MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Dose-escalation designs for combination & dose-schedule studies

Lecture 7: Model-based designs for combinations

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Setting

- Consider a two-drug combination study
  - Agent A has J dose levels: $A_1 < \cdots < A_J$
  - Agent B has K dose levels: $B_1 < \cdots < B_K$
- $d_{jk} = (A_j, B_k)$ is the combination of Agent A at dose level j and Agent B at dose level k
- Probability of DLT at combination d_{jk} is denoted p_{jk}
- Goal: find maximum tolerated dose combinations (MTDC's) (maximum tolerated contour, MTC).

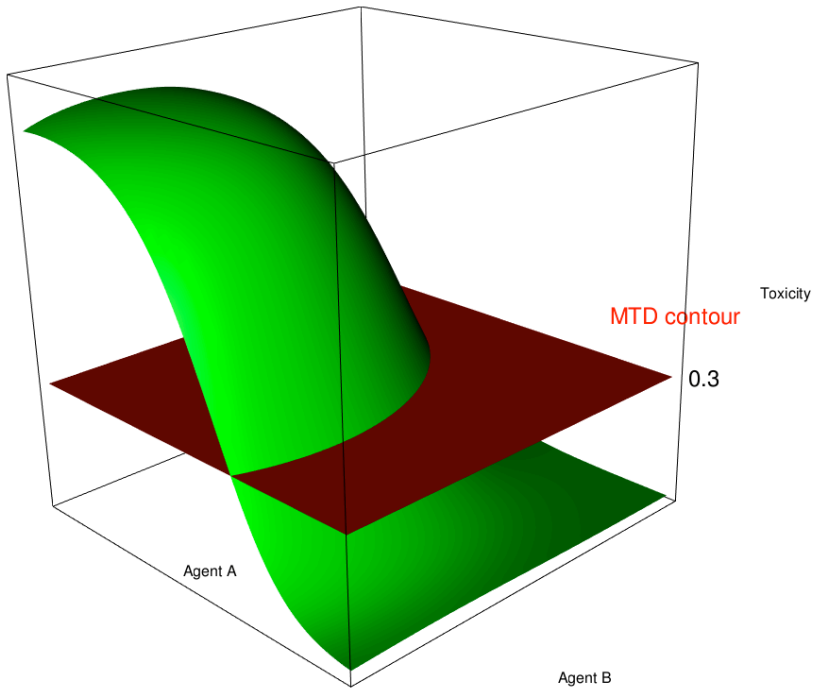
Challenges with dual-agent methods

The problems with model-based dual-agent dose-escalation

1. Complexity
   Flexible combination-toxicity models require many parameters
2. Convergence of parameter
   Estimation can be poor given a small sample size
3. What model should one pick?
4. If there are **few combinations** is a model worthwhile?

General modelling approach

- Assume a parametric model for probability of toxicity
- Put a prior distribution on parameters
- Estimate a single target combination or the maximum tolerated contour;
- Choose an allocation rule;

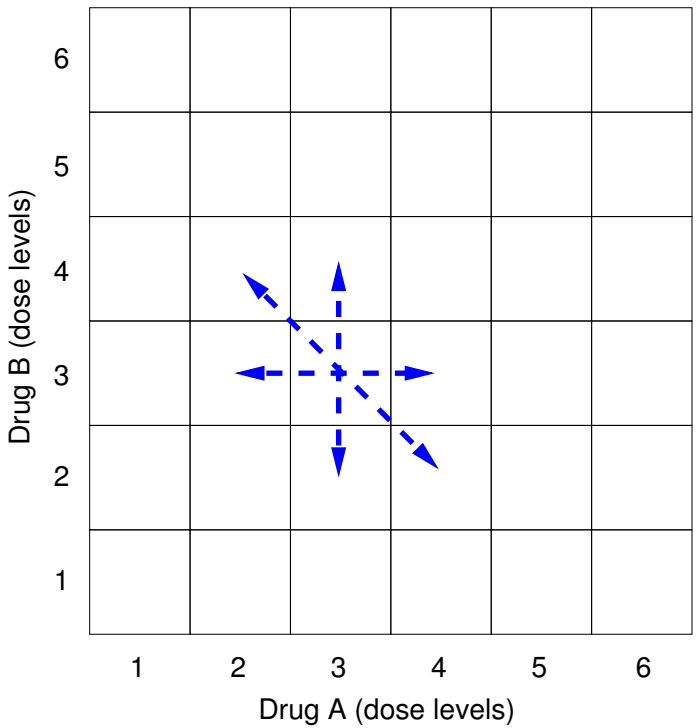


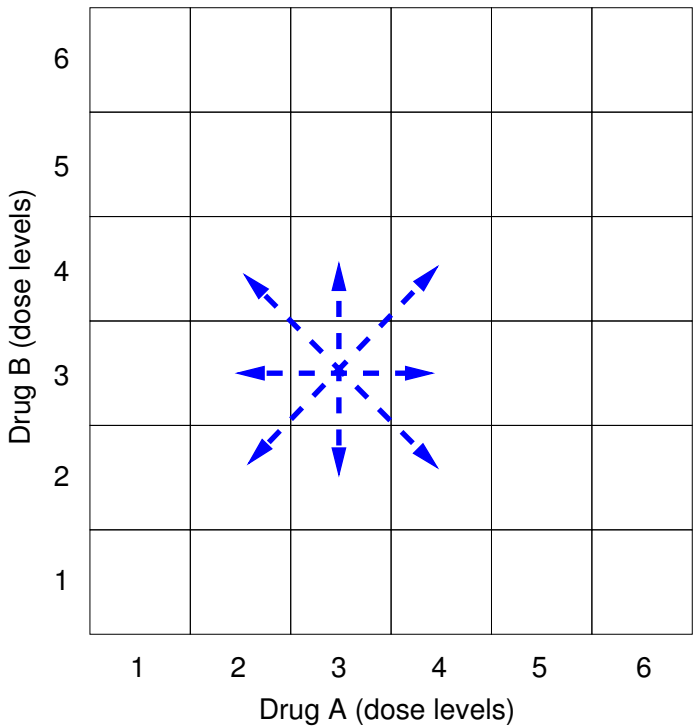
Escalation and updating

- Specify an initial dose-combination for first cohort
- Count the number of toxicities to occur
- Given a parametric dose-toxicity model, p_{ij}, with priors
  - Obtain new posterior distribution
- Choose next dose combination based on
  1. A set of admissible dose combinations
  2. A decision rule to choose between admissible doses, using the posterior distribution
- Continue recruiting patients until either
  - a fixed sample size is obtained
  - the precision of a certain quantity reaches a pre-specified level

Admissible dose combinations

- For a discrete set of dose levels, constraints are placed on escalation
  - Strategy Ω_{ndiag}: Non-diagonal escalation
  - Strategy Ω_{diag}: Diagonal escalation





Dose-escalation based on the logistic model

The combination-toxicity model by Riviere et.al (2016):

$$\text{logit} p_{jk} = \beta_0 + \beta_1 u_j + \beta_2 v_k + \beta_3 u_j v_k$$

- $\beta_0, \beta_1, \beta_2, \beta_3$ are the unknown parameters to be estimated;
- $u_j = \log \frac{p_j}{1-p_j}$, $v_k = \log \frac{q_k}{1-q_k}$;
- p_j and q_k are the standardised (skeleton for each agent);
- Requires specification of the prior distributions.

Decision-rules

- c_e be the probability threshold for dose escalation;
- c_d the probability threshold for dose de-escalation ($c_e + c_d > 1$)
- Let the current dose combination be $d_{j,k}$;

- Decision-rules:
  - If $P\left(p_{j,k} < TTL)\right) > c_e \rightarrow$ escalate to an adjacent combination with toxicity risk closest to TTL;
  - If $P\left(p_{j,k} > TTL)\right) > c_d \rightarrow$ de-escalated to an adjacent combination with toxicity risk closest to TTL.
  - If $P\left(p_{j,k} < TTL)\right) \leq c_e$ and $P\left(p_{j,k} > TTL)\right) \leq c_d \rightarrow$ stay

The recommended MTC is the combination with the highest posterior probability of the toxicity risk being close to TTL.

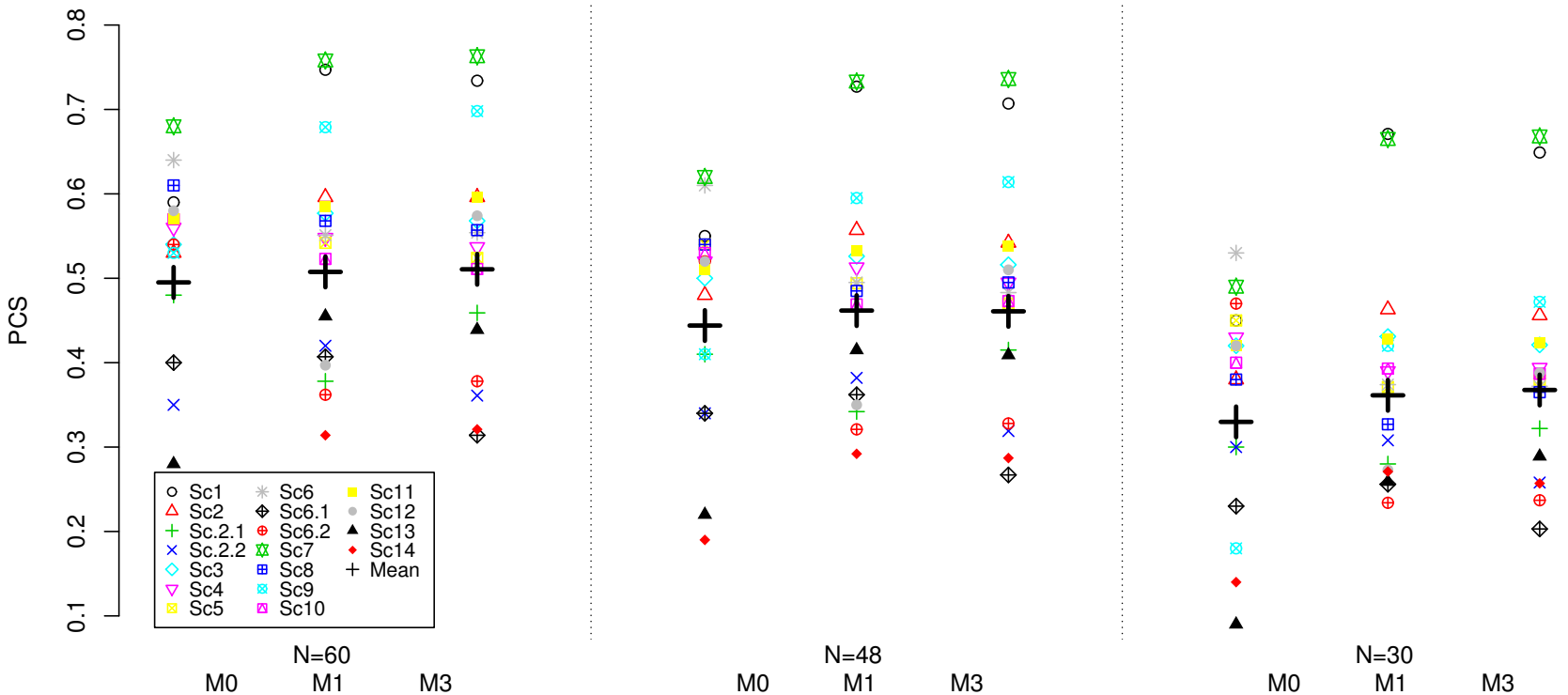
Do we need to model interaction?

While the interaction of compounds is important aspect of a combination trial, its inclusion can be controversial

- Small number of patients (especially, at early stage of the trial) makes the estimation of an extra parameter more challenging
- Even when included, the interaction parameter is close to 0 (Jimenez *et.al.*, 2018)
- Cunanan (2014) found that modelling interaction in Phase I/II does not provide any benefits
- One can still **fit the interaction model after** the working model was used to collect the data

Do we need to model interaction?

- M0 is the original logistic model (with interaction);
- M1 is the logistic model without interaction;
- M3 is M1 with joint prior on the model parameters



Two-dimensional BLRM (2BLRM): Model

- Let $odds(p_{jk}) = \frac{p_{jk}}{1-p_{jk}}$ be the odds transformation;
- Then the model assumes:

$$odds(p_{jk}) = odds(p_{jk}^{(0)}) \times \exp\left(\eta \frac{A_j}{A_*} \frac{B_k}{B_\star}\right),$$

- $p_{jk}^{(0)}$ is the joint toxicity risk under no-interaction assumption;

$$p_{jk}^{(0)} = 1 - (1 - p_j)(1 - p_k),$$

- $p(\cdot)$ is a single-dose model;

$$logit(p_j) = \alpha_{01} + \alpha_{11} \times \log(A_j/A_*),$$

$$logit(p_k) = \alpha_{02} + \alpha_{12} \times \log(B_k/B_*),$$

- η is the interaction coefficient.

2BLRM: Prior and Decision Rules

- Prior distribution

$$(\alpha_{0i}, \log(\alpha_{1i})) \sim \mathcal{N}(\mu_i, \Sigma_i)$$

  where μ_i is the vector of means and Σ_i is the covariance matrix.
- After each cohort, the set of safe combination is defined

$$\mathbb{P}\left(p_{jk} > TTL + \epsilon\right) < c_{safety}.$$

- Among them, the combination most likely to be around the TTL is chosen

$$\mathbb{P}\left(p_{jk} \in (TTL - \epsilon, TTL + \epsilon)\right).$$

- The trial continues until the maximum number of patients N is reached or the trial is stopped for the safety.

2BLRM: Comments

- The **information from single-agent studies** can be directly included in the model as the single-agent parameter have exactly the same interpretation as before;
- Interaction and no-interaction have shown similar performance in terms of accuracy/safety;
- Both the logistic model and 2BLRM can (and often do) result in **highly skewed** selection of MTCs (in scenarios with several MTCs);
- Can be extended to more agents but not dose-schedule problem (at least not without strong assumptions)
- Time consuming to evaluate (due to MCMC);

Partial Ordering Continual Reassessment Method

- R feasible orderings of the combinations;
- r – index of ordering, $r = 1, \ldots, R$;
- i – index of the combination, $i = 1, \ldots, J \times K$;
- π_{ir} – standardised combination level;
- p_{ir} – probability of a Dose Limiting Toxicity (DLT).

$$p_{ir} = \pi_{ir}^{\exp(\alpha_r)}.$$

Models π_{ir} are constructed from a skeleton $\tilde{\pi}_i$ by re-ordering it.

POCRM: Toy Example

Agents A and B; two doses of each.

$(A_1; B_2)$ [3]	$(A_2; B_2)$ [4]
$(A_1; B_1)$ [1]	$(A_2; B_1)$ [2]

Complete orderings:

1. 1, 2, 3, 4;
2. 1, 3, 2, 4.

Partial orderings:

1. 1, 2, 4;
2. 1, 3, 4.

Skeleton: $\pi = (0.10, 0.20, 0.30, 0.40)$

	Combinations			
Ordering	$(A_1; B_1)$	$(A_2; B_1)$	$(A_1; B_2)$	$(A_2; B_2)$
1	$(0.10)^{\alpha_1}$	$(0.20)^{\alpha_1}$	$(0.30)^{\alpha_1}$	$(0.40)^{\alpha_1}$
2	$(0.10)^{\alpha_2}$	$(0.30)^{\alpha_2}$	$(0.20)^{\alpha_2}$	$(0.40)^{\alpha_2}$

POCRM: Design (I)

- The first cohort is allocated to the starting combination;
- After DLT outcomes are evaluated, PO-CRM fits a (single-agent) CRM model under each of R orderings;
- Given prior distribution of orderings $\{q_0^{(1)} \ldots, q_0^{(R)}\}$, posterior probability of ordering r after n patients being the true one

$$q_n^{(r)} = \frac{q_0^{(r)} \int_{\mathbb{R}} \mathcal{L}_n^{(r)}(u) f_0(u) \mathrm{d}u}{\sum_{r=1}^{R} q_0^{(r)} \int_{\mathbb{R}} \mathcal{L}_n^{(r)}(u) f_0(u) \mathrm{d}u}.$$

  - f_0 is the prior distribution of α
  - $\mathcal{L}_n^{(r)}(u)$ is the binomial likelihood under ordering r after n patients;

POCRM: Design (II)

- Ordering with the highest posterior probability of being the true one is selected $\rightarrow r^{\star}$.
- For chosen model $r^{\star}$, let $\tilde{\alpha}^{\star}$ be the posterior mean, and the DLT probability $p^{(r^{\star})}(d_i, \tilde{\alpha}_n^{\star})$
- The next group of patients is assigned the combination closest to the TTL;
- Repeat until the maximum number of patients N has been treated;

Two-stage POCRM

- There are two versions of the (PO)CRM
  - Bayesian POCRM (what we have considered so far in this course)
  - Two-stage likelihood approach

  For the two-stage design
- **At Stage 1**, we follow predefined dose-escalation scheme until the first DLT is observed (no modelling);

  e.g. escalate agent A first, and then agent B.
- **At Stage 2**, after the first DLT is observed we fit the the POCRM with no prior used, only the likelihood.
- Does not require prior (but still requires skeleton).

How to specify orderings for the POCRM?

- The POCRM design requires the orderings to be specified **prior to the trial**;
- This should represent **plausible** complete orderings for the given setting
  regardless of how likely they are (at this stage)
- In setting with small number of possible orderings, these could be all of them

Orderings for the combination-schedule trial

Studying combinations under different schedules:

Regimen	R_1	R_2	**R_3**	**R_4**	**R_5**	R_6
Cycle 1		S_1	S_2	S_3	S_3	S_4
Cycle 2	S_1	S_2	S_2	S_3	S_4	S_4
Notation	[1]	[2]	[3]	[4]	[5]	[6]

Six toxicity orderings

- 1, 2, 3, 4, 5, 6;
- 1, 2, 3, 5, 4, 6;
- 1, 2, 4, 3, 5, 6;
- 1, 2, 4, 5, 3, 6;
- 1, 2, 5, 3, 4, 6;
- 1, 2, 5, 4, 3, 6;

How to specify orderings for the POCRM?

- In setting with large number of possible orderings:
  - In the 3×3 setting, there 42 orderings;
  - in the 4×4 setting, there are 1046 orderings.

  Instead of specifying them all,
- Ordering can be chosen from **statistical considerations** (Wages and Conway, 2014 provide recommendations), and
- Ordering can be chosen from the **clinical considerations**;

Orderings for the dual-agent 3× 3 trial.

Combination Grid:

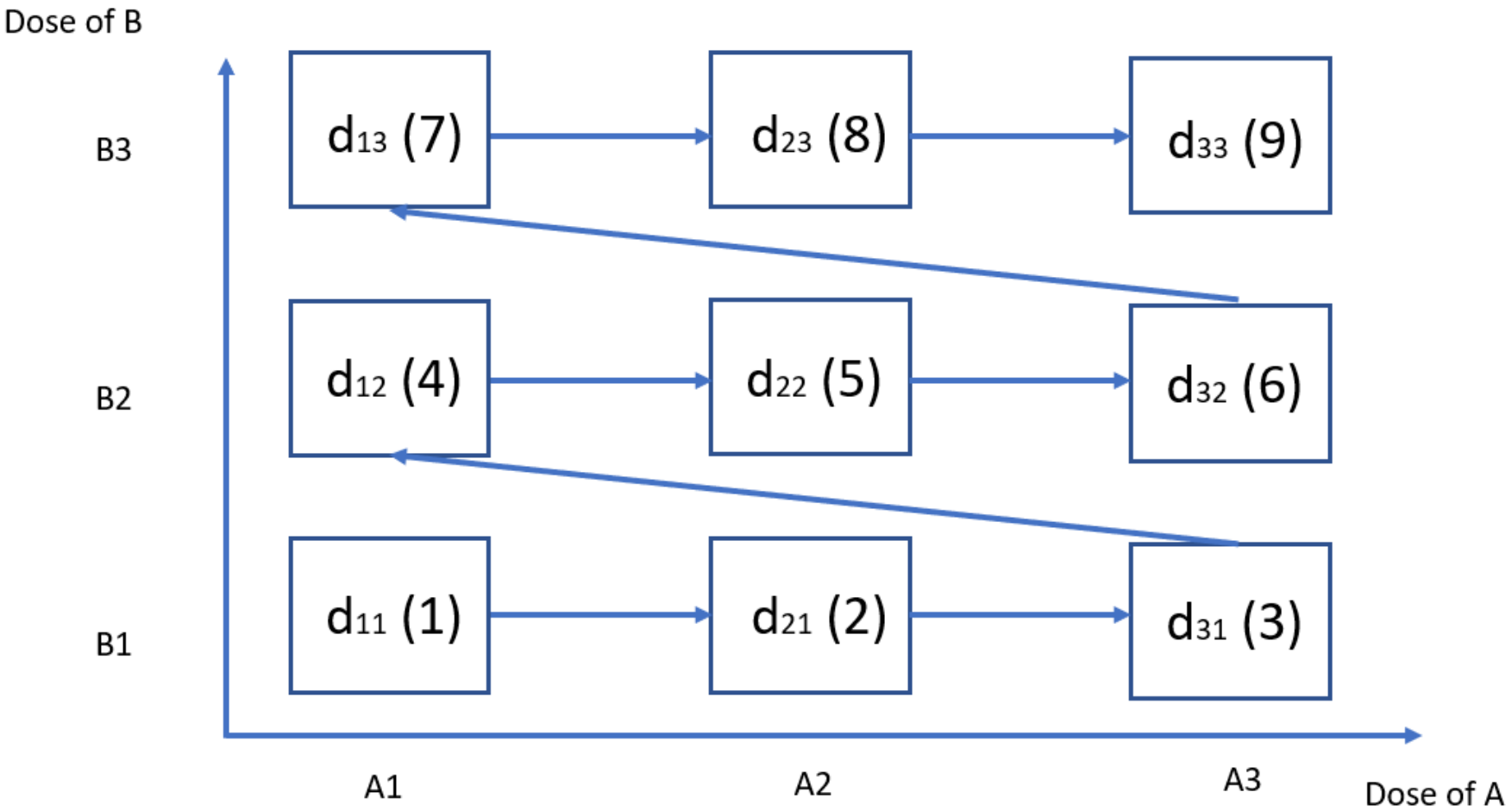
(A_1, B_3) [7]	(A_2, B_3) [8]	(A_3, B_3) [9]
(A_1, B_2) [4]	(A_2, B_2) [5]	(A_3, B_2) [6]
(A_1, B_1) [1]	(A_2, B_1) [2]	(A_3, B_1) [3]

Specified orderings:

#										Comment
	Orderings from statistical considerations (Wages & Conway, 2014)									
1	1	2	3	4	5	6	7	8	9	Toxicity is driven by B
2	1	4	7	2	5	8	3	6	9	Toxicity is driven by A
3	1	2	4	3	5	7	6	8	9	“Up diagonals”: Change in B is more toxic
4	1	4	2	7	5	3	8	6	9	“Down Diagonals”: Change in A is more toxic
5	1	2	4	7	5	3	6	8	9	“Up-Down Diagonals”: Primary driver changes
6	1	4	2	3	5	7	8	6	9	“Down-Up diagonal”: Primary driver changes
	Orderings from clinical considerations (example)									
7	1	4	7	2	3	5	6	8	9	Tox driven by A for lower dose
...										

How to illustrate orderings

Ordering 1 (Toxicity is driven by B)



How to specify probability of ordering;

The POCRM requires specification of **the prior probability for each ordering being the true one**:

- Default: all orderings are equally likely;
- If there is prior clinical knowledge suggesting that not all orderings are equally likely:
  - For small number of orderings, these could be specified directly ;
  - With more orderings, this can be challenging;
- Instead, eliciting the prior probability of the pairs of the combination standing on the anti-diagonal, e.g.

(A_1, B_3) [7]	(A_2, B_3) [8]	(A_3, B_3) [9]
(A_1, B_2) [4]	(A_2, B_2) [5]	(A_3, B_2) [6]
(A_1, B_1) [1]	(A_2, B_1) [2]	(A_3, B_1) [3]

How likely is (A_1, B_2) being more toxic than(A_2, B_1)?

How to specify probability of ordering;

- Inclusion of less likely orderings needed to protect from making overly strong assumptions on the drivers of the toxicity;
- Importantly, the probability of orderings will be updating as the data come in, so the design appreciates the uncertainty in the specified orderings;

Comments on the POCRM

- Flexible (can be used for both combination, schedule, and combination-schedule problems);
- Can use your favourite model in the modelling stage (not only one-parameter one);
- Quick to evaluate (the two-stage version even quicker);
- Robust to the choice of the prior distribution;
- Results in even selection of the MTCs (in scenarios with several MTCs)

What method should I choose?

It depends...

- It might appear that the POCRM requires more preparation (ordering, prior probabilities of ordering), but...
- The prior distributions on the BLRM-like model also implies orderings but just implicitly and should be carefully;
- Is the objective to explore combination-toxicity relationship (i.e. fit the surface)?
- Do we have data in the monotherapy?
- How many agents? Schedules?

Simulation study. Setting

- Dual-agent combination; 3 $\times$ 7 grid; Target of 30% (20%,33%)
- Preferred escalation path: escalate B first, then A;
- Comparing
  - 2BLRM;
  - BLRM by Riviere et.al
  - POCRM
- 20 scenarios (different locations of MTCs)
- Performance characteristics:
  - Proportion of optimal selections;
  - Proportion of correct selections;
  - Average proportion of DLTs;
  - Proportion of patients experimented on good combinations;

Simulation study. Results: Summary

	M	SD	M	SD
	Optimal		Good	
2BLRM	41	19	81	10
BLRM	41	19	80	6
POCRM	40	15	74	11
	DLTs		Good Exp	
2BLRM	28	5	61	13
BLRM	26	5	61	10
POCRM	27	5	58	14

Simulation study. Results: One scenario

True probability of risk of toxicity (Scenario):

	A_1	A_2	A_3	A_4	A_5	A_6	A_7
Sc 5	10	12	15	20	**30**	40	50
	12	15	20	**30**	40	50	60
	15	20	**30**	40	50	60	70

2BLRM

	A_1	A_2	A_3	A_4	A_5	A_6	A_7
B_1	0	0	1	2	**4**	2	0
B_2	0	2	23	**34**	10	1	0
B_3	0	4	**13**	5	0	0	0

BLRM

	A_1	A_2	A_3	A_4	A_5	A_6	A_7
B_1	1	0	0	0	**0**	1	0
B_2	0	2	7	**8**	2	0	0
B_3	2	21	**42**	12	1	0	0

POCRM

	A_1	A_2	A_3	A_4	A_5	A_6	A_7
B_1	0	0	1	7	**13**	5	0
B_2	0	1	7	**18**	7	1	0
B_3	1	9	**19**	9	1	0	0