Rigorous Type I error control for randomized BOP2-TE designs under minimal assumptions

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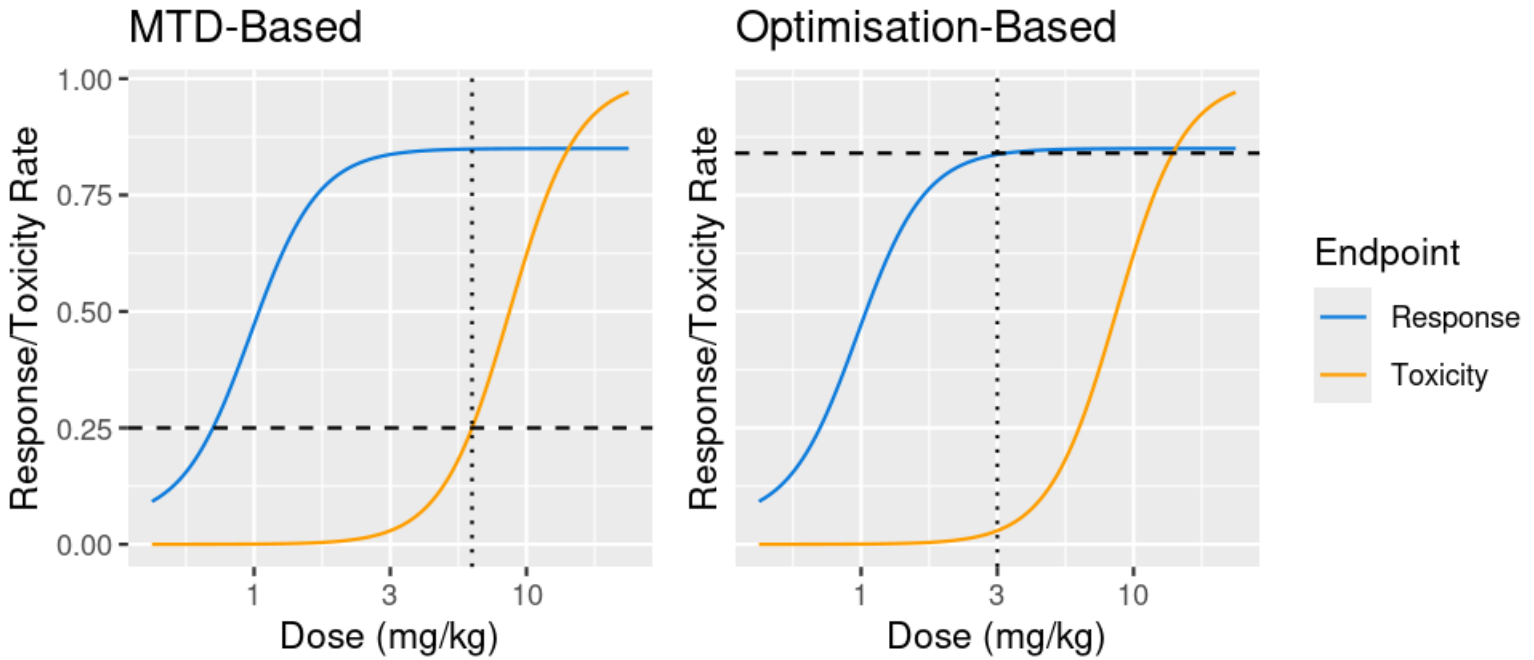
Why we need better dose optimisation designs

Development programs often enter Ph2 with uncertainty around efficacy **and** safety profiles **and** optimal dosing

- Increasing recognition of the importance of dose optimization
  - FDA Project Optimus - Move toward optimizing both safety and efficacy
  - Dose uncertainty is leading cause of failed initial FDA new drug application*
  - 45% of modified doses post-approval were in oncology†



Dose Determinations at Drug Approval Reviews: FDA-Approved Drugs in Past 5 Years - PMC 2014;311;(4):378-384. doi:10.1001/jama.2013.282542

Partial Solution: BOP2-TE design

Positives:

- Jointly evaluate efficacy and toxicity
- Arbitrary number of interim analyses
- Bayesian design, frequentist control
- Look-up table

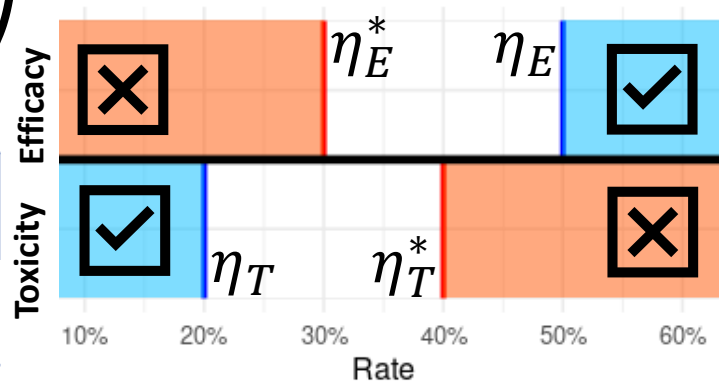
Shortcomings:

- Single arm only
- No dose optimization

How it works:

- Controls type 1 error for multiple null hypotheses
- Specify:
  - Maximum type 1 error rates for all null hypotheses
  - Target and unacceptable efficacy and tox rates
  - Sample sizes at all analyses (interims & final)
- Produces look-up table that optimises P(Claiming success $|H_{11}$) ('Power')

Eff. \ Tox.	Toxic	Safe
Futile	H_{00}	H_{01}
Effective	H_{10}	H_{11}



Analysis	# of patients	Stop if # response ≤	Stop if # toxicity ≥
IA1	10	--	4
IA2	20	6	7
FA	30	12	10

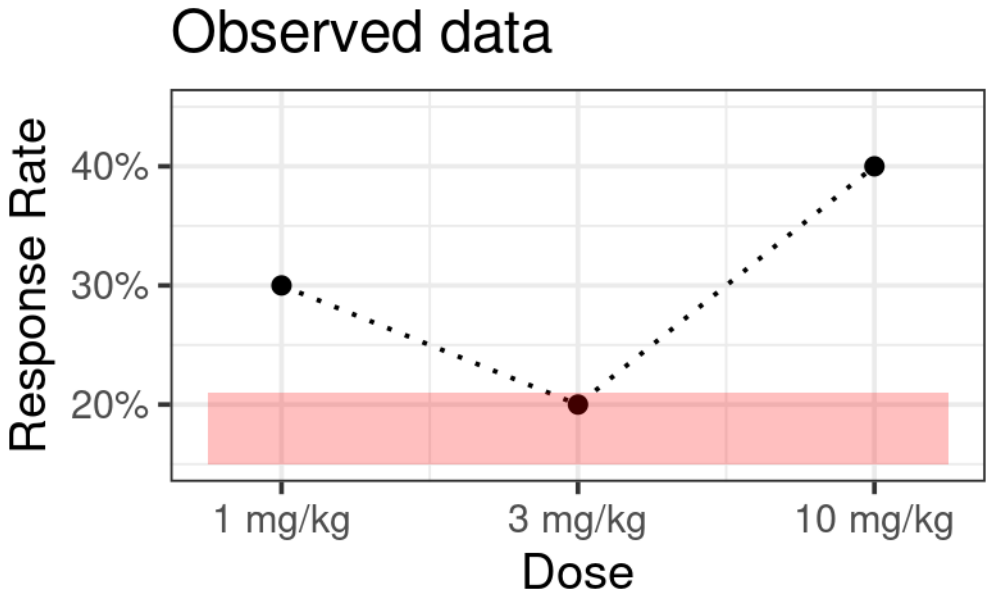
Possible Extensions of BOP2-TE with multiple doses

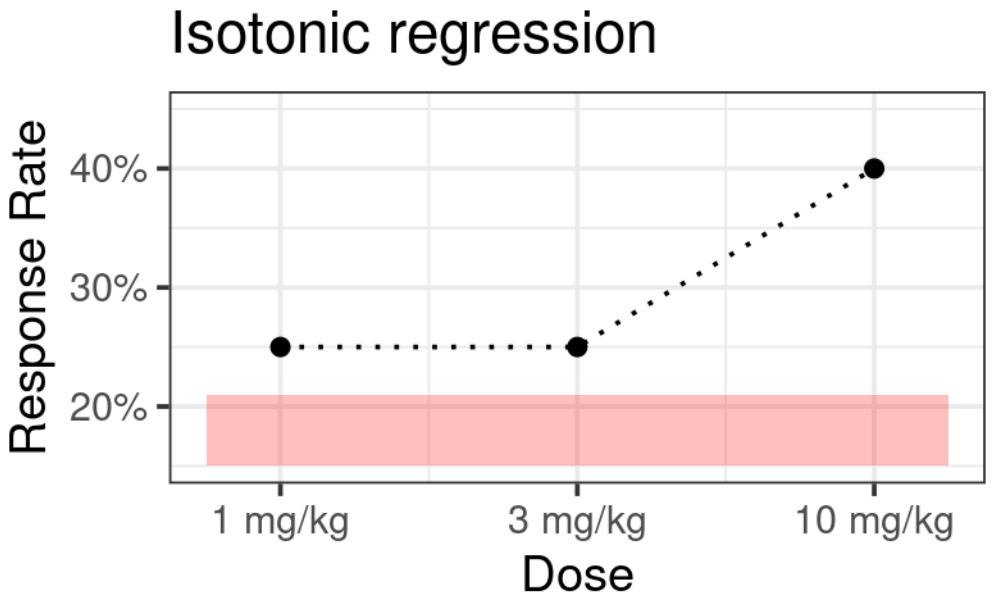
Extension 1 - independent arms

- No relationship between arms assumed, all analyses ran independently
- Any non-stopped arms are compared at end of study to recommend final dose
- **Potential for counterintuitive decisions**

Extension 2 - Isotonic regression

- Forces non-decreasing estimated toxicity & response rates (removes counterintuitive decisions)
- **Overall type I error rates no longer controlled**





How to ensure all error rates controlled?

1. **Assume** non-decreasing dose-response & dose-toxicity relationships

2. **Create** viable designs (look-up tables) fulfilling single-arm error rate constraints

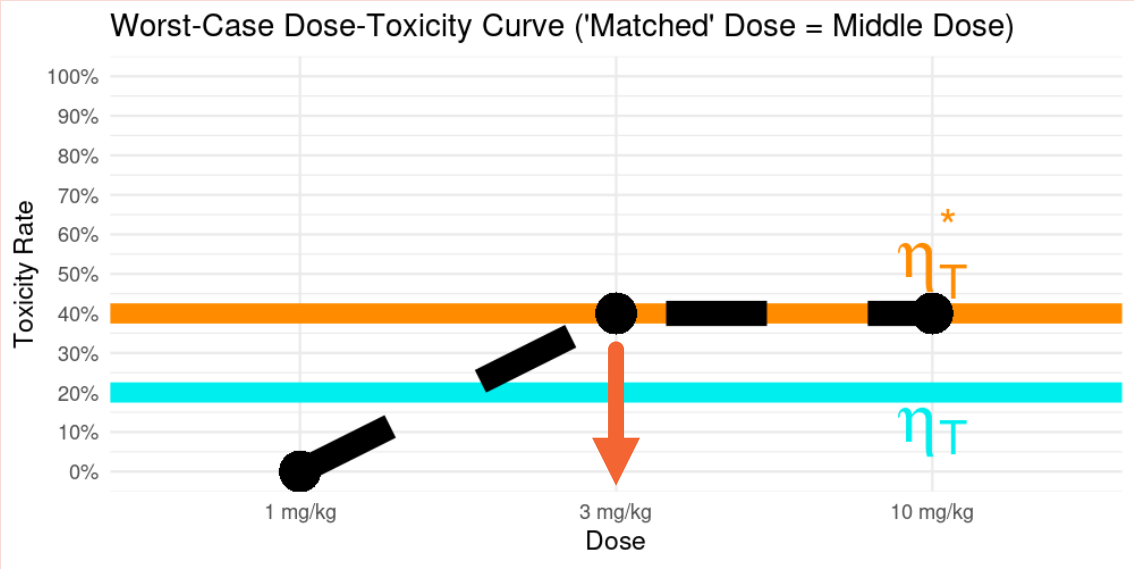
3. **Estimate** worst case type I error for all multi-arm permutations

4. **Choose** one design that maximises power from viable set

Worst-case type I error (one permutation)

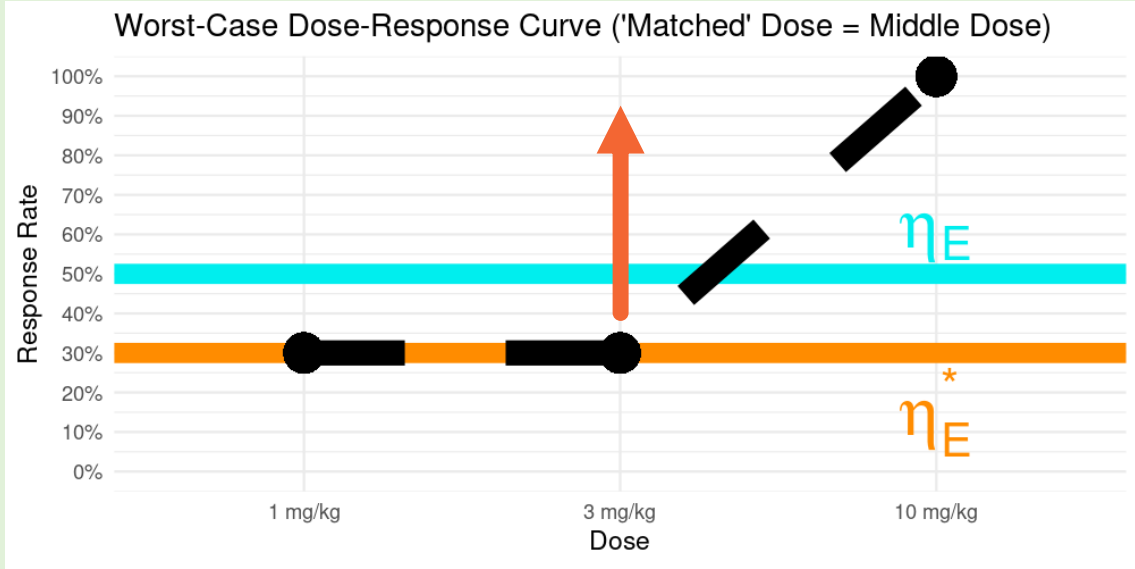
Use properties of isotonic regression to get worst-case (upper bound) type I error estimates

Toxicity



$\downarrow P(\text{Tox} \mid H_{00}) \Rightarrow \uparrow$false positive rate

Efficacy



$\uparrow P(\text{Eff} \mid H_{00}) \Rightarrow \uparrow$false positive rate

Repeat for H_{01} & H_{10} using hypothesis specific worst-cases

GSK

Which arms match the hypothesized rates? Check all permutations

- Solution: check all possible combinations
  - Reported type I error is maximum within each hypothesis
- Type I error is the probability that any matching dose is declared promising

Type	Symbol
Low	▼
Matching	●
High	▲

Analysis	# of patients	Stop if # response ≤	Stop if # toxicity ≥
IA1	10	--	4
IA2	20	6	7
FA	30	12	10

Power = 67.2%

	H_{00}	H_{01}	H_{10}
▼▼●	0.013	0.086	0.116
▼●▲	0.016	0.093	0.151
●▲▲	0.016	0.083	0.142
▼●●	0.015	0.095	0.147
●●▲	0.016	0.092	0.150
●●●	0.016	0.096	0.153

Which arms match the hypothesized rates? Check all permutations

- Solution: check all possible combinations
  - Reported type I error is maximum within each hypothesis
- Type I error is the probability that any matching dose is declared promising

Type	Symbol
Low	▼
Matching	●
High	▲

Analysis	# of patients	Stop if # response ≤	Stop if # toxicity ≥
IA1	10	--	4
IA2	20	6	7
FA	30	12	~~10~~ **9**

Power = ~~67.2~~ 64.4%

	H_{00}	H_{01}	H_{10}
▼▼●	0.008	0.083	0.073
▼●▲	0.009	0.091	0.092
●▲▲	0.009	0.082	0.080
▼●●	0.009	0.091	0.085
●●▲	0.010	0.091	0.085
●●●	0.009	0.092	0.081

Summary

BOP2-TE RCT extension gives…

Flexibility: Strict error rate control for efficacy & safety hypotheses in Ph2 with arbitrary number of doses & interim analyses for toxicity or futility stopping

Practicality: An easy-to-use look-up table for all decision-making

Reassurance & rigour: A Bayesian design with frequentist control measures (type I error & power)

	Single-arm BOP2-TE	BOP2-TE RCT (indep. arms)	BOP2-TE RCT (isotonic reg.)	BOP2-TE RCT (isotonic reg. w/ error rate control)
Decisions made via look-up table				
Efficacy & safety monitoring				
Dose-optimisation				
Guaranteed ‘sensible’ decisions				
Error-rate control				