MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Dose-escalation designs for combination & dose-schedule studies

Lecture 10: How to set-up a design for a dose-escalation trial

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How to use what you have learnt

- We have learnt about many advanced designs that can deal with many complex dose-escalation settings, but
- How do we know which to apply and when?
- When we know which, how do we make it work for **your particular trial**?

What is the research question?

- What is the objective of the trial?
- What is the patient population?
- What is the primary endpoint? Safety only? Safety and efficacy?
- What is after this trial?
- ...

Modelling questions

- Combinations? Schedules? Both?
- Is there an uncertainty in the ordering? [belief or knowledge?]
- How many compounds?
- How many schedules? Doses? Discrete or continuous?
- How can we expect the compound interact in terms of the toxicity and/or efficacy?
- Distribution of the endpoint? [Binary/Ordinal/Continuous...]
- ...

Should it be a controlled Phase I study?

- What is the objective of the trial? Overall TTL or additional TTL?
- Can the clinicians reliable attribute the toxicity to the experimental agent?
- Are there any other reasons to have a control?

Prior information

- Is there available prior information relevant to the studied drug(s)?
- Were there previous studies conduct in any of the studied compounds?
- Relevant to this population?
- Relevant to the proposed endpoint?

Parameters to be defined

Parameters	**Motivation and method(s) for choosing**	**Considerations**
Target toxicity rate	Motivated by safety considerations. Clinical decision	DLT defnition should be consciously specified, with acceptable toxicity determined by clinical context
Tolerance around target	Motivated by safety considerations. Clinical decision	Any given set of doses is unlikely to have target risk, so flexibility around the target should be considered.
Upper toxicity bound	Motivated by safety considerations. Clinical decision	Level of unacceptable toxicity
# of Doses	Clinical decision [with statistical considerations]	Should ensure that the dose / combo -toxicity curve is explored
Cohort size	Safety, practical and statistical considerations	Enough patients to make decisions on dose escalation; how often the model will be updated.
Sample Size	Practical and statistical considerations	Sample size should ensure an accurate selection of target doses with high probability
Parameters of prior distribution	Elicited from clinical knowledge; Via simulations; Hybrid; Literature	A trade-off between the accuracy and safety
Overdosing threshold	Simulations; reference in the literature	A trade-off between the accuracy and safety

Purpose of the design

- It is important to decide on how the proposed design/model will be used for the decision-making;
- Typically, the safety review committee (SRC) can overrule the decisions by the model;
- Can the design still be useful in this case?
- What information is needed to support the decision-making?

What is needed for decisions?

(A_1, B_3) [7] n=xx—DLTs=xx Mean Tox=0.xx 95%CI=(0.xx,0.xx) Overdose=xx% Target=xx% Under=xx%	(A_2, B_3) [8] n=xx—DLTs=xx Mean Tox=0.xx 95%CI=(0.xx,0.xx) Overdose=xx% Target=xx% Under=xx%	(A_3, B_3) [9] n=xx—DLTs=xx Mean Tox=0.xx 95%CI=(0.xx,0.xx) Overdose=xx% Target=xx% Under=xx%
(A_1, B_2) [4] n=xx—DLTs=xx Mean Tox=0.xx 95%CI=(0.xx,0.xx) Overdose=xx% Target=xx% Under=xx%	(A_2, B_2) [5] n=xx—DLTs=xx Mean Tox=0.xx 95%CI=(0.xx,0.xx) Overdose=xx% Target=xx% Under=xx%	(A_3, B_2) [6] n=xx—DLTs=xx Mean Tox=0.xx 95%CI=(0.xx,0.xx) Overdose=xx% Target=xx% Under=xx%
(A_1, B_1) [1] n=xx—DLTs=xx Mean Tox=0.xx 95%CI=(0.xx,0.xx) Overdose=xx% Target=xx% Under=xx%	(A_2, B_1) [2] n=xx—DLTs=xx Mean Tox=0.xx 95%CI=(0.xx,0.xx) Overdose=xx% Target=xx% Under=xx%	(A_3, B_1) [3] n=xx—DLTs=xx Mean Tox=0.xx 95%CI=(0.xx,0.xx) Overdose=xx% Target=xx% Under=xx%

Means of the evaluation

- Individual trial output;
- Dose-transition pathways;
- Simulation study;

How to choose the parameters

- Literature (?)
- Prior elicitation;
- Operational prior
  [chosen from statistical considerations to achieve good OC];
- Hybrid approach.

Operational prior

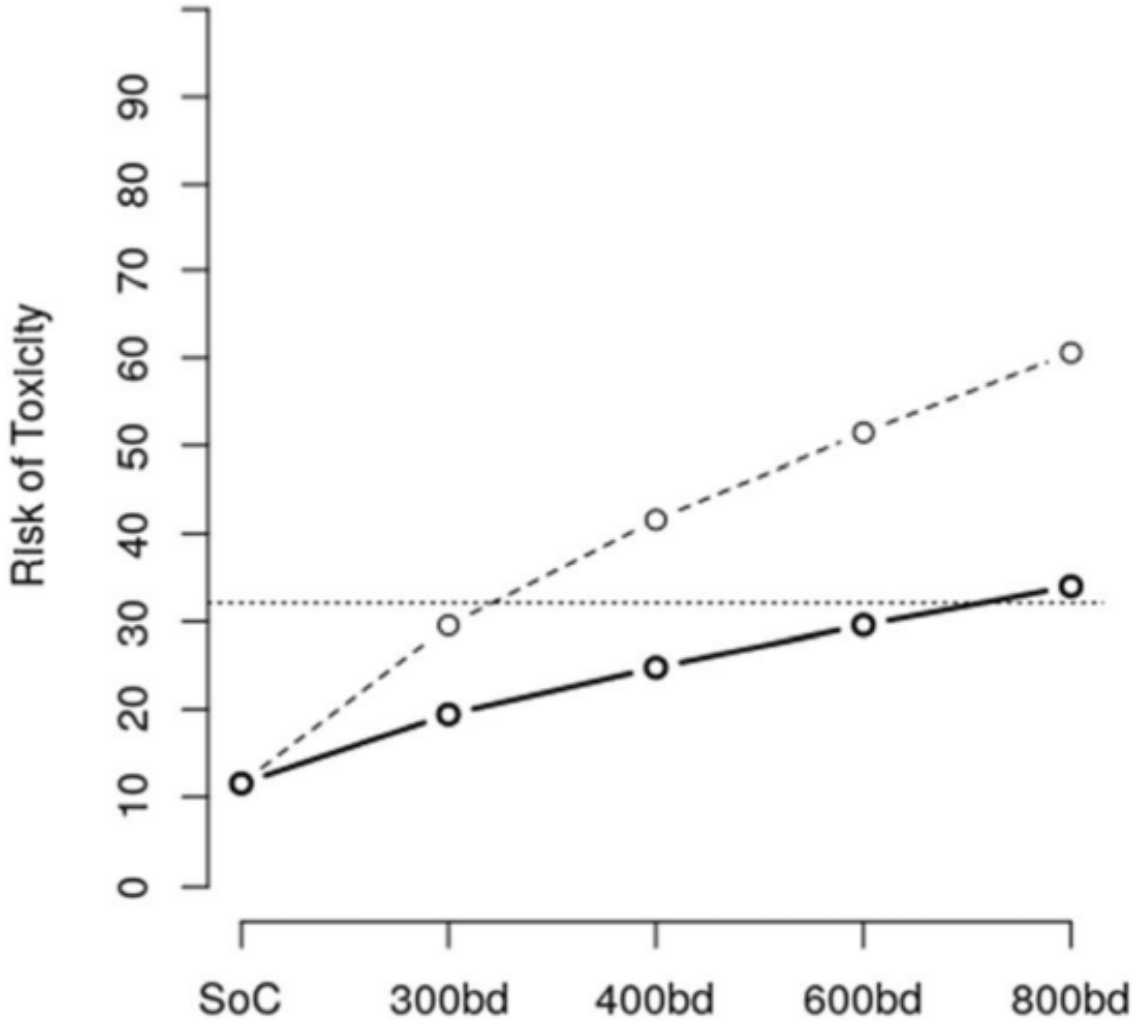
- Grid search over combination of parameters.

  For example, for the single-agent BLRM:

  - the hyper-parameters for the intercept μ_0, σ_0
  - the hyper-parameters for the slope μ_1, σ_1
  - Overdosing threshold probability;

Operational prior: How to choose grid

- The combination of hyper-parameters on the grid should induce **sufficiently different** underlying combination-toxicity curve



Operational prior: How to narrow down the grid

- The combinations of the parameters are subject to the clinically intuitive decisions in the first cohorts
  - If 0/3 DLTs in the first cohort is observed ...
  - If 1/3 DLTs in the first cohort is observed ...
  - ...

Scenarios

- Choose the combination of the parameters that yield high accuracy and acceptable safety.
- Over what scenarios?
- All set of scenarios should cover all plausible clinical scenarios and locations of the MTCs.

All possible scenarios in 3 $\times$ 3 case

Scenario 1		
0.50	0.60	0.70
0.45	0.50	0.60
0.30	0.45	0.50

Scenario 2		
0.50	0.60	0.70
0.45	0.50	0.60
0.20	**0.30**	0.45

Scenario 3		
0.45	0.50	0.60
0.20	0.45	0.50
0.10	0.20	**0.30**

Scenario 4		
0.45	0.60	0.70
0.30	0.50	0.60
0.20	0.45	0.50

Scenario 5		
0.45	0.50	0.60
0.20	**0.30**	0.50
0.10	0.20	0.45

Scenario 6		
0.20	0.45	0.50
0.10	0.20	**0.30**
0.00	0.10	0.20

Scenario 7		
0.30	0.50	0.60
0.20	0.45	0.50
0.10	0.20	0.45

Scenario 8		
0.20	**0.30**	0.50
0.10	0.20	0.45
0.00	0.10	0.20

Scenario 9		
0.10	0.20	**0.30**
0.00	0.10	0.20
0.00	0.00	0.10

Scenario 10		
0.45	0.50	0.60
0.30	0.45	0.50
0.20	**0.30**	0.45

Scenario 11		
0.30	0.50	0.60
0.20	0.45	0.50
0.10	**0.30**	0.45

Scenario 12		
0.45	0.50	0.60
0.30	0.45	0.50
0.10	0.20	**0.30**

Scenario 13		
0.30	0.50	0.60
0.20	0.45	0.50
0.10	0.20	**0.30**

Scenario 14		
0.45	0.50	0.60
0.20	**0.30**	0.45
0.10	0.20	**0.30**

Scenario 15		
0.20	**0.30**	0.50
0.10	0.20	0.45
0.00	0.10	**0.30**

Scenario 16		
0.30	0.45	0.60
0.20	**0.30**	0.50
0.10	0.20	0.45

Scenario 17		
0.30	0.45	0.50
0.10	0.20	**0.30**
0.00	0.10	0.20

Scenario 18		
0.20	**0.30**	0.45
0.10	0.20	**0.30**
0.00	0.10	0.20

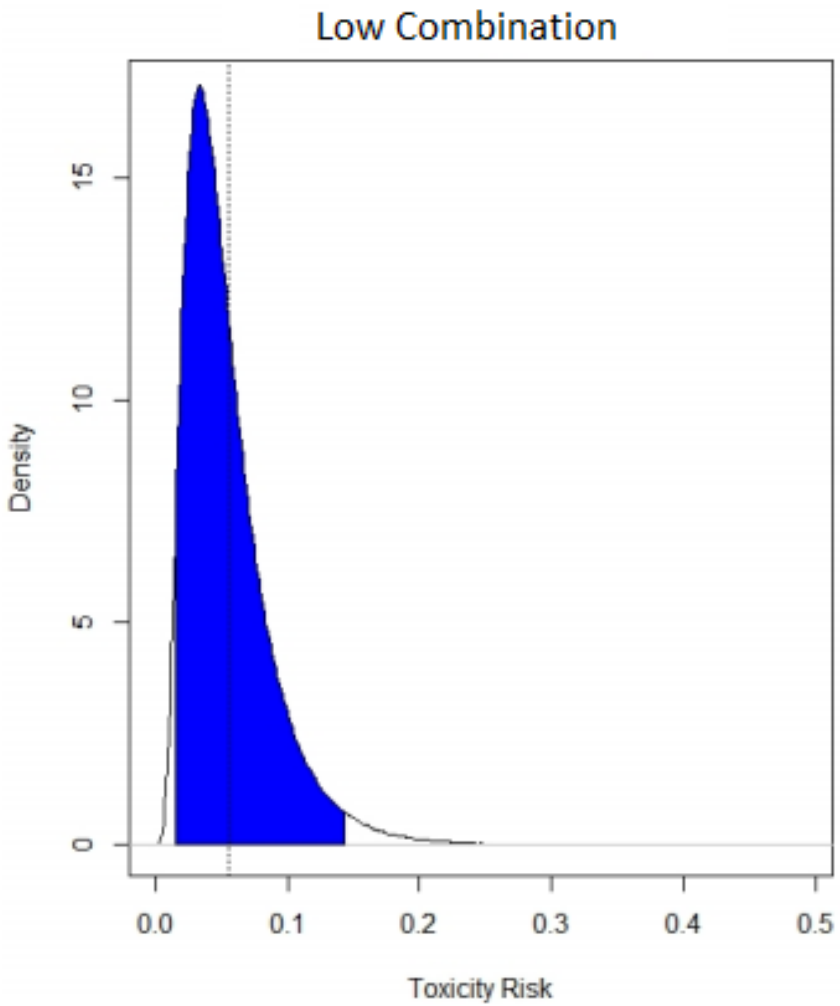
Scenario 19		
0.30	0.45	0.50
0.20	**0.30**	0.45
0.10	0.20	**0.30**

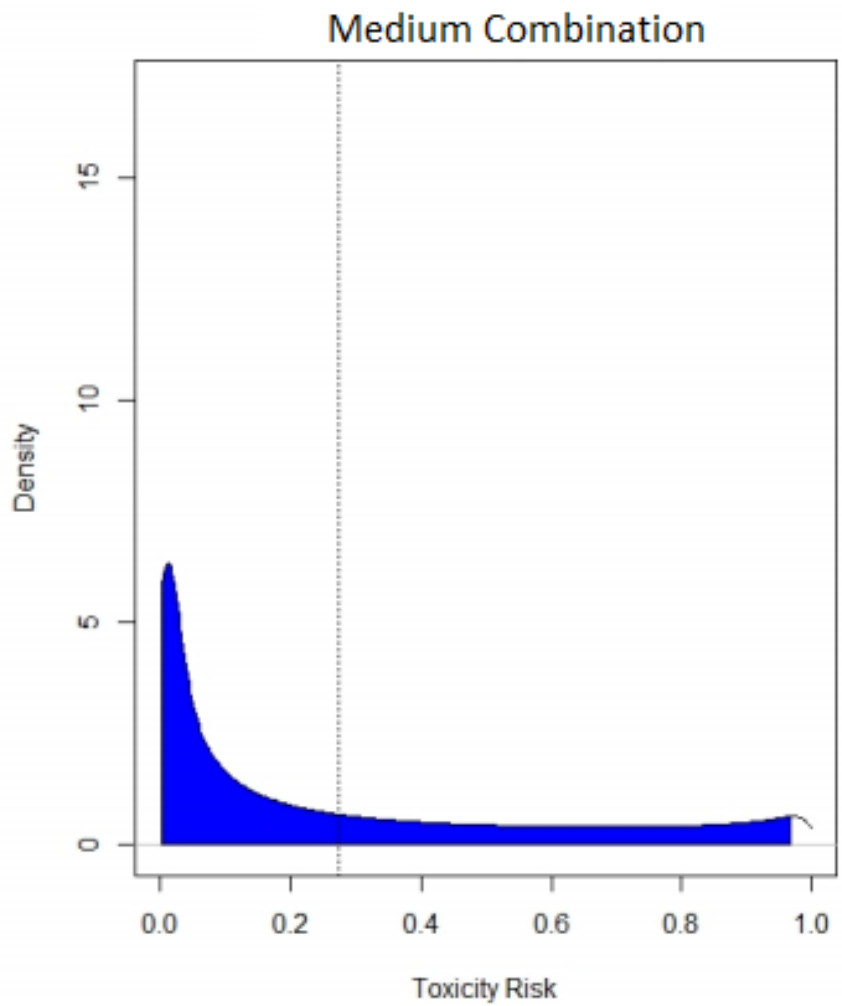
Operational prior: Scenarios

- Due to computational costs, we commonly have to choose a subset of these scenarios;
- Scenarios should cover sufficiently different clinical scenarios, e.g.
  - Very steep combination-toxicity curve (MTC is low);
  - Very flat combination-toxicity curve (MTC is high)

Prior distribution of the DLT rate

- The prior distribution is chosen on the unit-less scale.
- What prior distribution on the toxicity risk does it induce?

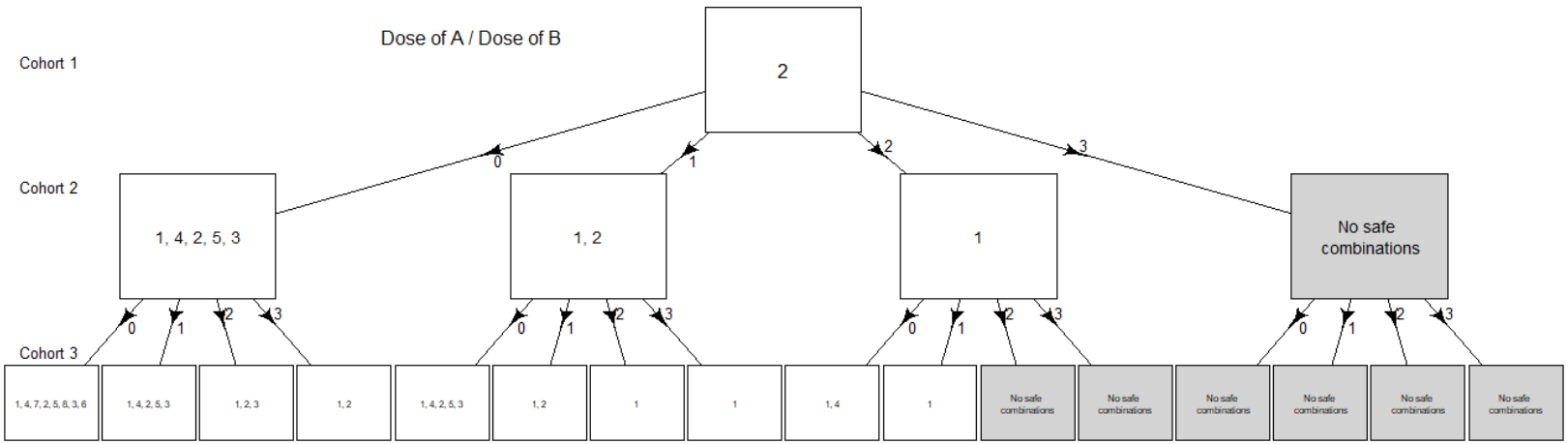




Dose-transition pathways

- Once the hyper-parameters are calibrated, we need to overcome a “black box” concern, and
- To demonstrate/confirm that the proposed design leads to intuitive escalation/de-escalation decisions.
- Presenting the information relevant for the decision-making;

Dose-transition pathways



Example output

- Once the prior distribution is satisfying, and
- The escalation-decisions are aligned,
- The next mean of the evaluation is the complete output after 1/2/3 cohorts
  - The behaviour of the estimates of the combination-toxicity curve;
  - To demonstrate/confirm possible decisions that could be taken at this point;
  - Training component for the clinical team.

Example output: 0/3 at the first cohort

A_1, B_3	A_2, B_3	A_3, B_3
n=0—DLTs=0	n=0—DLTs=0	n=0—DLTs=0
Mean Tox=0.22	Mean Tox=0.24	Mean Tox=0.26
95%CI=(0.03,0.82)	95%CI=(0.03,0.87)	95%CI=(0.03,0.91)
Overdose=20%	Overdose=23.2%	Overdose=26.4%
Target=17.9%	Target=18%	Target=18%
Underdose=62.1%	Underdose=58.8%	Underdose=55.6%
A_1, B_2	A_2, B_2	A_3, B_2
n=0—DLTs=0	n=0—DLTs=0	n=0—DLTs=0
Mean Tox=0.16	Mean Tox=0.18	Mean Tox=0.2
95%CI=(0.03,0.58)	95%CI=(0.03,0.69)	95%CI=(0.03,0.77)
Overdose=9.1%	Overdose=13.1%	Overdose=16.6%
Target=15.4%	Target=16.7%	Target=17.5%
Underdose=75.5%	Underdose=70.2%	Underdose=65.9%
A_1, B_1	A_2, B_1	A_3, B_1
n=0—DLTs=0	n=3—DLTs=0	n=0—DLTs=0
Mean Tox=0.08	Mean Tox=0.11	Mean Tox=0.13
95%CI=(0.02,0.21)	95%CI=(0.02,0.33)	95%CI=(0.02,0.46)
Overdose=0.2%	Overdose=2.1%	Overdose=5.6%
Target=2.9%	Target=8.7%	Target=12.8%
Underdose=96.9%	Underdose=89.2%	Underdose=81.6%

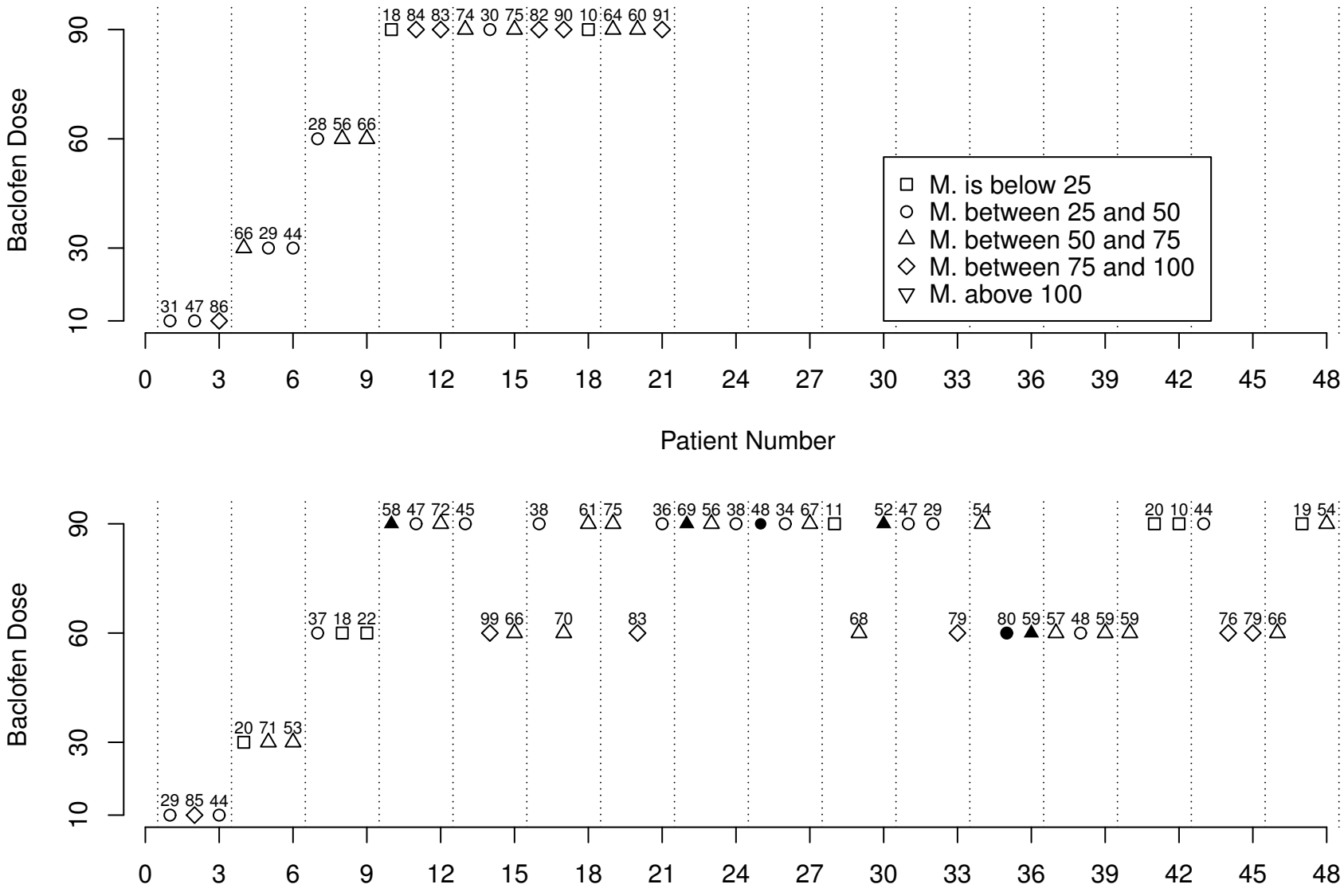
Simulation study: performance metrics (example)

- Proportion of the optimal combination selections (30%);
- Proportion of the combination selections in the target interval (20%-35%);
- Proportion of the overtoxic combination selections ($>$35%);
- Average number of DLTs;
- Proportion of the trial terminations (for safety).

Example of alternative output: DTP

- There could be setting in which presenting all possible paths (even for 3 cohorts) might be cumbersome or might be impossible at all;
- For example, the detoxification trial with individual (continuous) doses of one agent;
- Solution: generate dose-escalation strategies for different doses and DLT/no-DLT outcomes and assess them;

Dose-transition pathways



Other settings

- No two trials are the same, and the relevant outputs in trials will be different;
- But these means of assessment (in one form of another) are fundamental for the concious decision on the design