An overview of modern dose-finding designs for Phase I clinical trials: Part I

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9:30 – 10:10	Part I: Introduction to Dose-Escalation Trials The truth about “3+3” design Model-based Dose-Finding for Single-Agent Trials
10:40 – 11:20	Part II: Dose-Finding in Health Volunteers Dose Finding Design for Combination Phase I Trials

Medical & Pharmaceutical Stats (MPS) Research Unit

MPS develops and evaluates novel methods of study design & data analysis for use in the pharmaceutical and medical research community.

We offer number of services:

- Advice on design and analysis of clinical trials
- Develop novel methods for clinical & pre-clinical studies
- Professional Development Courses
  - Design and Analysis of Bioequivalence Studies
  - Pharmacological Modelling
  - Survival and Event History Analysis
  - Adaptive Methods in Clinical Research
  - **(!)** Designing Early Phase Studies
  - **(!)** Dose-Finding Designs for Combination Trials

Success rates

According to a recent review (Wong, Siah & Lo, Biostatistics, 2019), between 2000 and 2015

- **41.0%** of confirmatory clinical trials overall and
- **64.5%** of confirmatory clinical trials in oncology

have been unsuccessful.

Reasons for failed confirmatory trials

One of the reasons for failed confirmatory trials are thought to be:

- taking forward treatments that should have been abandoned during early efficacy studies due to insufficient precision when;
  - determining the maximum tolerated dose (MTD);
  - assessing safety;
  - determining the optimal dose.

Consequences

- Avoid going straight into large and expensive Phase III;
- Take more care during Phase I and Phase II trials.

Introduction to Phase I trials

- First experimentation of a new drug in humans
- The emphasis is on **safety**
- Trials are small, typically 20-50 patients
- Patients are added sequentially after side-effects from previous patients have been assessed

Introduction to Phase I trials

- Subjects
  - **Healthy volunteers** for relatively non-toxic agents
  - **Patients** when drugs are toxic (e.g. in cancer)
- Aim: Find the highest dose with acceptable level of toxicity
  - This is known as the **maximum tolerated dose** (MTD)
  - Based on the assumption that **both benefit** (efficacy) **and risks** (toxicity) of treatment **increase with the dose**
- Setting (of Part I):
  - Binary toxicity outcome (e.g. a *dose-limiting toxicity* (DLT))
  - A *target toxicity level* (TTL) (the desired toxicity at the MTD)

Seeking a quantile

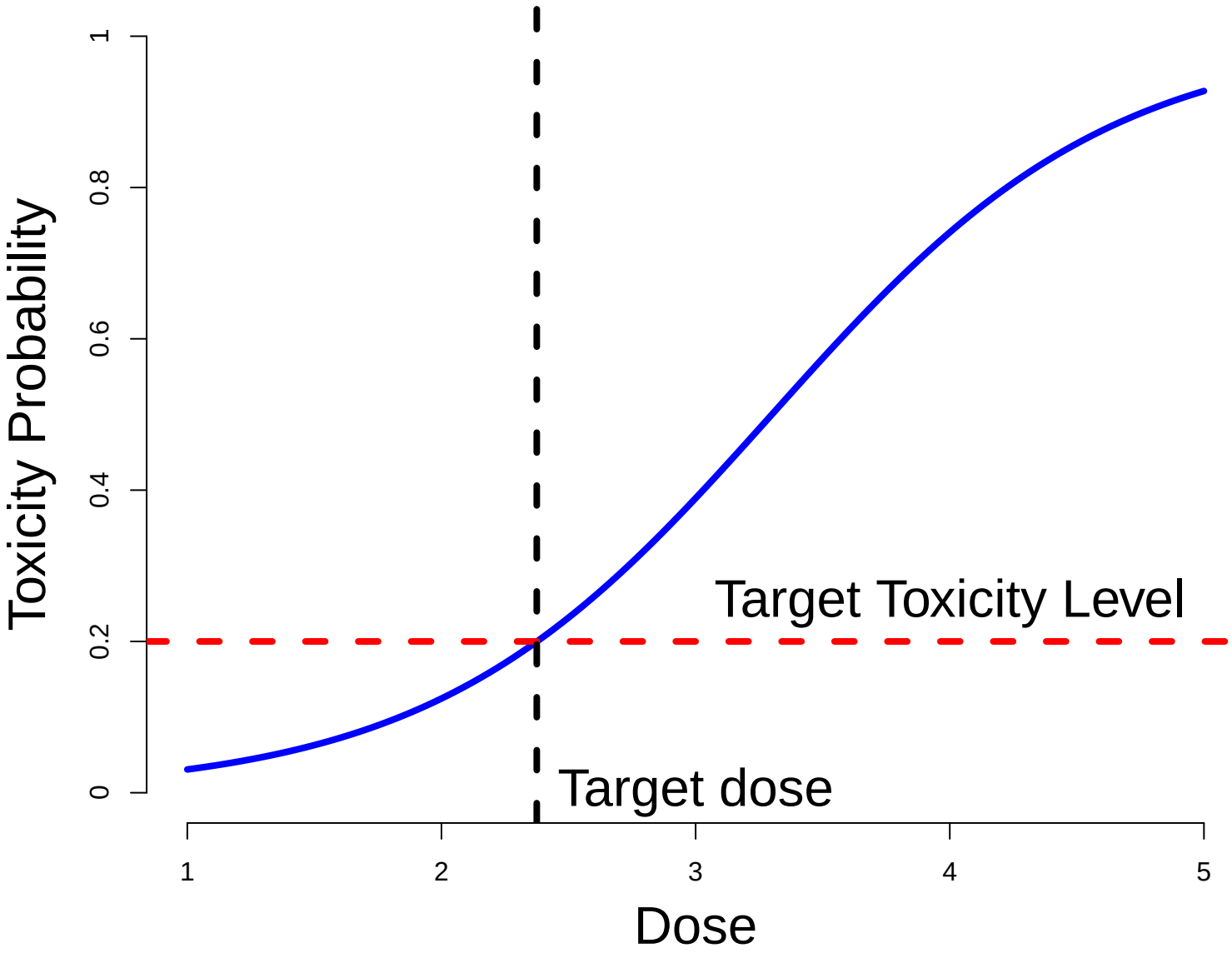
MTD – maximal dose acceptably tolerated by a particular patient population

$\rightarrow$ vague

$TD100\theta$ – dose at which the probability of toxicity is θ (for $0 < \theta < 1$), e.g. TD20

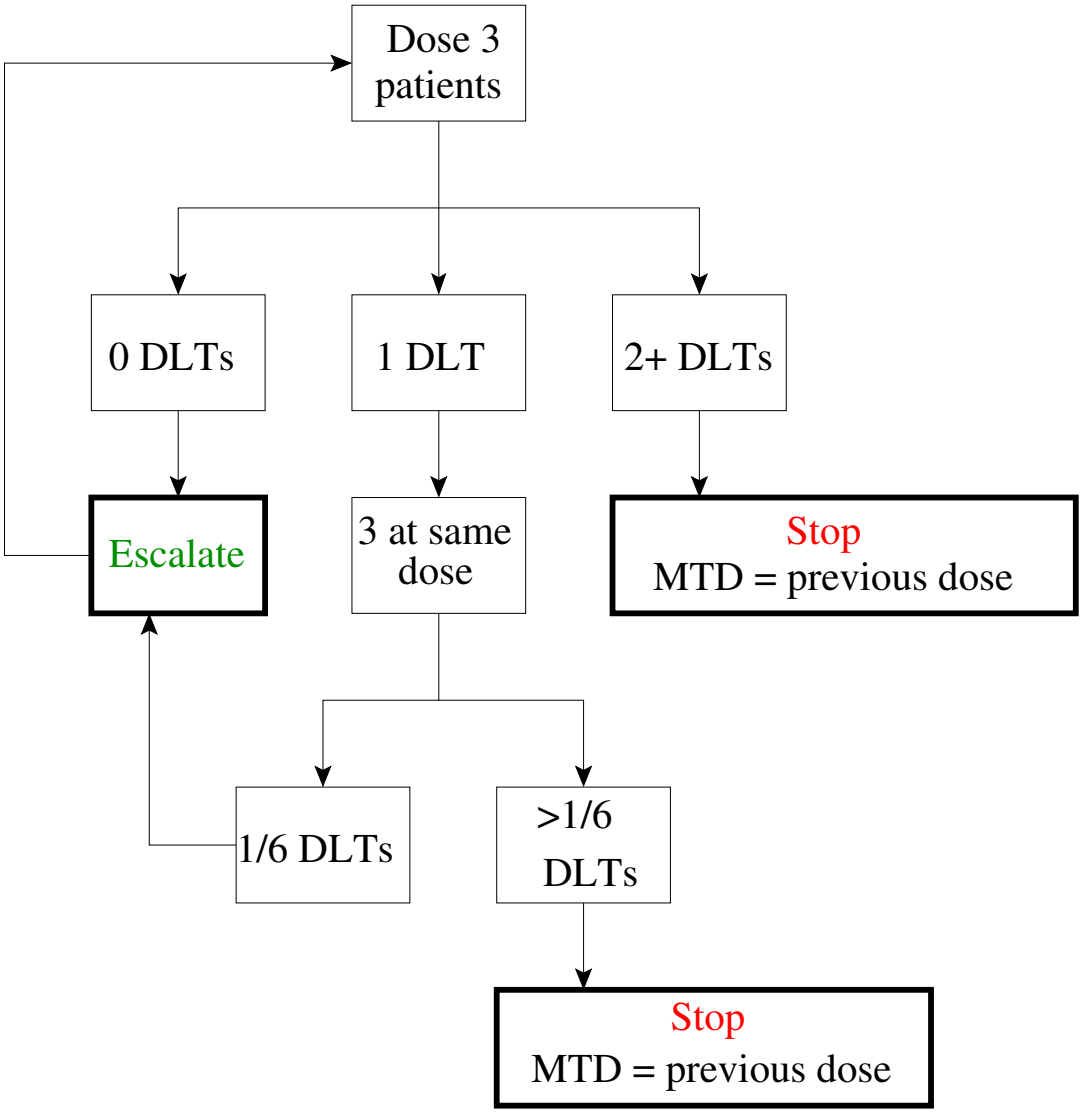
$\rightarrow$ more specific

TD20


Toxicity Probability
0
0.2
0.4
0.6
0.8
1
Target Toxicity Level
Target dose
1
2
3
4
5
Dose

3+3 design with escalation only

Storer (1989)



- Dose Limiting Toxicity (DLT)
- Simple rule based approach
- No need for a statistician
- Actual dose not used
- The data to declare an MTD are either $0/3$ or $1/6$

The truth about the 3+3 design

- Example with 4 doses. True toxicities: $(0.04, 0.29, 0.36, 0.74)$
  - The percentage of patients experimented on each dose are $(35\%, 43\%, 17\%, 5\%)$ —averaged over all possible trials
  - The recommended MTD probabilities are $(48\%, 31\%, 19\%, 0\%)$, 2% no recommended doses
- The 3+3 design
  - tends to underestimate the MTD
  - is inflexible and memoryless
  - According to a recent study by Conaway & Petroni (2019), the 3+3 design leads to a up to 10% noticeably lower success rates in a Phase III trial compared to model-based alternatives.

A web application for A+B designs:

`https://graham-wheeler.shinyapps.io/AplusB/`

Single-Agent Dose-Finding Study

k increasing doses : $d_1 < d_2 < \cdots < d_k$

Response: $x = \begin{cases} 1 \text{ if a patient experienced a DLT} \\ 0 \text{ otherwise} \end{cases}$

Structure: treat successive cohorts of c subjects

Objective: find the “highest safe dose”

Based on the monotonicity assumption: “**the more the better**”:

Both toxicity and efficacy increase with the dose.

Designs for in-patients Phase I trials

Three classes:

- Rule-based designs (e.g. “3+3” design)
- Model-based designs (e.g. CRM, EWOC, etc.)
- Model-assisted (shape-free) designs (mTPI, BOIN, etc.)

Review of advantages Jaki *et al*. (2013)

General (Bayesian) model-based design

Before the trial:

1. Choose doses $d_1, \ldots, d_k$;
2. Choose a form of dose-response relationship $p(d_i, \boldsymbol{\alpha})$ where α are model parameters;
3. Impose a prior distribution for $\boldsymbol{\alpha}$;
4. Choose a criterion to allocate patients;
5. Choose stopping rules (e.g. estimated accurately enough).

During the trial:

1. Sequentially update estimates of α ;
2. Select the dose for the next cohort using the criterion;
3. Stop if at least one of the stopping rules is met.

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Continual Reassessment Method (CRM)
by O'Quigley et al (1990)

Response:	Binary
Model:	$p(\pi_i, \alpha) = \pi_i^{exp(\alpha)}$, π_i are standardised doses
	(skeleton) calculated from prior estimates of p_i
Prior on α:	Normal $\alpha \sim \mathcal{N}(\mu, \sigma^2)$
Allocation Rule:	$\min \lvert p_i(\pi_i, \hat{\alpha}) - \theta \rvert$ where $\hat{\alpha} = \mathbb{E}(\alpha)$

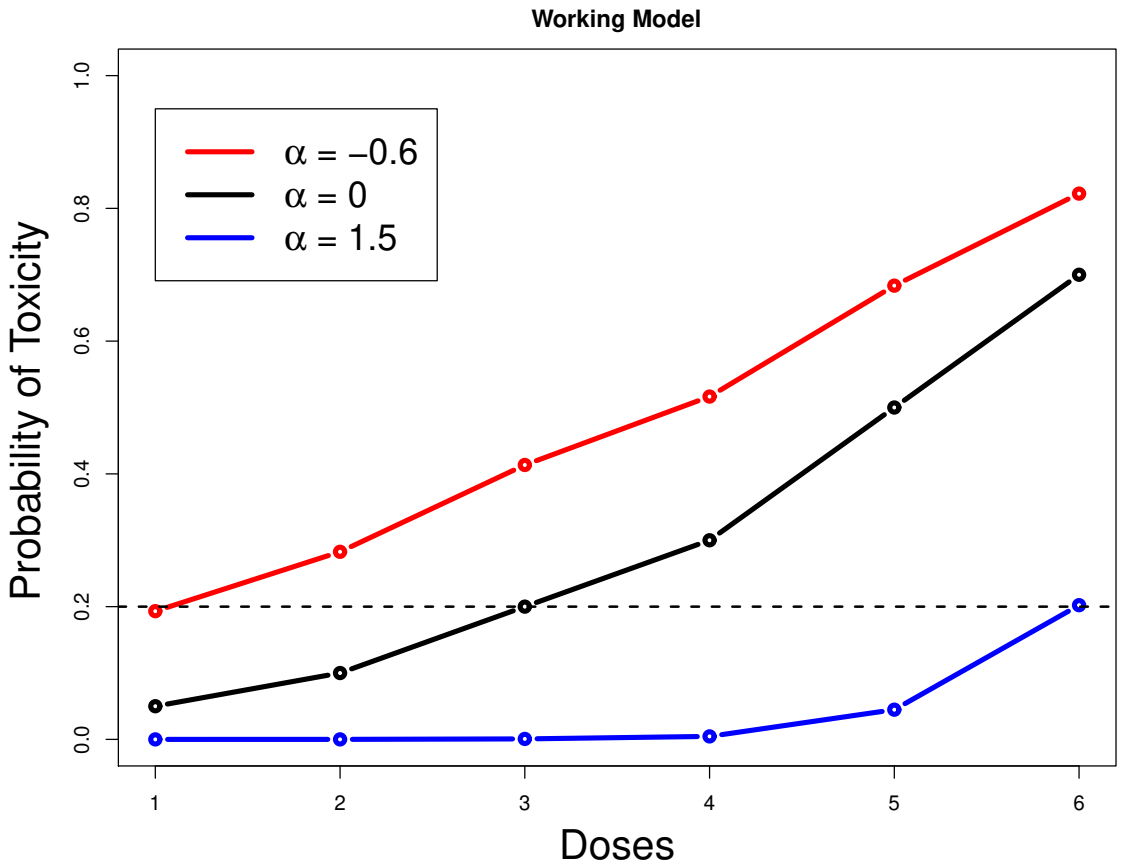
This form of the CRM is extensively studied in the literature:

- Prior for α: $\mathcal{N}(0, 1.34) \rightarrow$ all doses has the same prior probability to be the MTD
- Operational skeleton: given "equivalent interval" $\rightarrow$ an optimal spacing between skeleton

Representation of the model

Starting values for π_i

π_1	π_2	π_3	π_4	π_5	π_6
0.05	0.10	0.20	0.30	0.50	0.70



Bayesian updating

1. Specify the prior distribution of α
2. Assign the first cohort to the lowest dose
3. Given the observations (data) and the prior distribution, update the (posterior) distribution of α

$$\text{Posterior} \propto \text{Prior} \times \text{Data}$$

4. Given the posterior find the "best" guess of α: $\hat{\alpha}$
5. Find estimates of toxicity probabilities as $\hat{p}_i = \pi_i^{\exp(\hat{\alpha})}$
6. Allocate the next cohort to the dose having the estimated toxicity closest to the target level θ.
7. Repeat steps 4-6 using the obtained Posterior as Prior.

Alternative dose-toxicity model

Model:

- Two-parameter logistic regression model

$$p(d_{(j)}) = \frac{\exp\{\alpha_1 + \alpha_2 \log(d_{(j)})\}}{1 + \exp\{\alpha_1 + \alpha_2 \log(d_{(j)})\}}$$

- where $d_{(1)} < \cdots < d_{(k)}$ are doses (!)

Requires a **prior** distribution on (α_1, α_2)

Similar to the one-parameter CRM, there is a recommendation for this prior that leads to good operating characteristics

$$(\log \alpha_1, \log \alpha_2) \sim \mathcal{N}\left(\begin{bmatrix} 2.15 \\ 0.52 \end{bmatrix}, \begin{bmatrix} 0.84^2 & 0.134 \\ 0.134 & 0.80^2 \end{bmatrix} \right)$$

Allocation Criteria

- Escalation with Overdose Control (EWOC):

$$\mathbb{E}\left(\nu(\theta - p_i)^+ + (1-\nu)(p_i - \theta)^+\right)$$

  e.g. $\nu = 0.25$

- NCRM by Neuenschwander et al (2008):
  - Maximising the probability of being in the target interval
  - while safeguarding the patients (controlling the probability that dose is too toxic)

Comments on the implementation

Planning and conducting the trial using model-based designs

- Model-based designs would required more effort to be implemented. However, there is a variety of software implementing these designs.
- There are several ready-to-use interactive Web Applications for the designs covered above that require **no programming/statistical skills**

  They can be used for **simulation and implementation** of different model-based designs

  - 1-parameter CRM `uvatrapps.shinyapps.io/crmb/`
  - 2-parameter + prior elicitation `lancs.shinyapps.io/Design/`


Babb, J., Rogatko, A. and Zacks, S. (1998) Cancer phase i clinical trials: efficient dose escalation with overdose control.
Statistics in medicine, **17**, 1103–1120.


Mozgunov, P., Jaki, T. and Paoletti, X. (2018) Randomized dose-escalation designs for drug combination cancer trials with immunotherapy.
Journal of Biopharmaceutical Statistics, 1–19.


Neuenschwander, B., Branson, M. and Gsponer, T. (2008) Critical aspects of the bayesian approach to phase i cancer trials.
Statistics in medicine, **27**, 2420–2439.


O'Quigley, J., Pepe, M. and Fisher, L. (1990) Continual reassessment method: a practical design for phase 1 clinical trials in cancer.
Biometrics, 33–48.


O'Quigley, J. and Zohar, S. (2010) Retrospective robustness of the continual reassessment method.
Journal of Biopharmaceutical Statistics, **20**, 1013–1025.


Wheeler, G. M., Sweeting, M. J. and Mander, A. P. (2017) Toxicity-dependent feasibility bounds for the escalation with overdose control approach in Phase I cancer trials.
Statistics in Medicine, **36**, 2499–2513.


Whitehead, J. and Williamson, D. (1998) Bayesian decision procedures based on logistic regression models for dose-finding studies.
Journal of Biopharmaceutical Statistics, **8**, 445–467.


Yap, C., Billingham, L. J., Cheung, Y. K., Craddock, C. and O'Quigley, J. (2017) Dose transition pathways: the missing link between complex dose-finding designs and simple decision-making.
Clinical Cancer Research, **23**, 7440–7447.


Zhou, Y. and Whitehead, J. (2003) Practical implementation of bayesian dose-escalation procedures.
Drug Information Journal, **37**, 45–59.