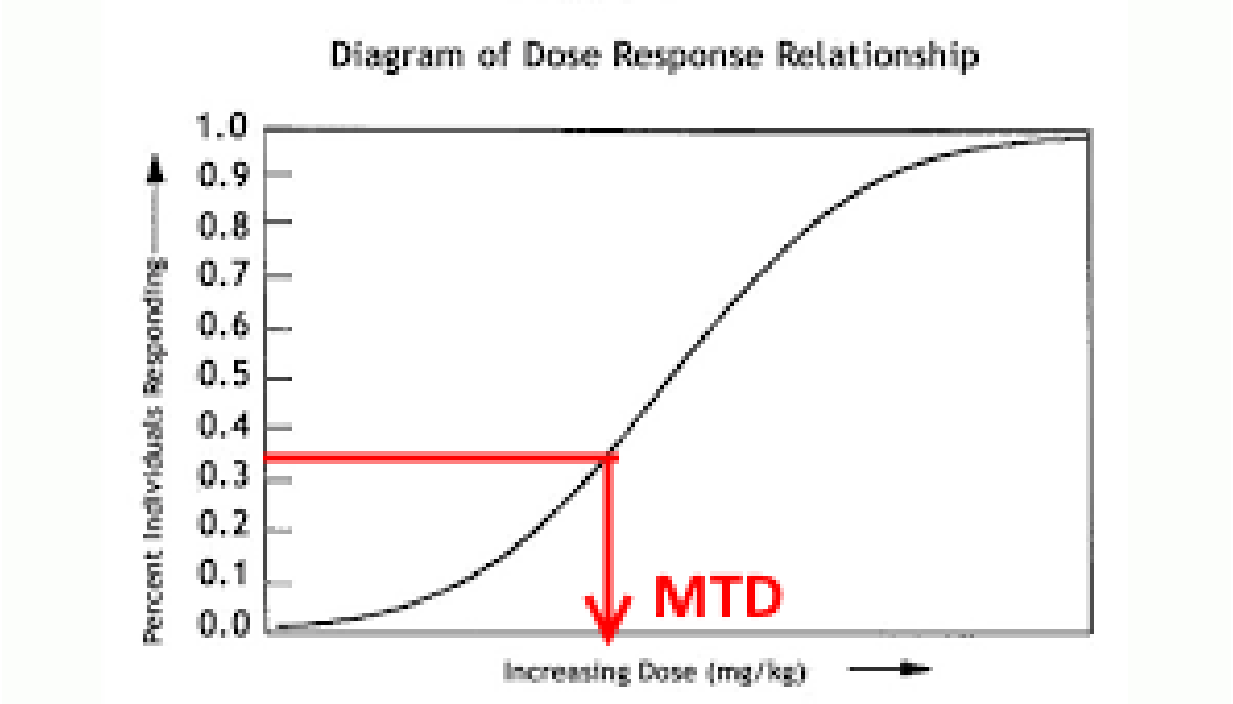
We can ordinarily assume that the probability of a dose-limiting adverse event increases monotonically with dose
In that circumstances, the Maximum Tolerated Dose (MTD) is the dose associated with the specified probability of a dose-limiting toxicity (DLT)

Diagram of Dose Response Relationship



Health Effects Discussion and Determination of Final PEL, OSHA

Diagram of Dose Response Relationship

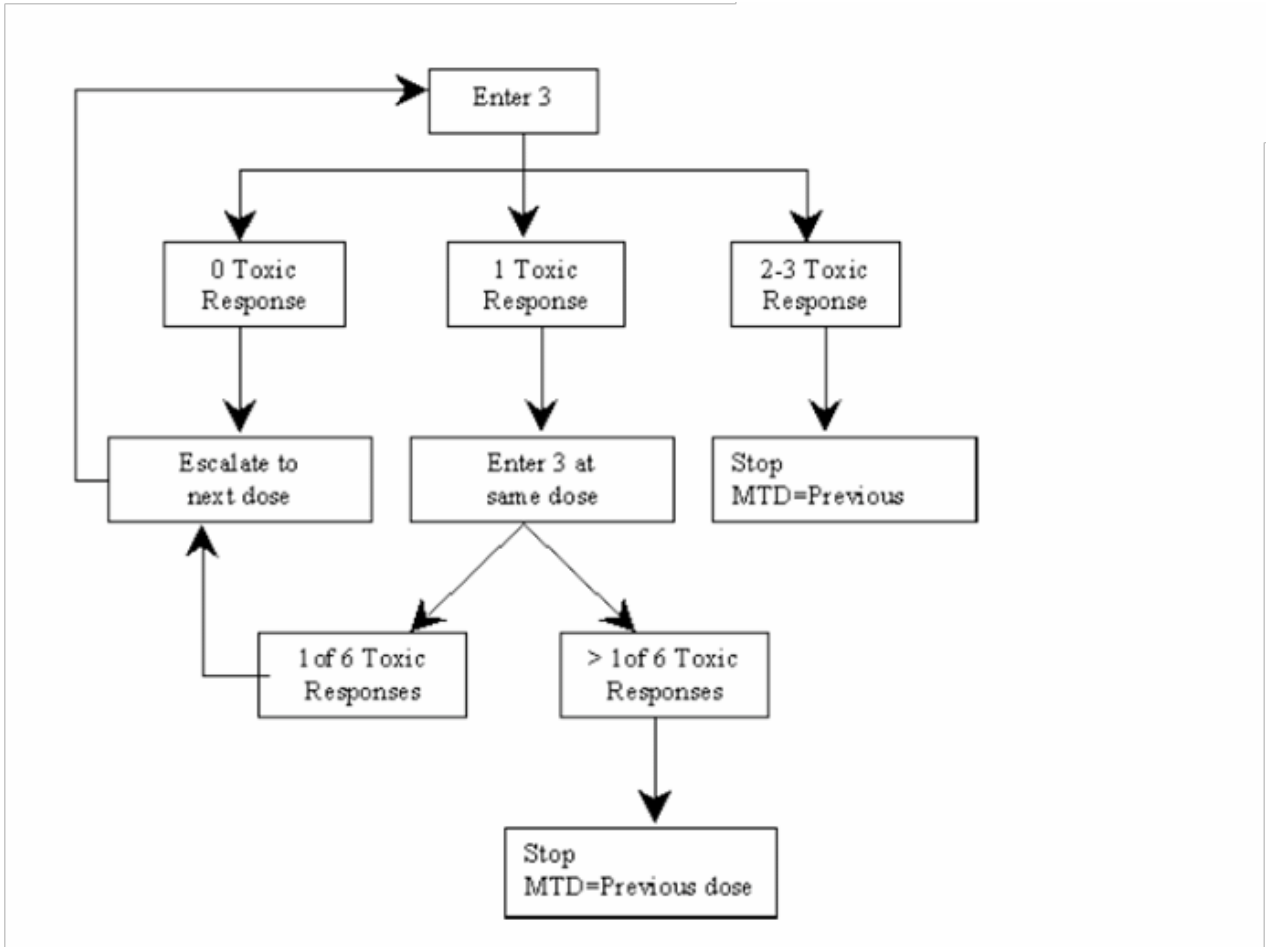


Health Effects Discussion and Determination of Final PEL, OSHA

Rules based models

- Make no assumptions about the form of the dose-toxicity curve
- Often called "up-and-down" designs because they allow dose escalation and de-escalation
- The dose is increased or decreased depending on the occurrence of dose-limiting toxicities (DLT)
- More than 90% or Phase I trials in cancer are rule-based (*J Natl Cancer Inst 2009; 101:708-720*)

Conventional 3+3 Design

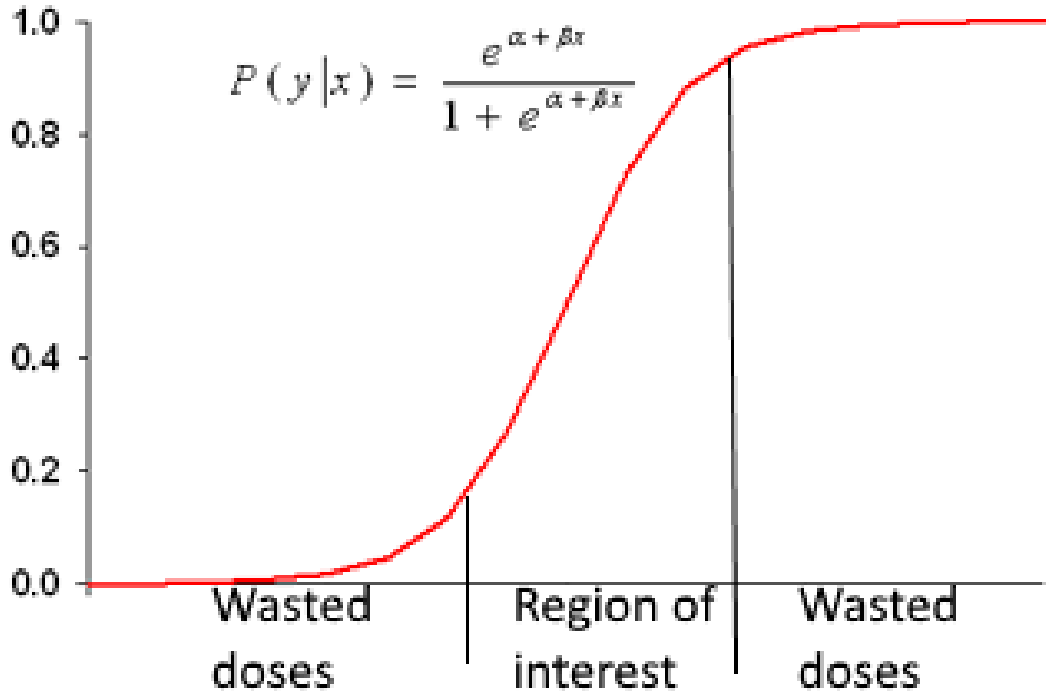


Model Based Design

- Specify a mathematical model for dose-response curve
- Choose the initial dose based on expert opinion
- After each dose, re-estimate the model and choose the next dose as the dose estimated to have the specified probability of a DLT, eg. 0.33

Model Based Design

One popular model is the logistic model, which has only two parameters, an intercept and a slope



Comparing Rule and Model-Based Design

Rule Based Design	Model Based Designs
Easy to describe	Difficult to describe
Easy to implement	Require statistical support
Possibly inefficient	May be more efficient

Outcome adaptive statistical models

- Continual Reassessment method
- Bayesian Logistic Regression

They incorporate uncertainty regarding patient outcome by using Bayesian probability models:

- learning from accruing data
- choosing doses for successive patient cohorts
- describing various probabilities graphically

Illustrative Trial: Renal Cell Carcinoma (RCC) Trial

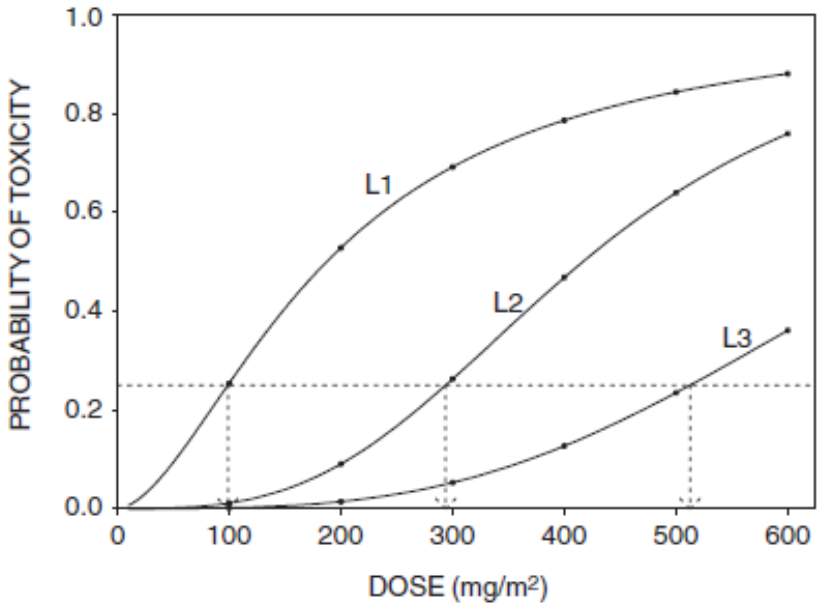
- Patients with renal cell carcinoma (RCC) that was progressive after previous treatment with interferon were eligible.
- Treatment consisted of fixed doses of 5-Fluorouracil (5-FU) and interferon, plus one of six doses of gemcitabine (GEM):
  - 100, 200, 300, 400, 500 or 600mg/m2.
- Toxicity was defined as grade 3 or 4 diarrhea, mucositis, or hematologic toxicity.
- A total of 36 patients were treated in cohorts of size 3, with the first cohort given 200mg/m2 of GEM.

Dose Toxicity Probability Models

The probability of toxicity P_{TOX} depends on the dose given to the patient

$$P_{TOX}(100) < P_{TOX}(200) < \ldots < P_{TOX}(600)$$

underlying assumption: a larger dose necessarily implies a greater risk of toxicity, e.g $P_{TOX}(dose)$ must increase with dose



Three possible dose-toxicity probability curves described by the logistic regression model

Dose Toxicity Probability Models

A model based method requires specifying a fixed P_{TOX} value as *target* for the dose-finding problem. In the RCC trial, the target is 0.25:

- it is clinically acceptable if on average 1 patient in 4 receiving the treatment at the MTD experiences toxicity
  - targets in the range 0.10 to 0.40 are usually specified (the particular value varies depending on the definition of toxicity, the disease, the trial's entry criteria)

Bayesian Logistic Regression

The Bayesian regression model has linear term

$$\eta(x, \theta) = \mu + \beta x, \qquad \mu \in R, \beta > 0$$

which is linked to the probability toxicity $\pi(d, \theta)$ by a suitable link function

$$\pi(d, \theta) = g^{-1}\{\eta(x_j, \theta)\}, \qquad g(\pi) = \log \frac{\pi}{1 - \pi}$$

To determine the prior on (μ, β) elicited prior means $\pi(d_1, \theta)$ and $\pi(d_2, \theta)$ at two distinct doses d_1 and d_2 are used to determine priors on (μ, β).

Bayesian Logistic Regression: simplified prior elicitation approach

A simpler approach can be adopted:

- μ and β are assumed independent normal
- solves for the means of μ and β based on elicited $\pi(d_1, \theta)$ and $\pi(d_2, \theta)$
- choose their variances to obtain a vague prior

Bayesian Logistic Regression: simplified prior elicitation approach

$$\pi(d_1, \theta) = g^{-1}\{\eta(x_j, \theta)\} = g^{-1}(\mu - 0.18\beta) = 0.25$$

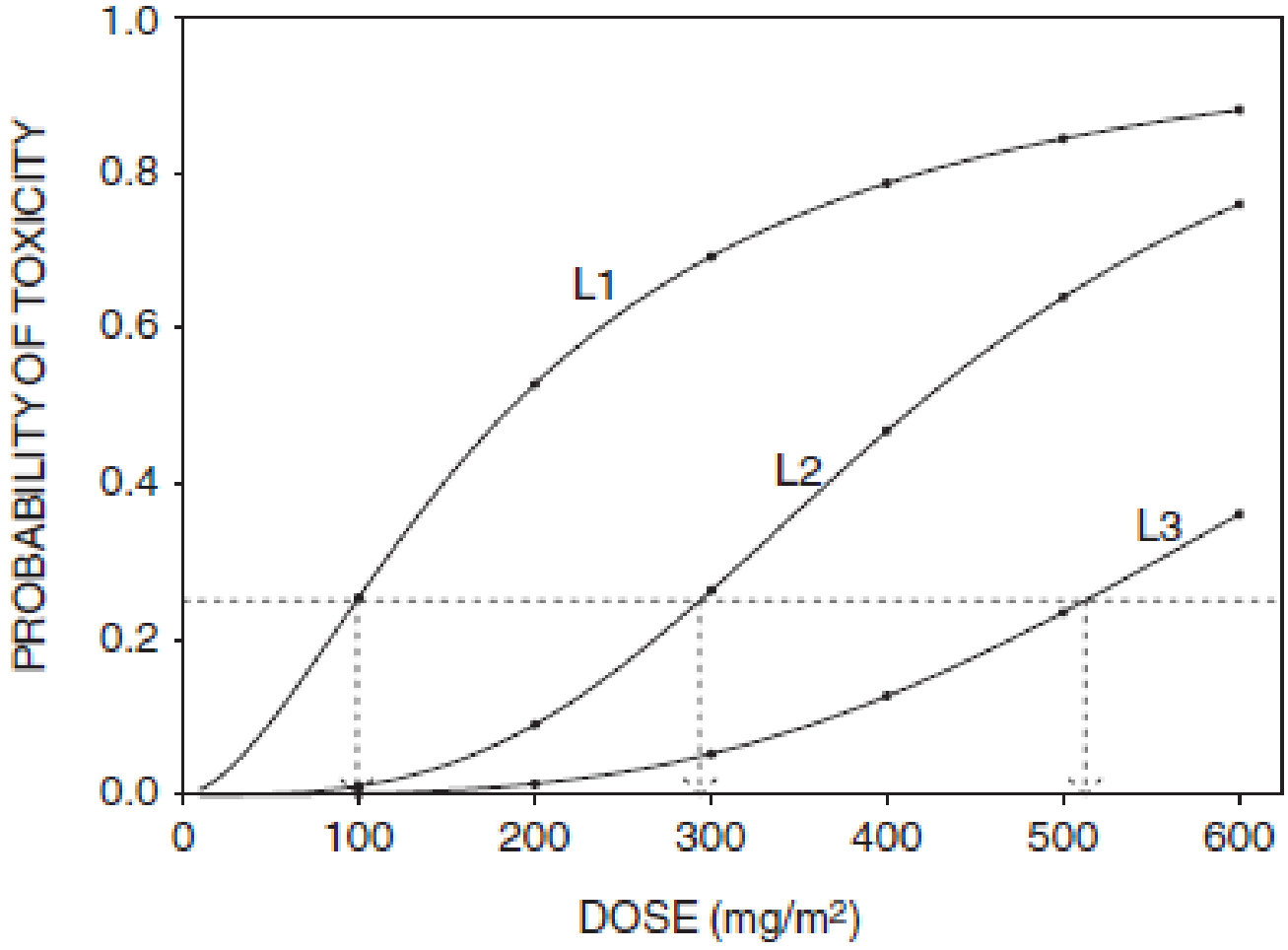
$$\pi(d_2, \theta) = g^{-1}\{\eta(x_j, \theta)\} = g^{-1}(\mu + 0.22\beta) = 0.75$$

given doses $d_1 < d_2 < \ldots < d_k$, x_j is the standardized dose $x_j = \log(d_j) - \frac{\log(d_1)+\ldots+\log(d_k)}{k}$. Thus $d_1 = 200, x_1 = -0.18$ and $d_2 = 500, x_2 = 0.22$
Solving (1) and (2):

$$E(\mu) = -0.1313, \qquad E(\beta) = 2.3980$$

We chose $\sigma_\mu = \sigma_\beta = 2$

Example


PROBABILITY OF TOXICITY
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
DOSE (mg/m²)
L1
L2
L3

RCC Trial

- Patients with renal cell carcinoma (RCC) that was progressive after previous treatment with interferon were eligible.
- Treatment consisted of fixed doses of 5-Fluorouracil (5-FU) and interferon, plus one of six doses of gemcitabine (GEM):
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Continual Reassessment Method (CRM)

- Model-based Bayesian method introduced by J. O'Quigley (*Biometrics* 1990)
- Parametric model for dose-response relationship and fixed target for P_{TOX}
- It requires a skeleton of fixed probabilities corresponding to the dose levels
- It requires prior information
- The study begins by dosing the first patient at the *best* dose
- The analysis is updated given the data obtained
- For the next patient pick the "best" dose and continue

CRM: single parameter working model

$$P(d, \alpha) = \text{probability of a toxicity at dose d}$$

The following working models were suggested in (Biometrics 1990)

- 1- parameter logistic: $P(d, \theta) = \frac{\exp(-3+\theta d)}{1+\exp(-3+\theta d)}$
- power: $P(d, \theta) = d^{\exp(\theta)}$
- hyperbolic tangent: $P(d, \theta) = \left(\frac{\exp(d)}{\exp(d)+\exp(-d)}\right)^{\theta}$

CRM: Prior information

α is the parameter that is going to be updated during the trial

- exponential prior $\pi(\theta) = \exp(-\theta)$ with mean 1
- normal prior $\pi(\theta) = Normal(0, var(\theta))$ with $1 \leq var(\theta) \leq 10$

Given the data for doses x_i and outcomes y_i, the likelihood is

$$f(x|\theta) = \prod_i P(x_i, \theta)^{y_i}(1 - P(x_i, \theta))^{1-y_i}$$

and the posterior is

$$\pi(\theta|x) = \frac{f(x|\theta)\pi(\theta)}{\int_0^\infty f(x|\theta)\pi(\theta)d\theta}$$

computed by numerical integration or MCMC methods

Example: RCC trial

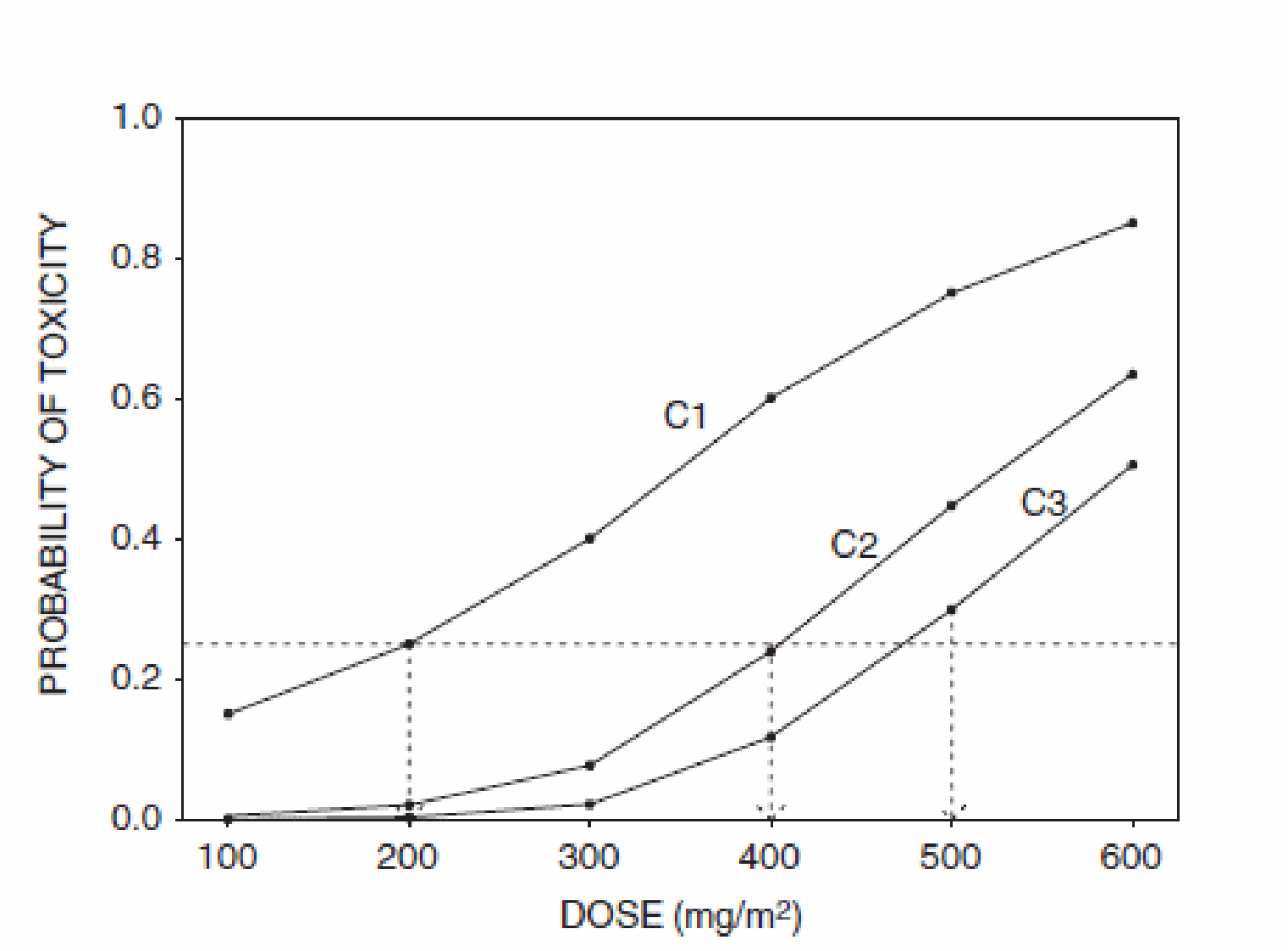
- The prior probabilities for each toxicity (*skeleton*) for 6 dose levels need to be specified

doses	100	200	300	400	500	600
probabilities	0.15	0.25	0.40	0.60	0.75	0.85

The skeleton is fixed throughout the trial and dictates the shape of the curve

- Target (TTL) is specified at 0.25
- Default working model is exponential
- Default prior is Normal(0, 1.8)

CRM


PROBABILITY OF TOXICITY
1.0
0.8
0.6
0.4
0.2
0.0
C1
C2
C3
100
200
300
400
500
600
DOSE (mg/m²)

CRM

Under either model:

- denoting $Y_i = 1$ if the ith patient suffers toxicity
- denoting $Y_i = 0$ if not,
- denoting $d(i)$ that patient's dose

the likelihood for n patients is

$$\prod_{i=1}^{n} \pi(d_i, \theta)^{Y_i} \times (1 - \pi(d_i, \theta))^{(1-Y_i)}$$

The posterior of θ and each posterior mean $E(\pi(d_j, \theta)|data)$ may be computed using either numerical integration or Markov chain Monte Carlo methods.

CRM stopping rules

The additional rule that stops the trial if the lowest dose is excessively toxic is given formally by

$$Prob\{\pi(d_1, \theta) > \pi^* | data\} > p_U$$

where p^* is the fixed target and p_U is a fixed upper probability cut-off, usually in the range 0.95 to 0.99.

References

- Thall, P. F. and Lee, S.-J. (2003), Practical model-based dose-finding in phase I clinical trials: Methods based on toxicity. International Journal of Gynecological Cancer, 13: 251261
- O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase I clinical trials in cancer. Biometrics 1990; 46: 33-48.
- Le Tourneau C, Lee JJ, Siu LL. Dose Escalation Methods in Phase I Cancer Clinical Trials. JNCI Journal of the National Cancer Institute. 2009;101(10):708-720.