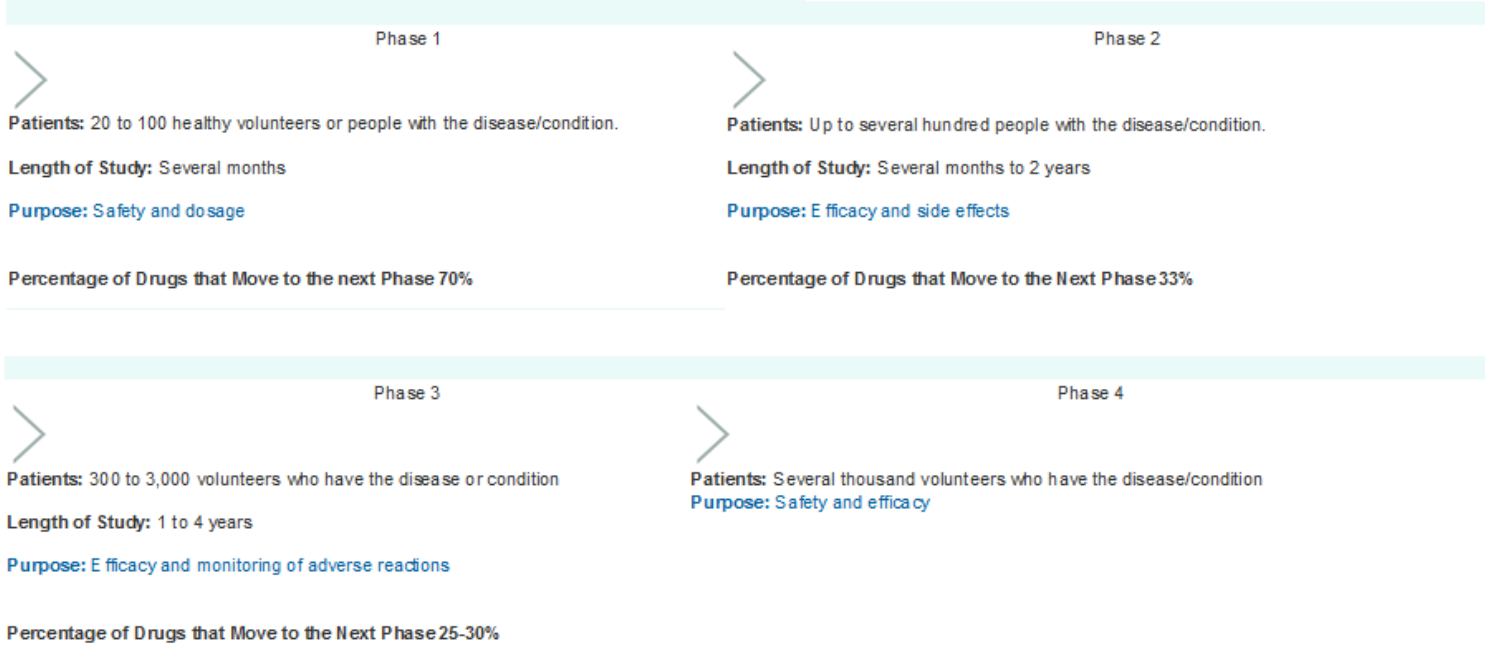
Bayesian Clinical Trials

Brief introduction to phase I and phase IIA trials

Phases of drug development process



FDA

Phase I study

- Goal: the first step in evaluating a potential new agent is to determine a dose having an acceptable level of toxicity.
- Key elements:
  - the starting dose d_{start}
  - the dose-limiting toxicity (DLT)
  - the target toxicity level (TTL)
  - a dose escalation scheme consisting of
    - a dose increment
    - a dose assignment
    - a cohort size

- Dose levels have historically been chosen according to some variation of a Fibonacci sequence. A Fibonacci sequence is a sequence of numbers where each number is the sum of the two previous numbers in the sequence; an example is $\{1,1,2,3,5,8,\ldots\}$.
- Based on dose assignment, phase I trials can be classified into rule-based methods and model-based methods

Rule based designs

- Traditional 3+3 design
  - If none of the first 3 patients experiences a DLT at d_{start} $=>$ 3 more patients will be treated at the next higher dose level (*escalation*).
  - If 1 of the first 3 patients experiences a DLT $=>$ 3 more patients will be treated at the same dose level.
  - If 2 or 3 patients out of 3 experience a DLT $=>$ 3 more patients will be treated at the next lower dose level (*de-escalation*).
  - The dose escalation/de-escalation continues but stops as soon as at least 2 patients experience DLTs, among a total of up to 6 patients (i.e. probability of DLT at the dose 33%).

Rule based designs

Example

Cohort	Dose 1	Dose 2	*Dose 3*	Dose 4
1	0/3			
2		1/3		
3		0/3		
4			1/3	
5			1/3	

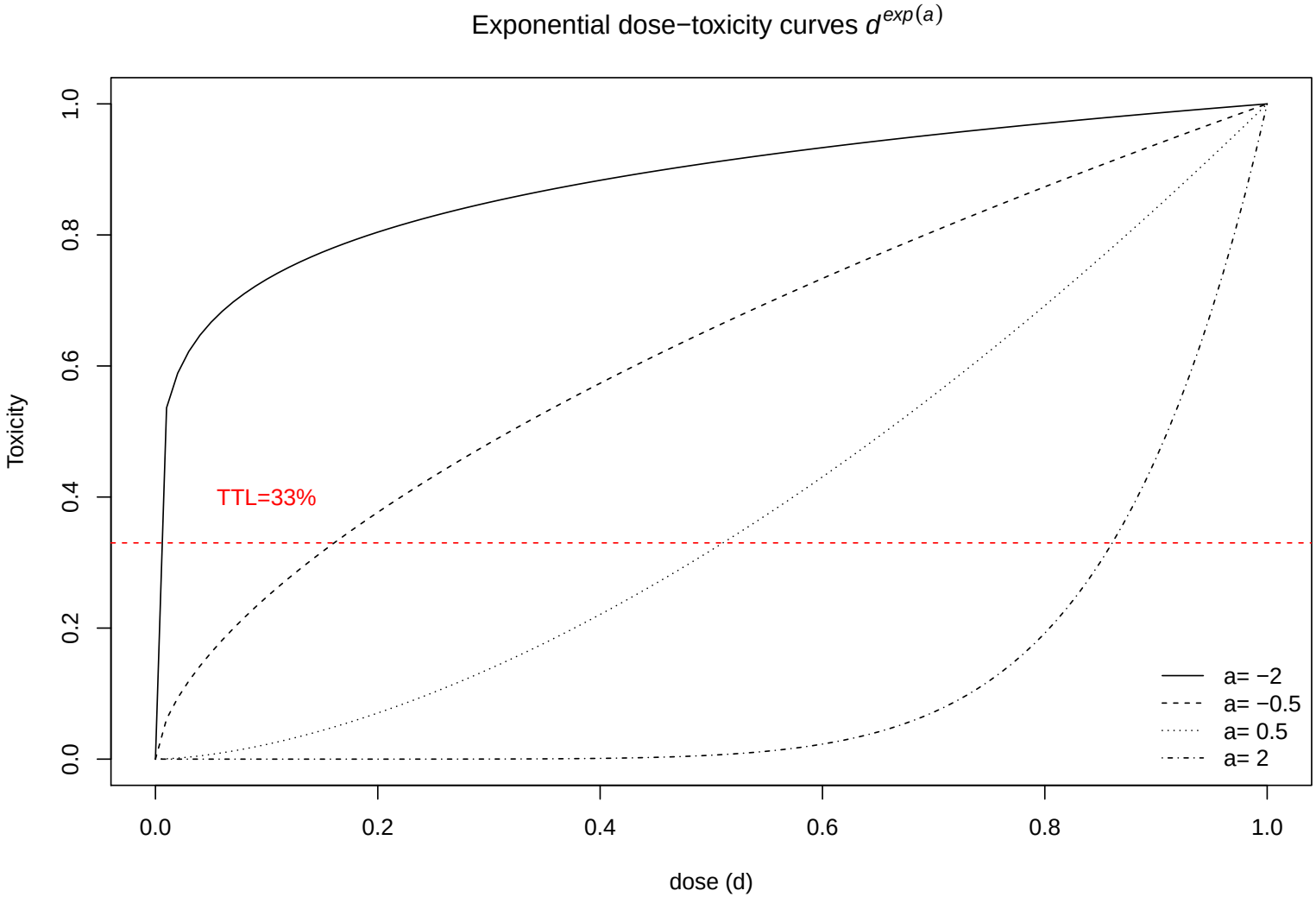
Rule based designs

- Alternative statistical approaches are needed to make a better use of the complex data generated by phase I trials. Their applications require a close collaboration between all actors of early phase clinical trials (Paoletti et al, 2015).

Model based

- Model-based methods for finding the MTD assume that there is a monotonic dose-toxicity relationship. In this approach, a dose-toxicity curve as well as the TTL are explicitly defined.
- The goal for the phase I clinical trial is, through treating patients in a dose escalation fashion, to seek a suitable quantile of the dose-toxicity curve; specifically,a dose that will induce a probability of DLT at a specified TTL.
- This method is most conveniently carried out under the Bayesian framework. Simple one- or two- parameter parametric models are often used to characterize the dose-toxicity relationship, with the Bayesian posterior distribution used to estimate the parameters.

Model based


Exponential dose−toxicity curves $d^{exp(a)}$
Toxicity
dose (d)
TTL=33%
a= −2
a= −0.5
a= 0.5
a= 2
0.0
0.2
0.4
0.6
0.8
1.0

Model based

- The continual reassessment method (CRM) seems to have been the first Bayesian model-based phase I design introduced in the literature (O'Quigley et al, 1990).
- Many modifications were proposed to overcome its greatest weakness - i.e. its potential for exposing patients to overly toxic doses if the first few patient responses are atypical or the model is misspecified - and its limitations such as the use of a single binary endpoint. See Berry et al (2011) for a review.

Phase II studies

After the toxicity profile and/or the MTD for a treatment has been investigated, phase II studies are conducted at the MTD or an optimal biological dose estimated from phase I.

- Goal: to examine whether a drug has sufficient efficacy to warrant further developmentand and to refine knowledge of its toxicity profile.
  - Phase IIA is single arm
  - Phase IIB is multi-arm

Phase IIA designs

To provide an initial efficacy assessment, a phase IIA trial is often designed as a single-arm,open-label study that requires treating 40 to 100 patients in a multistage setting.
The primary endpoint is often a binary endpoint of response/no response or success/failure.
Multi-stage designs are useful here for early stopping due to lack of efficacy should the interim data indicate that the study drug is inefficacious.

Phase IIA designs

- Simon (1989) optimal and minimax designs:
  - Optimal design minimize the expected sample size under the null hypothesis; minimax design can be constructed that minimizes the maximum trial sample size.
  - After the inclusion of a pre-determined number of patients, n_1, the trial is paused, and the response rate is evaluated.
  - If a pre-specified minimal response rate, r_1/n_1 has not been achieved, the treatment is not worth pursuing and the trial is ended.
  - Otherwise, enrollment continues until a pre-determined number n of additional patients are accrued. The drug will be declared effective or ineffective depending on the achievement of an overall response rater/n.

Phase IIB designs

After passing the initial efficacy assessment of a new agent in a phase IIA study, the subsequent phase IIB trial is often a randomized, multi-arm study.
Phase IIB trials are by definition smaller and less definitive than phase III trials.
They use earlier endpoints, such as disease-free survival, rather than overall survival in order to shorten study duration.
They also often have larger Type I and Type II error rates than their phase III counterparts.
They do not yield sufficient statistical power for a head-to-head comparison between the treatment arms.

References

- Paoletti X, Ezzalfani M, Le Tourneau C. Statistical controversies in clinical research: requiem for the 3 + 3 design for phase I trials. Ann Oncol 2015 Jun 18. pii: mdv266.
- 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.
- Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989; 10: 1-10.
- Berry S.M., Carlin B.P., Lee J.J. , Muller P. Bayesian Adaptive Methods for Clinical Trials. 2011 Chapman & Hall.