Incorporating uncertainty in dose-escalation studies: Extending the Partial Ordering Continual Reassessment Method

Luka Kovacevic

Supervisors: Dr Helen Barnett, Dr Pavel Mozgunov

MRC Biostatistics Unit

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Outline

Background: AGILE Platform

- Aim: *"To shorten the time taken to identify safe, effective and affordable treatments for COVID-19."*
- Candidate Schedule Treatments with AGILE:

Schedule	Dose Level (mg)		
	Morning	Afternoon	Evening
d_0 (SoC)	0	0	0
d_1	1500	0	1500
d_2	1000	1000	1000
d_3	1500	0	2000

- We know that d_1 is less toxic d_3, hence, we have the following partial orderings:

$$1: \quad d_1 \to d_2 \to d_3$$

$$2: \quad d_1 \to d_3 \to d_2$$

$$3: \quad d_2 \to d_1 \to d_3$$

Optimal dose-finding in Phase I clinical trials

- Aim: Estimate Maximum Tolerable Dose (MTD) determined by Target Toxicity Level (TTL)
- Probability of toxicity for each dose estimated by whether a patient experiences a Dose-Limiting Toxicity (DLT)
- In what order do we escalate?
- What do we do in scenarios where there are uncertainties in orderings?
- Maximise benefit for patient, minimise risk

Partial Ordering Continual Reassessment Method

- Based on Bayesian CRM developed by O'Quigley (1990), extended by Wages et al. (2011).
- Consider the following working model,

$$\tau_i \doteq \psi_m(d_i, a) = \alpha_{mi}^{\exp(a)},$$

corresponding to the i-th dose and m-th ordering.

- α_{mi} is the skeleton probability corresponding to the i-th dose under the m-th ordering.
- a is a model parameter with prior/posterior density $f_m(a)/f_m(a|\text{data}_j)$,
- each ordering has a corresponding prior/posterior model probability $p(m)/p(m|\text{data}_j)$.

where data_j denotes the data set up to the j-th patient.

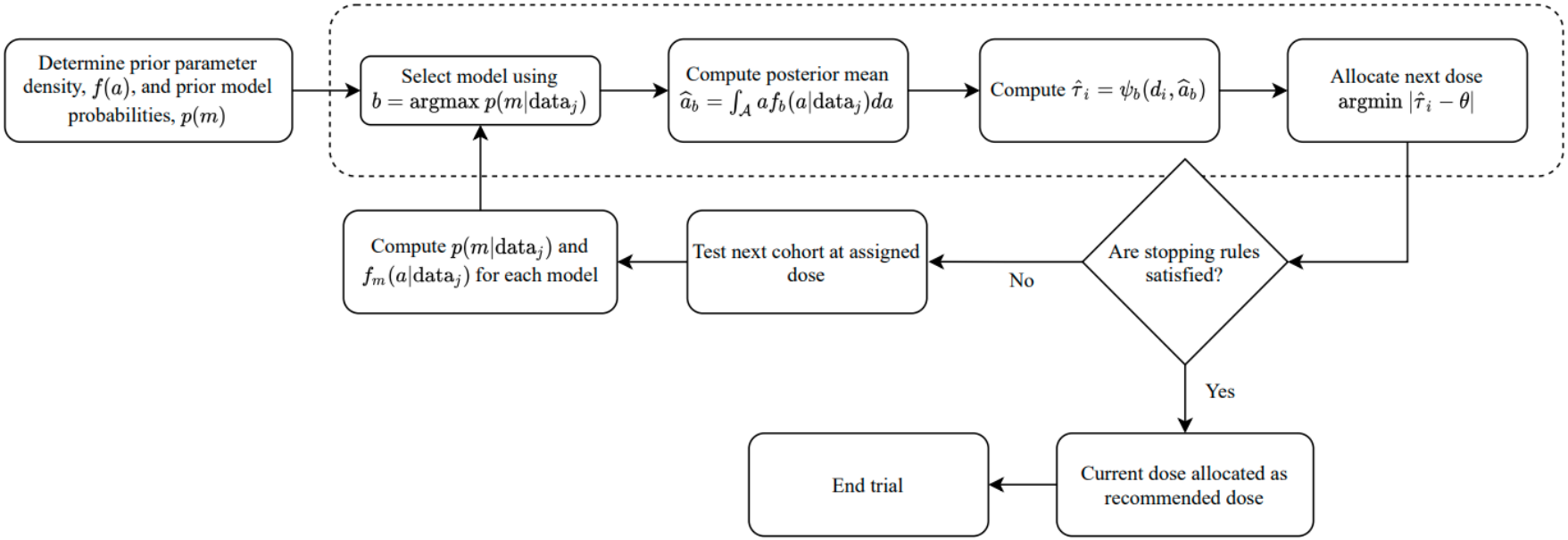
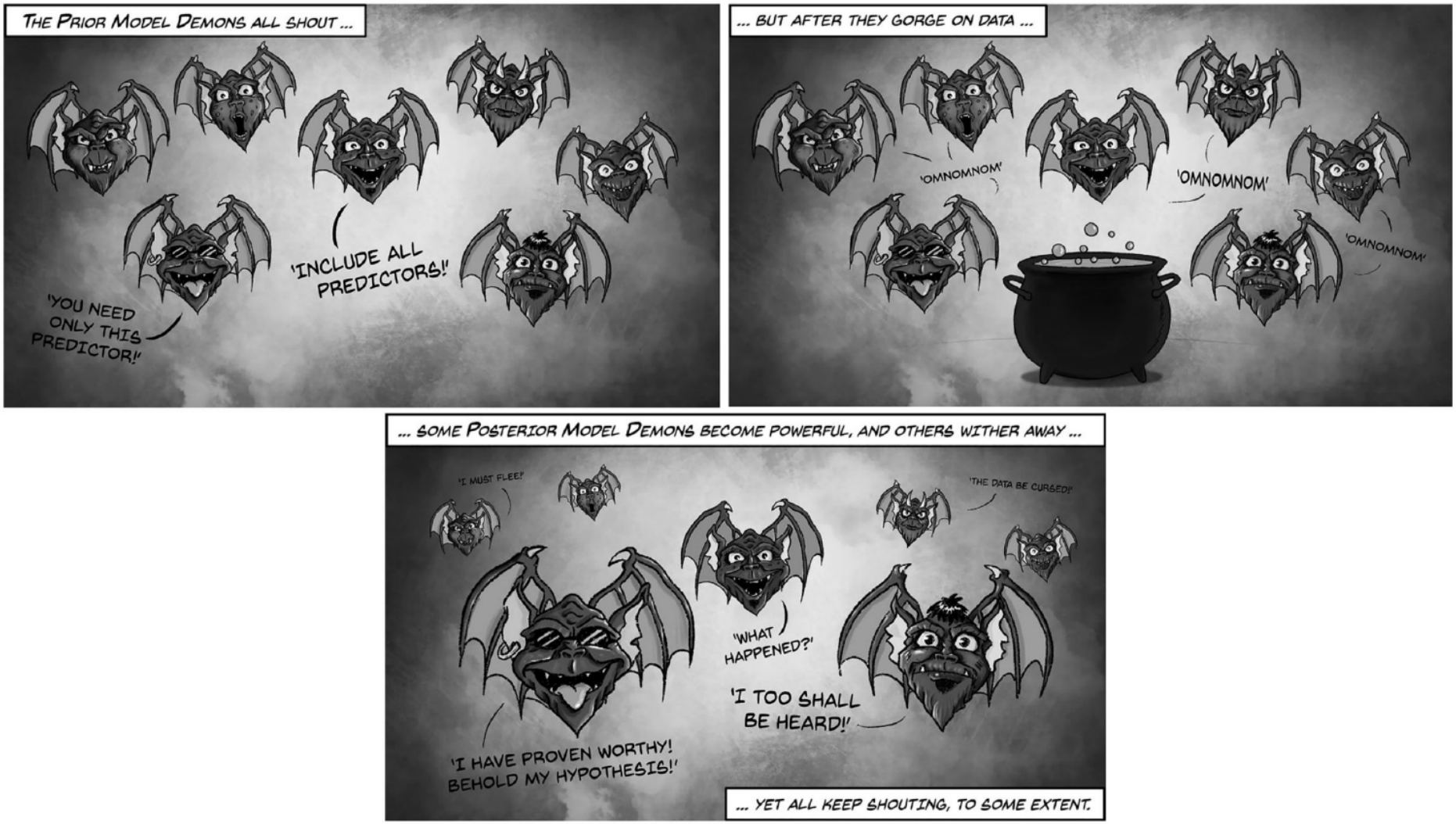


Figure: Outline of the POCRM approach with the distinct features highlighted.

Drawbacks:

- Assumes single ordering for each prediction.
- Ignores uncertainty in dose orderings $\rightarrow$ overconfident inferences.
- Example: $p(m = 1) = 0.40, p(m = 2) = 0.39$

Bayesian Model Averaging



Hinne et al. (2020)

POCRM with mixture distributions

- Since the probability of toxicity for the i-th dose, τ_i, is modelled by a function of the parameter a then $f_m(\tau_i|\text{data}_j)$ is computed.
- Finally, we can apply BMA to combine each of the densities corresponding to each ordering as shown below.

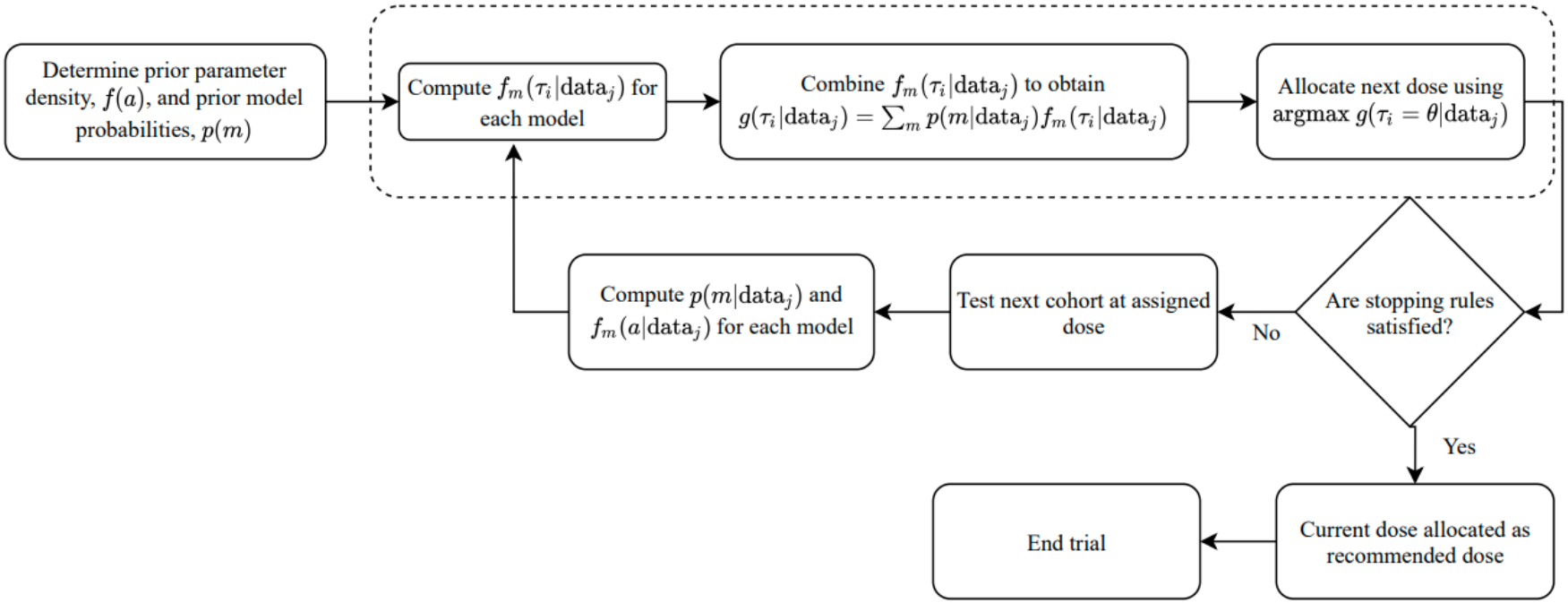


Figure: Outline of the mixture distribution method.

– Alternatively, the expected value of τ_i can be used for dose allocation.

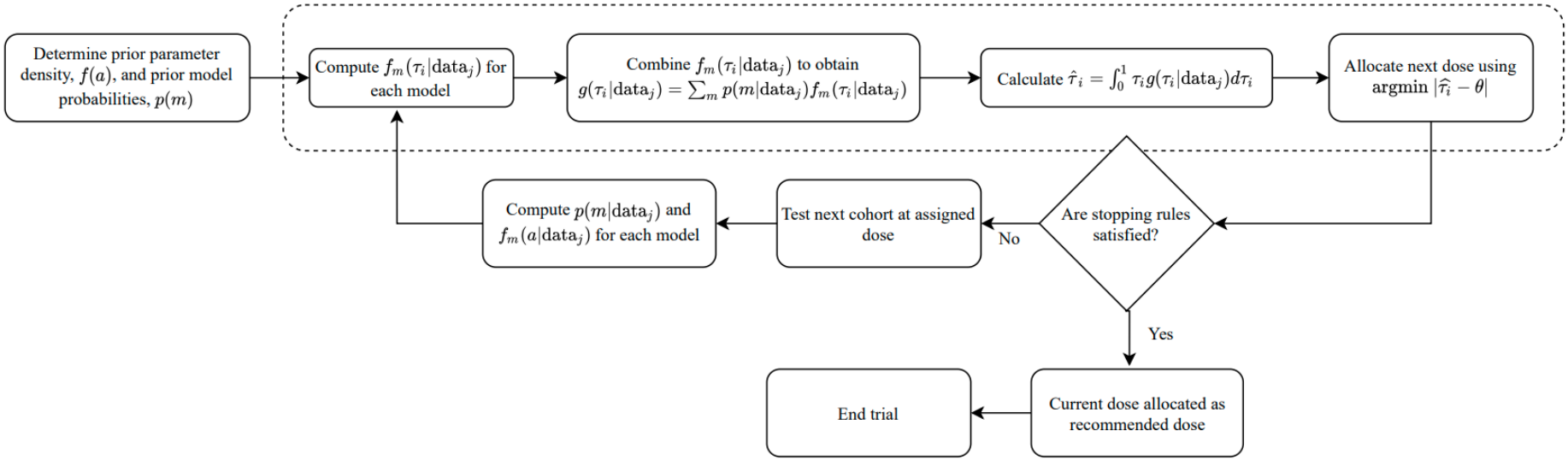
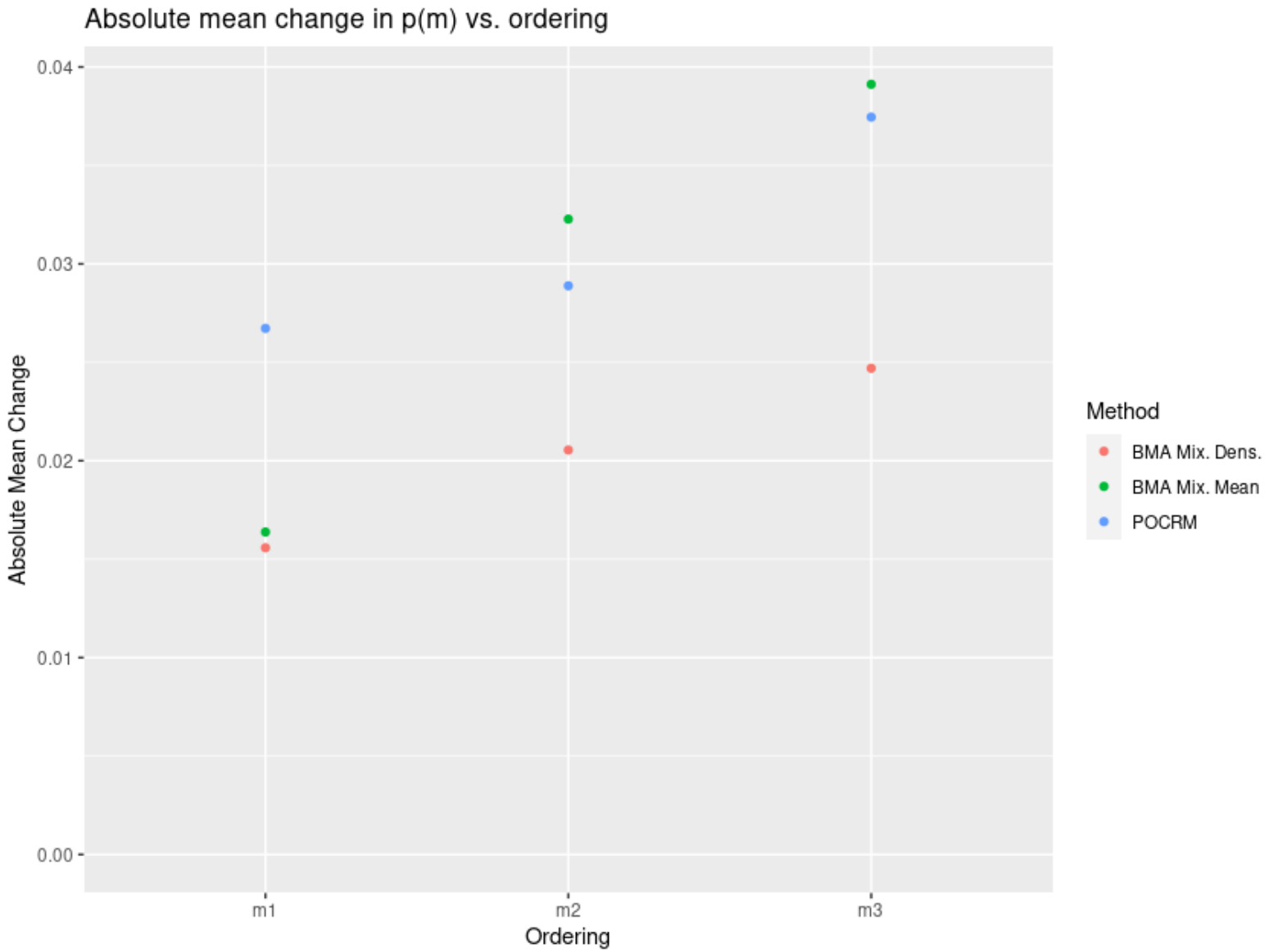


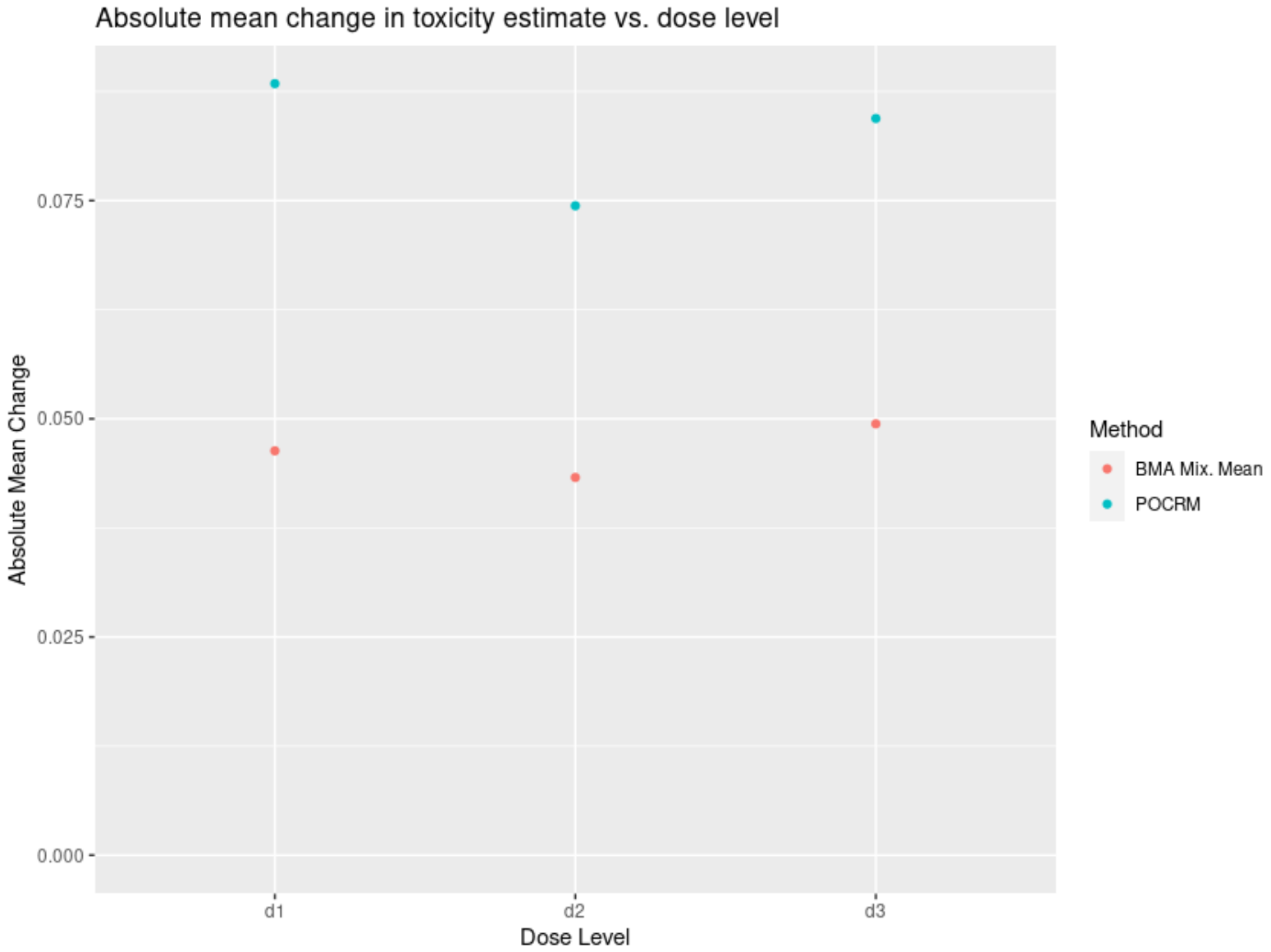
Figure: Outline of the mixture distribution method which uses the expected probabilities of toxicity to allocate dose with the distinct features highlighted.

Single Trial Simulation Study

- Scenarios based on AGILE trial partial ordering problem.
- Each scenario leads to different number of likely orderings (i.e. 1, 2 or 3 likely orderings).
- Each trial has 20 cohorts with 1 patient.
- Randomisation based on Mozgunov et al. (2020):
  - Tolerance for each patient is drawn from $\mathcal{U}(0,1)$, denoted as $u_j \in (0,1)$ for the j-th patient.
  - If true probability of toxicity for i-th dose, τ_i, satisfies $\tau_i > u_j$, a DLT is experienced by j-th patient at i-th dose.

Results


Absolute mean change in p(m) vs. ordering
Absolute Mean Change
0.04
0.03
0.02
0.01
0.00
m1
m2
m3
Ordering
Method
BMA Mix. Dens.
BMA Mix. Mean
POCRM


Absolute mean change in toxicity estimate vs. dose level
Absolute Mean Change
0.075
0.050
0.025
0.000
d1
d2
d3
Dose Level
Method
BMA Mix. Mean
POCRM

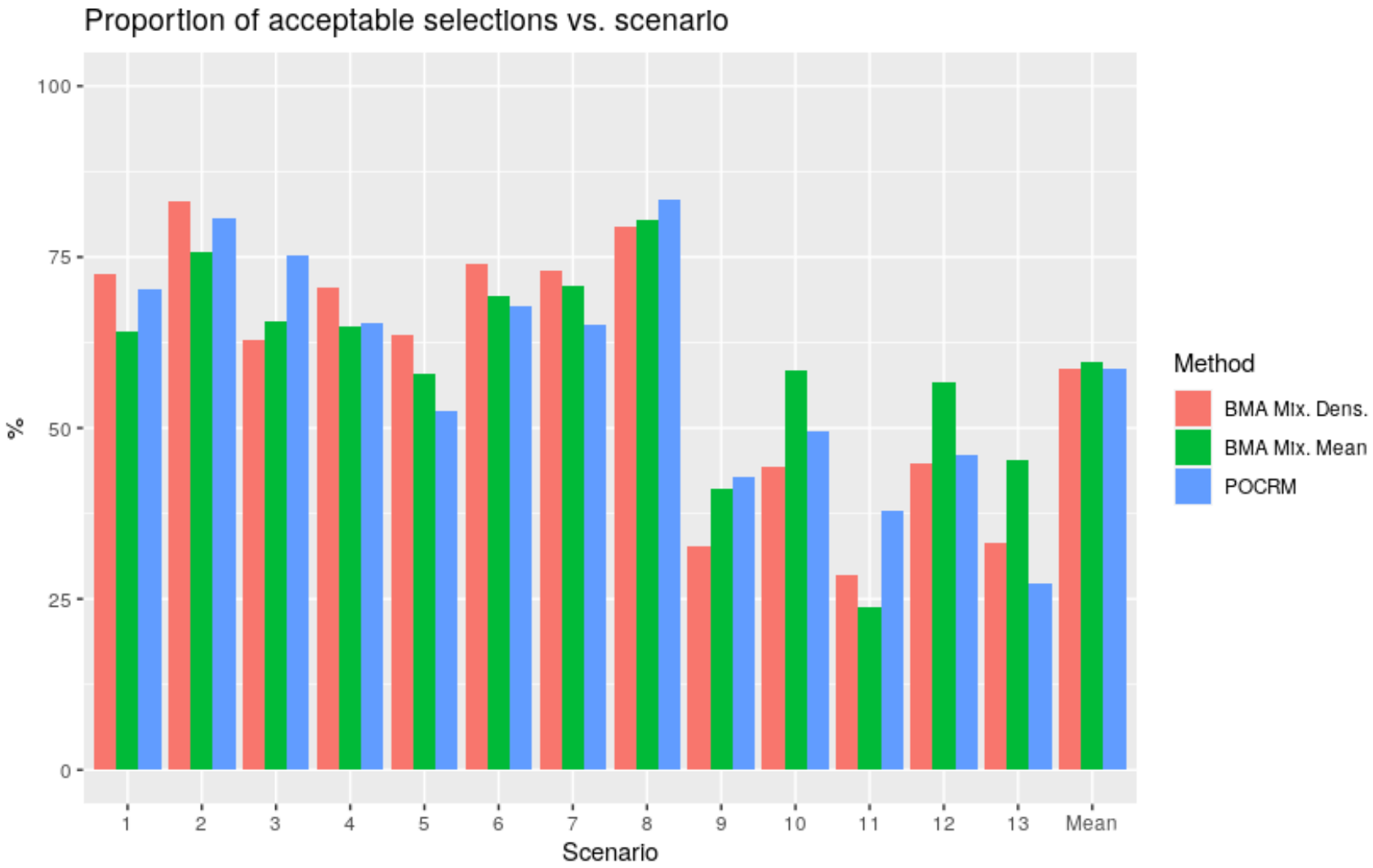
Multiple Trial Simulation Study

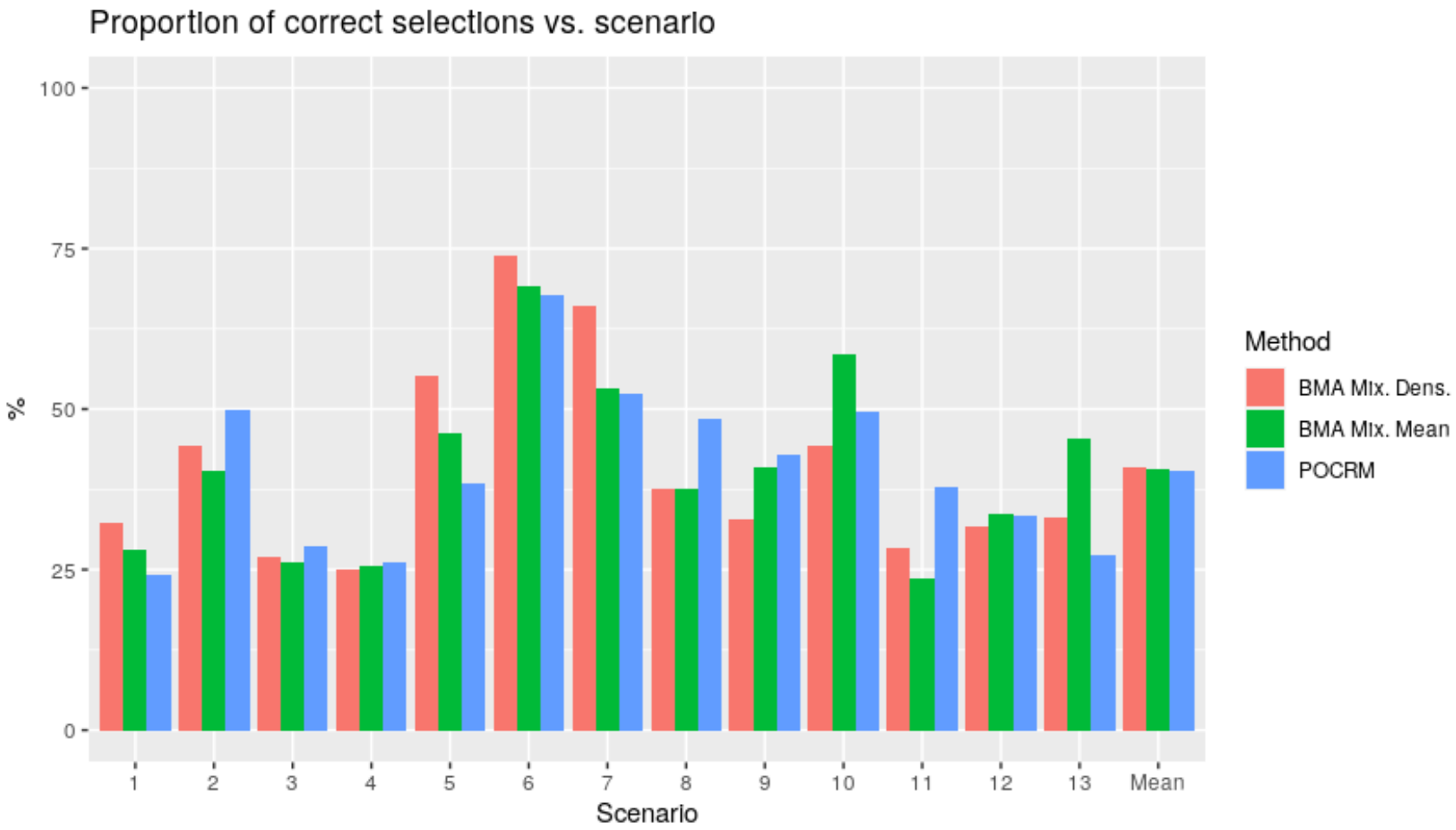
- 1000 simulation runs carried out on 13 scenarios based on Barnett et al. (2021).
- Each scenario has different location for MTD and different number of overly toxic doses.
- Dual drug trial with 9 possible drug combinations.
- 6 orderings chosen based on Wages et al. (2013).

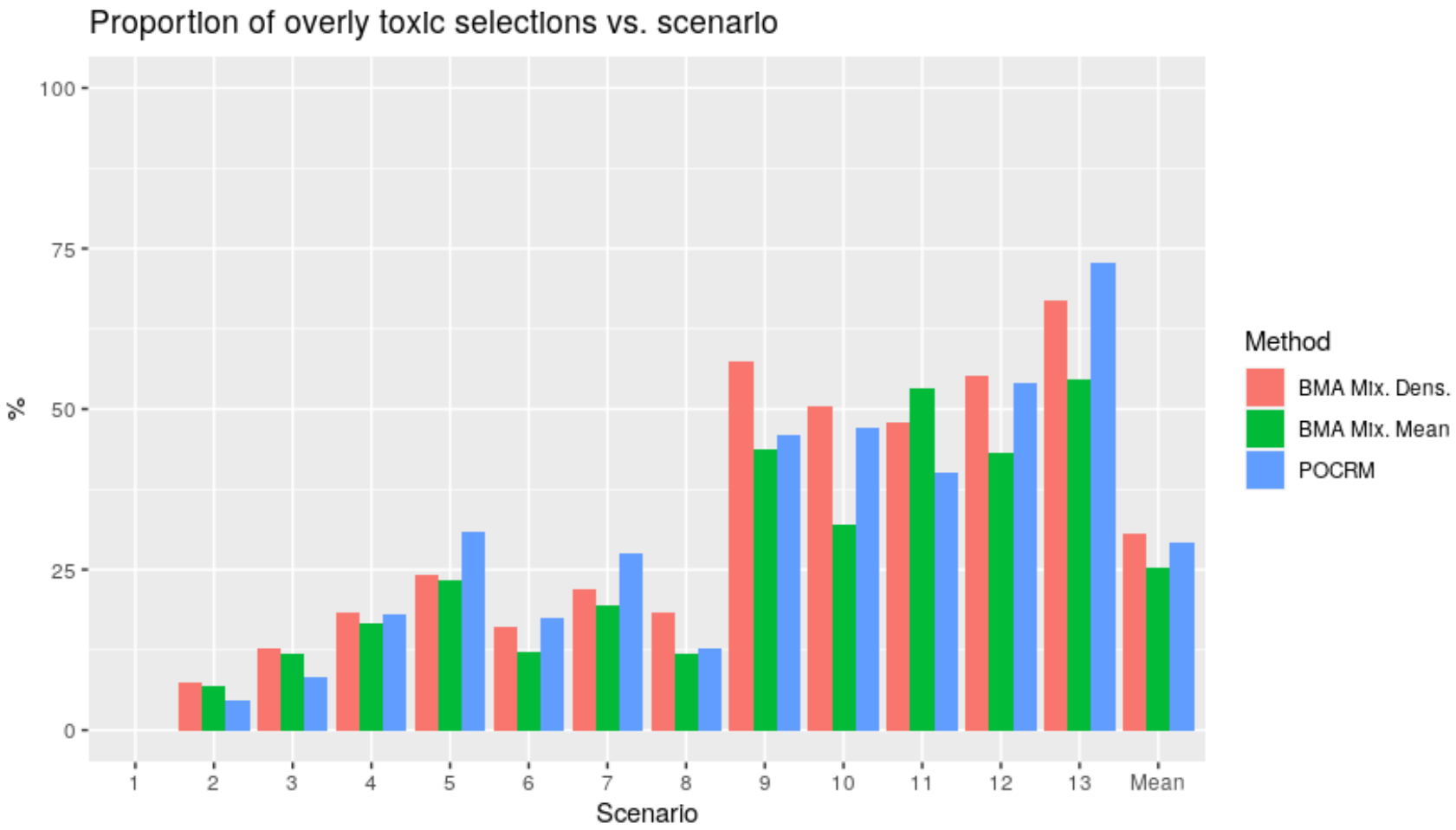
Assessment Metrics

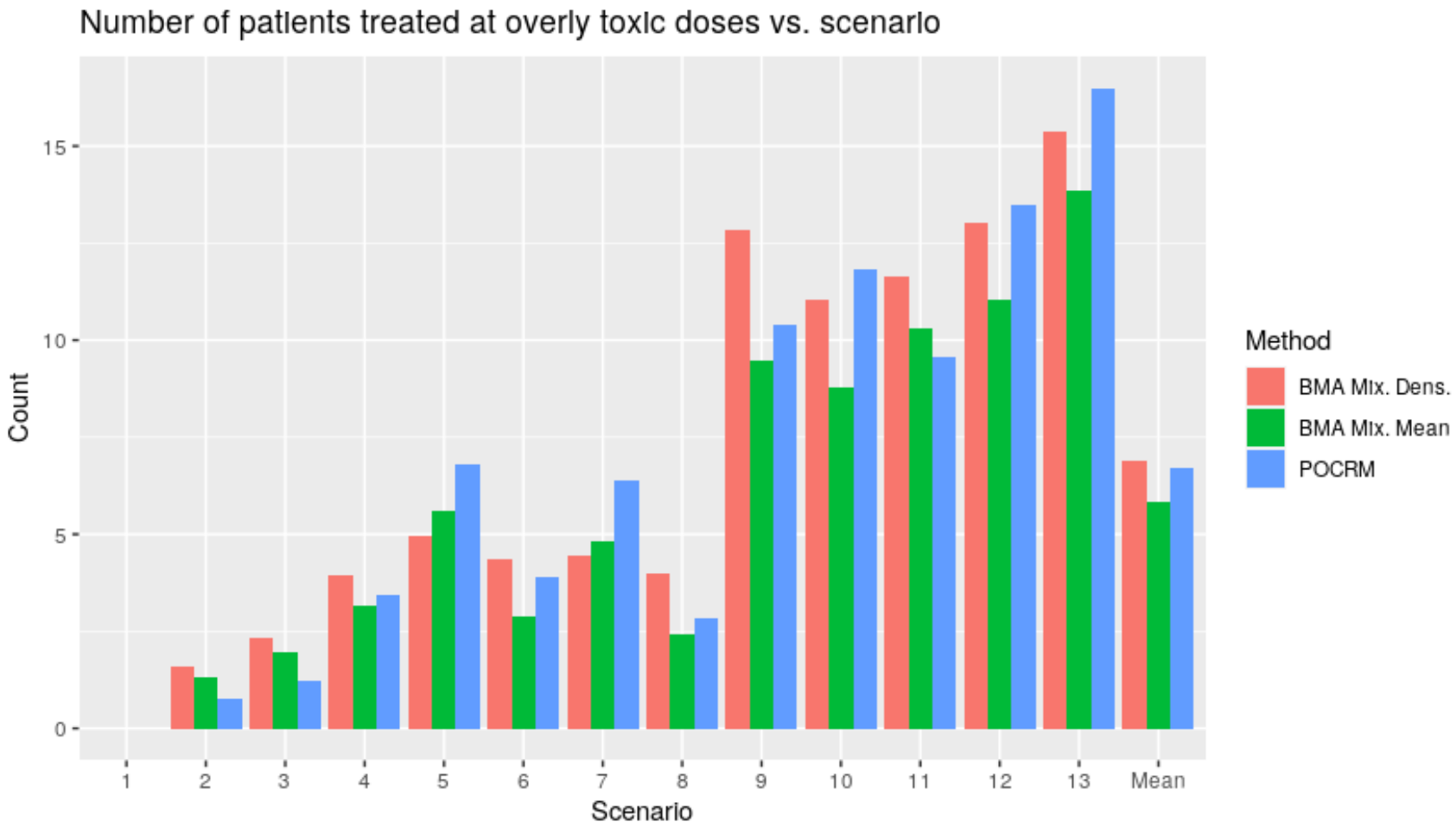
- Measures of accuracy:
  - Proportion of correct selections.
  - Proportion of acceptable selections.
- Measures of safety:
  - Proportion of overly toxic selections.
  - Number of patients treated at overly toxic doses.

Results


Proportion of acceptable selections vs. scenario
100
75
50
25
0
%
1
2
3
4
5
6
7
8
9
10
11
12
13
Mean
Scenario
Method
BMA Mix. Dens.
BMA Mix. Mean
POCRM


Proportion of correct selections vs. scenario
100
75
50
25
0
%
1
2
3
4
5
6
7
8
9
10
11
12
13
Mean
Scenario
Method
BMA Mix. Dens.
BMA Mix. Mean
POCRM


Proportion of overly toxic selections vs. scenario
100
75
50
25
0
%
1
2
3
4
5
6
7
8
9
10
11
12
13
Mean
Scenario
Method
BMA Mix. Dens.
BMA Mix. Mean
POCRM


Number of patients treated at overly toxic doses vs. scenario
Count
0
5
10
15
1
2
3
4
5
6
7
8
9
10
11
12
13
Mean
Scenario
Method
BMA Mix. Dens.
BMA Mix. Mean
POCRM

Conclusions

- Clear improvement over POCRM with current simulations.
- Similar accuracy with better safety.
- Less erratic jumps in probability of toxicity estimates.

Further work:

- Develop and run simulations tailored to problem.
- Calibration and additional simulations for stopping rules, escalation restrictions which ones work best for these implementations.
- Fully integrate with AGILE platform including randomisation for standard-of-care treatment.