Adaptivity in Clinical Trials – BCLM 1.3

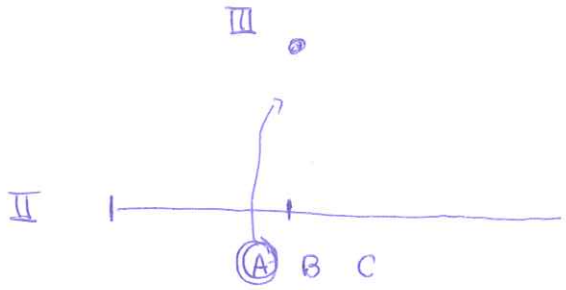
- Both frequentists and Bayesians mean a procedure that alters something based on the results of the trial so far.
- Frequentists: Any shift should be reflected in the Type I error calculation.
- Bayesians: enter a trial with nothing more than a stopping rule and a (possibly minimally informative) prior distribution (for example, no need to select the trial's sample size).
- From Bayesian point of view, what sorts of adaptation? in what sorts of settings (e.g., early versus late phase)?

- As of now, a great many non-fixed-sample-size trials are running across a variety of phases of the regulatory process.
- Ethically most important to be adaptive for early phase studies.

  ↻ The patients are often quite ill ⇒ more need making sudden treatment changes and do it more frequently.

  ↻ Phase I drug studies are typically about safety and dose-finding

  * Dose finding? the dose a patient receives is not fixed in advance, but rather determined by the outcomes seen in the patients treated to date.



- In phase II, typically seek to establish efficacy while still possibly guarding against excess toxicity and also futility.

  * Stop the trial early if any of the three conclusions (efficacy, toxicity, or futility) can be reached early (i.e., be adaptive!)

  * Drop unproductive or unpromising study arms.

  * Do adaptive randomization, allowing the assignment of more patients to the treatments that do better in the trial.

- In phase III and beyond, the need for adaptivity may be reduced but ethical treatment of the patients and efficient use of their data requires as more flexibility as possible.

- Seamless phase II/III trial: a trial may start with multiple doses of an experimental agent, where the first stage of the trial determines the dose arm to move forward to a second stage that undertakes a more transitional comparison to a control arm.

AMS 276
Lecture 8: Phase I Studies

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† DC Chapter 3 and BCLM Chapter 3.

† A population of interest, study questions and outcome variables are specified. The next task is **the specification of the experimental design**.

† A new intervention is developed.

⇒ go through several stages of trial (early phase trial designs)

⇒ do the ultimate definitive trial (the ultimate test for efficacy)

- New compounds are initially subjected to extensive biochemical and pharmacological analysis, progressing to experiments using animal and *in vitro* models and, increasingly, *in silico*, or computer models.
- Once these non-clinical studies are completed, the compound may make the transition from "mouse to man"

† An Overview of Drug Development

- Phase I: to determine the maximum dose that can be given without unacceptable toxicity.
- Phase II (or a series of phase II studies): to determine if the new intervention modifies a risk factor or symptom as desired, and to further assess safety
- Phase III: to compare to a control or standard intervention to assess efficacy and safety
- Phase IV: Trials of an approved treatment with long-term follow-up of safety and efficacy

† An Overview of Drug Development

Phase	Aim	Subjects	Trial Size
Pre-clinical	Phamacologic/chemical properties, Efficacy/safety in tissue and animals	tissue (cells,...), animals	–
I (first-in-human)	**Safety in humans (maximum tolerated dose), pharmacokinetics**	**Patients or healthy volunteers**	**10-50**
IIa (proof-of-concept)	**Any evidence of drug effect**	**(selected) patients**	**50-100**
IIb (dose-finding)	Characterize dose-response relationship: Drug effect large enough? Choose efficacious and safe dose(s) for Phase III.	target population	100-1000
III (confirmatory)	Large scale studies to show efficacy and safety of drug	target population	300-5000

∗ figure from P. Müller.

† **Phase I**: to determine the maximum dose that can be given without unacceptable toxicity (the maximum tolerated dose, MTD) and form of administration for an agent.

e.g.: the quantity of a drug, amount or duration of therapeutic radiation.

$\Leftrightarrow$ to find a safe and potentially effective dose for future Phase II/III trials.

- "broadly, a trial involving the first applications of a new treatment to human beings and conducted to generate preliminary information on safety" in Meinert (1996).
- Trials are typically small (10-50 patients)

- Use healthy voluntary or paid subjects when the expected toxicities are minor or, alternatively, extremely ill patients administered fairly toxic therapies for diseases such as cancer, having failed all standard options.
- MTD is quantitatively defined as the largest dose of a drug or other therapeutic agent that induces at most a set proportion, usually $1/3$, of subjects with predefined toxicities.
- Typically investigators pick a set of three to ten doses for evaluation.
- Ethical considerations: Give the first subjects a very low dose and then sequentially escalating the dose in subsequent patients or subjects until toxicities are observed.

- The goal is to estimate the MTD as the 33rd percentile of the dose-toxicity curve, while minimizing the number of subjects receiving toxic doses.

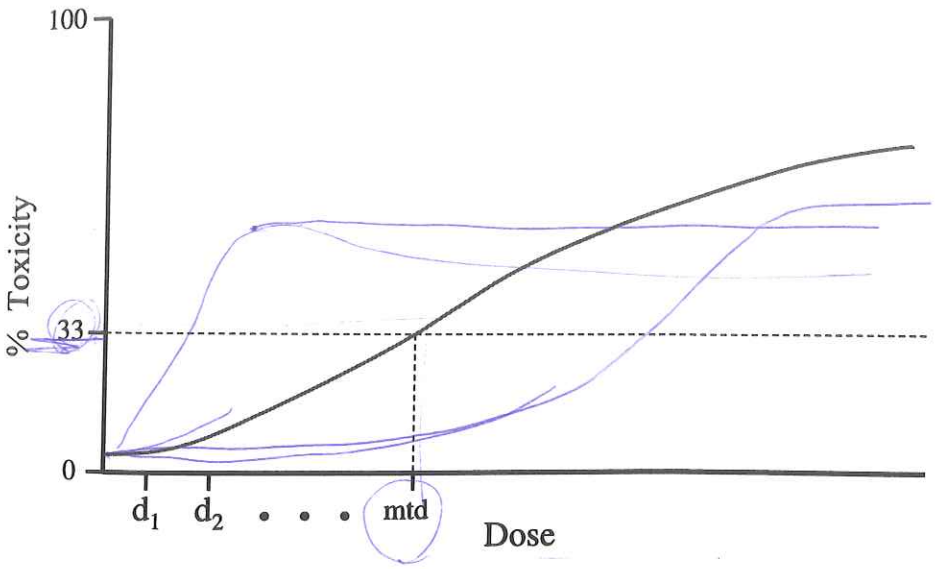

Figure 3.1 *Schematic of phase I trial.*

† Recall: The primary goal of a phase I trial is to identify MTD in a dose-escalation fashion.

† **Key Elements of phase I trials**:

- define the starting dose.

  e.g. For the first study in humans, the starting dose is often chosen as one tenth of the LD_{10} (a lethal dose for 10% of the animals in mice, or one third of the lowest toxic dose in dogs, as these doses have some to be safe in humans for cytotoxic agents.

† **Key Elements of phase I trials** (contd):

- define the toxicity profile and dose-limiting toxicities.

  ⋆⋆ **dose-limiting toxicities (DLTs)**: investigators must formulate definitions for adverse events severe enough (toxicity profile) so that their presence would curtail the use of the treatment.

  ⋆⋆ The sequential nature of traditional phase I trials requires these toxicities to be short-term, usually occurring within four to eight weeks of initial treatment.

† **Key Elements of phase I trials** (contd)

- define an acceptable level of toxicity, target toxicity level (TTL).

  ↻ The goal of a phase I trial in different words: to define the **recommended phase II dose** which yields an acceptable TTL.

  ↻ For developing a cytotoxic agent: to seek the highest possible dose level subject to DLT constraints.

  ⋆⋆ Monotonicity assumption: The benefit of a new treatment and the severity of its toxicity, both are expected to increase with dose.

  ⋆⋆ The target toxicity $\pi^\star$ is typically between 20% and 40%.

MTD has $P(\text{DLT occurs}) = \text{TTL}$

† **Key Elements** (contd)

• define a dose escalation scheme

♂ A dose escalation scheme contains three components;

⋆⋆ **a dose increment**

∗ Many studies use pre-determined dose increments at fixed doses, such as 10 mg, 20 mg, 30 mg, and so on.

∗ Not pre-determined: We specify a general scheme for setting the doses, such as doubling the current dose when no toxicities are observed, reducing to a 50% dose increment when non-dose-limiting toxicities are observed, and reducing to a 25% dose increment when a DLT is observed.

∗ "adaptive dose insertion" during the course of a dose-finding trial when none of prespecified doses in the trial are acceptable

- A dose escalation scheme contains three components; (contd)
  - **a dose assignment:**
    - How to assign new patients enrolled in the trial to dose levels.
    - Based on dose assignment, phase I trials can be classified into *rule-based methods* and *model-based methods*.
    - Investigators must balance the risk of toxicity with the risk of treating patients with drugs at ineffective doses.
  - **a cohort size:** We generally assume that new patients are treated in cohorts of a prespecified size (say, 1, 3, or 6).

† Upcoming topics: We will look at some specific designs.

- Rule-based designs: 3+3 (Section 3.1)
- Model-based designs: CRM (continual risk assessment) (Section 3.2.1)
- Event times: TITE-CRM (time-to-event CRM, Section 3.2.3)
- Ordinal toxicity intervals (Section 3.2.5)
- Combination therapy: 2 agents (Section 3.4.4)
- Limitations & strengths

† Rule-based Designs

- No assumption regarding the dose-toxicity curve
- Assign new patients to dose levels according to prespecified rules
- e.g.

  ⋆⋆ "up-and-down" designs (Gezm & Flournoy, 2006):

  * Allow dose escalation and de-escalation based on the absence or presence of toxicity in the previous cohort.

  * Find a dose corresponding to a probability of DLT around 50%.

  ⋆⋆ Traditional 3+3 design (Storer, 1989)

  * Find a dose corresponding to a probability of DLT $\leq 33\%$.

  * Very popular in clinical practice. Many variations of 3+3 are available.

2+4, 3+3+3, 3+1+1

- Algorithm 3.1: 3+3 design.

Algorithm 3.1 *(3+3 design)*

Step 1: Enter 3 patients at the lowest dose level

Step 2: Observe the toxicity outcome

0/3 DLT $\Rightarrow$ Treat next 3 patients at next higher dose

1/3 DLT $\Rightarrow$ Treat next 3 patients at the same dose

1/3 + 0/3 DLT $\Rightarrow$ Treat next 3 patients at next higher dose

1/3 + 1/3 DLT $\Rightarrow$ Define this dose as MTD

1/3 + 2/3 or 3/3 DLT $\Rightarrow$ dose exceeds MTD

2/3 or 3/3 DLT $\Rightarrow$ dose exceeds MTD

Step 3: Repeat Step 2 until MTD is reached. If the last dose exceeds MTD, define the previous dose level as MTD if 6 or more patients were treated at that level. Otherwise, treat more patients at the previous dose level.

Step 4: MTD is defined as a dose with $\leq 2/6$ DLT ■

- Example 3.1: Results from the taxotere trial reported by Pazdur et al (1992) – total number of patients: 39.

	Dose Level (mg/m^2/day x 5 days)					
Cohort	1	4[a]	8	12[c]	14[c]	16
1	0/3					
2		0/3				
3			0/3			
4						6/12[b]
5				2/10		
6					2/8	
MTD					***	

- 3+3 design: Two simple idealized illustrations

1.	Dose Level				
Cohort	1	2	3	4	5
1	0/3				
2		0/3			
3			1/3		
4			0/3		
5				2/3	
MTD			***		

2.	Dose Level				
Cohort	1	2	3	4	5
1	0/3				
2		0/3			
3			0/3		
4				2/3	
5			0/3		
MTD			***		

Figure 3.1 *Example of the traditional 3+3 design; entries are (number of DLTs/number of patients treated) by cohort and dose level.*

- ⋆⋆ **Left:** Dose level 3 is chosen as the MTD with estimated DLT rate, 1/6=0.167.
- ⋆⋆ **Right:** The same dose is chosen, but with estimated DLT rate 0/6 (note: 33.3% is also possible).

† Summary of Rule-based Designs

- Easy to implement and do not require specialized software
- The decision on dose allocation for future patients relies on information from the current dose level only with no regard to other dose levels (i.e. it dose not use all available information).
- The target toxicity level is fixed and implicitly specified once the rule is set.
- This design does not have any statistical convergence property and also has no specific toxicity target to aim for.
- In short, their performance may not be particularly attractive.
- **However**, still common despite generally preferable alternatives.

† Model-base designs for determining the MTD (BCLM 3.2 & CD 3.1)

- Assume there is a monotonic dose-response relationship between the dose and the probability of DLT for patients treated at that dose.

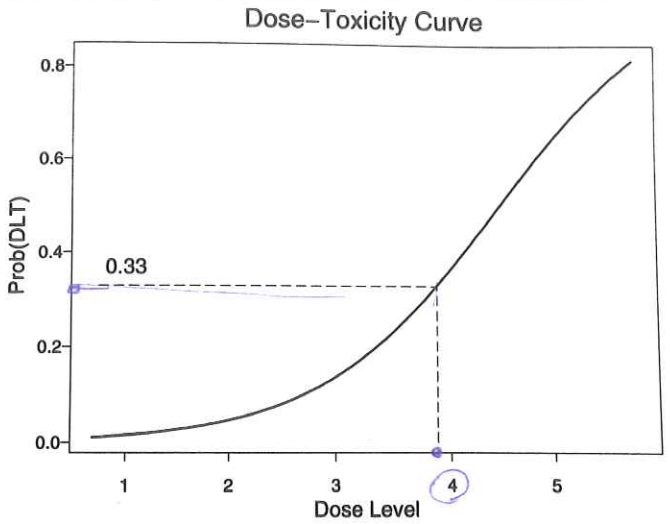

Figure 3.4 *Illustration of a dose-toxicity curve for a model-based design. If the target toxicity level (TTL) is 33%, dose level 4 is the MTD, since it comes closest to yielding the desired TTL.*

† Setting and Data: dose-toxicity curve (notation changes one design to another!)

- dose level: $d = 1, \ldots, m$
- toxicity outcome $y \in \{0, 1\}$, indicator for TOX
- dose-toxicity curve $p(d) \equiv p(y = 1 \mid d, \theta)$.
- patient index $i = 1, \ldots n$
- d_i and y_i: the dose level and toxicity outcome for patient i.

† Determine:

- Maximum tolerated dose (MTD)

  Defined, e.g., as max dose $d = d^\star$ with $p(d) \leq \pi^\star$, e.g., $\pi^\star = 30\%$

† CRM (Continual Reassessment Method, O'Quigley et al.(1990))

- A Bayesian model-based method to estimate $p(d)$ and to assign patient to a dose closest to the currently estimated MTD.

- Parametric model for the dose-toxicity curve e.g.

  ⋆⋆ Hyperbolic Tangent Model

$$p(d) = \{(tanh(d) + 1)/2\}^a = \left(\frac{\exp(d)}{\exp(d) + \exp(-d)}\right)^a$$

  ⋆⋆ Power Model

$$p(d) = (p_d^0)^{\exp(a)}$$

  where fixed (prespecified) p_d^0 (skeletons) and the prior is centered at $\exp(a) = 1$.

⋆⋆⋆ Logistic $p(d) = \dfrac{\exp(\beta_0 + \beta_1 d)}{1 + \exp(\beta_0 + \beta_1 d)}$

- Different shapes of the dose-toxicity curves for varying values of the parameter a.

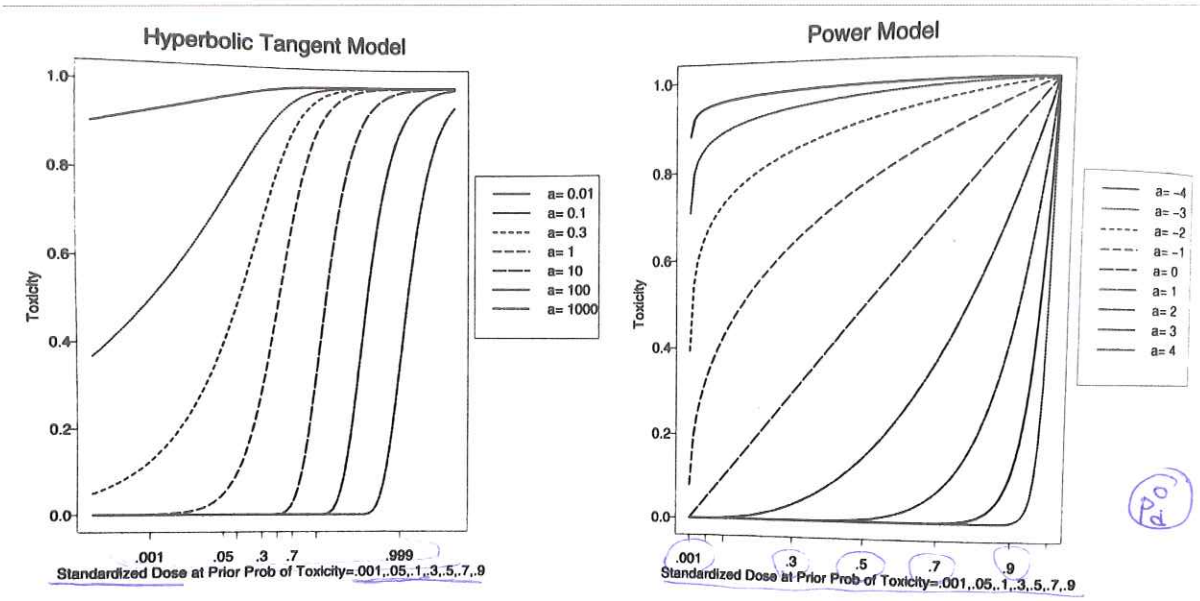

Figure 3.5 *Typical CRM dose-toxicity response curves: left, hyperbolic tangent; right, power.*

- The choice of the dose-toxicity curve and the initial estimate of a will be generally elicited from experts familiar with drug development.

- Sampling Model: CRM

$$p(\mathbf{y} \mid \theta) = \prod_{i=1}^{n} (p(d_i))^{y_i} (1 - p(d_i))^{1-y_i}$$

- Posterior distribution of a

$$p(a \mid \mathbf{y}) \propto p(\mathbf{y} \mid a) p(a).$$

Example 3.3 Suppose that in developing a new agent, six dose levels are to be studied. A hyperbolic tangent dose-toxicity curve with target toxicity level set at 20% is assumed.

$\pi^* = 20\%$

- ⋆⋆ We find the standardized dose: standardized dose $= tanh^{-1}(2p - 1)$ assuming $a = 1$ and initial guess of $p(d)$ is given for each d.

- ⋆⋆ Assume $p(a)$ to be an exponential distribution with mean 1.
  $\Rightarrow$ The prior probability of DLT at each dose centers around its initial estimate with a fairly wide credible interval.

	Dose Level					
	1	2	3	4	5	6
Dose (mg/m^2)	10	20	40	60	75	90
Prob(toxicity)	0.05	0.10	0.20	0.30	0.50	0.70
Standardized dose	−1.47	−1.1	−0.69	−0.42	0	0.42

Table 3.1 *Dose levels, standardized doses, and prior probabilities of toxicity, CRM example.*

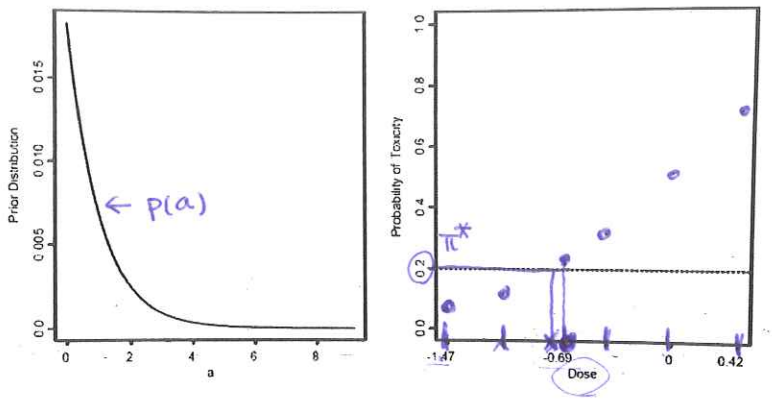

Figure 3.6 *Plots of the posterior distribution of a and the corresponding dose-toxicity curve for a CRM trial, Step 0: based only on the prior information; current MTD = dose 3.*

† CRM algorithm

- (Step 1) Start with a prior $p(a)$. Set $i = 1$.
- (Step 2) Treat 1 patient at $d_i = d^\star(y_1, \ldots, y_{i-1})$.
- (Step 3) Observe the toxicity outcome y_i.
- (Step 4) Update the posterior inference $p(a \mid y_1, \ldots, y_{i-1}, y_i)$ $\Rightarrow$ update the estimate of MTD based on the updated posterior distribution of a;

$$d^\star(\mathbf{y}) = \arg\min_d |\mathrm{E}(p(d) \mid \mathbf{y}) - \pi^\star|.$$

- (Step 6) Treat the next patient at the level closest to the updated estimate of MTD.
- (Step 7) Increment $i \equiv i + 1$, and repeat with step 1–3 until a reasonable estimate of a or maximum sample size N is reached.

Example 3.3 (Contd) The first patient is treated at dose 3 and no DLT is observed. With this information, the posterior of a is updated.

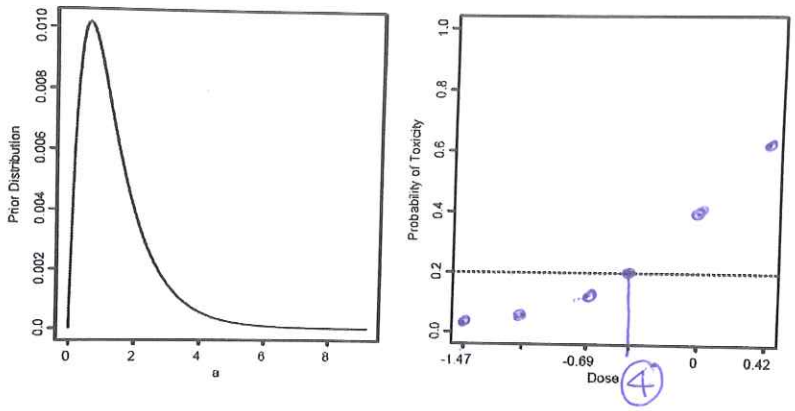

Figure 3.7 *Plots of the posterior distribution of a and the corresponding dose-toxicity curve for a CRM trial after Step 1: treat first patient at dose 3; result = no DLT; updated MTD = dose 4.*

$\Rightarrow$ The resulting dose-toxicity curve shows that the updated MTD estimate is now dose level 4.

Example 3.3 (Contd) The second patient is treated at dose 4 and no DLT is observed. With this information, the posterior of a is updated. $y_1 = 0,\ y_2 = 0$

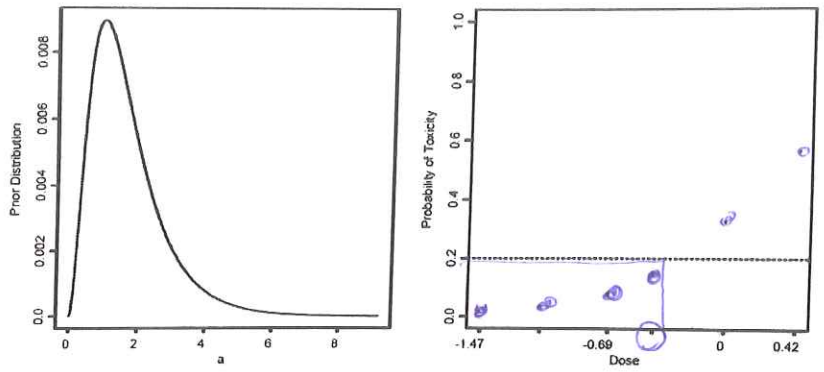

Figure 3.8 *Plots of the posterior distribution of a and the corresponding dose-toxicity curve for a CRM trial after Step 2: treat second patient at dose 4; result = no DLT; updated MTD = dose 4.*

$\Rightarrow$ The updated MTD estimate remains at dose level 4.