

A novel method for inserting dose levels mid-trial in early phase combination studies in oncology

Tuesday 16th June 2026

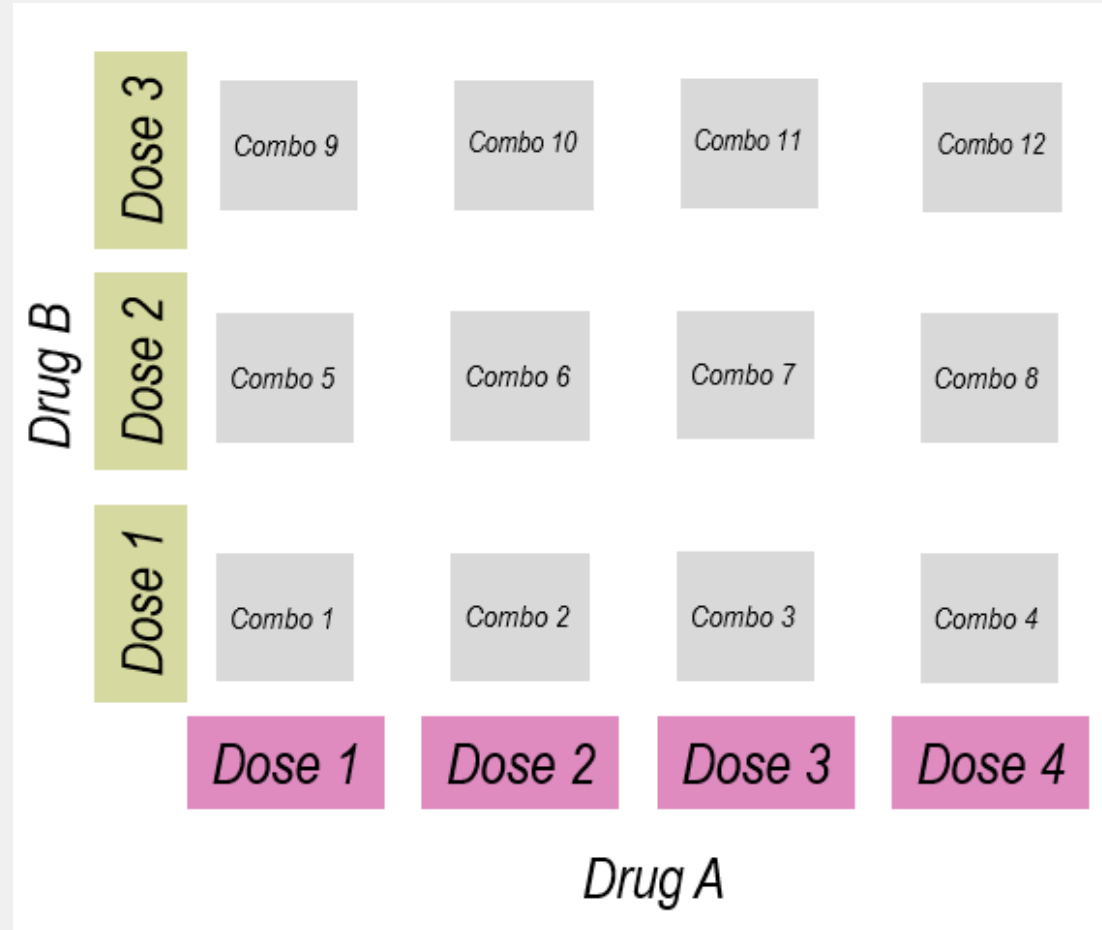
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The situation

Dose levels of each treatment are pre-specified

Aim: find target combination
(where 30% of patients have a toxic event)



What is a potential problem?

- **Potential problem:** What happens if we design a trial in which **none of the pre-specified combinations are close to the target toxicity?**
 1. Select a sub-optimal combination for phase II
 2. Perform ad hoc insertions
- Literature gap exists

Is there an efficient way of inserting doses mid-trial?

Our insertion method



Can be applied to any existing dose-finding design

- Key idea: Estimate the **maximum tolerated contour**
 - Defined as the line partitioning the grid into combinations **above** and **below** the target toxicity (30%)
 - If we estimate this with a degree of certainty, it implies there are no combinations close to the target toxicity (30%)

		Drug B		
		1 mg	2 mg	3 mg
Drug A	10 mg			
	20 mg			
	30 mg			

Our insertion method

- Key idea: Estimate the **maximum tolerated contour**
 - Defined as the line partitioning the grid into combinations **above** and **below** the target toxicity (30%)

		Drug B		
		1 mg	2 mg	3 mg
Drug A	10 mg	0/3	0/6	2/3
	20 mg	3/6	2/3	
	30 mg			

Contour #1: Unlikely to be the maximum tolerated contour

Our insertion method

- Key idea: Estimate the **maximum tolerated contour**
 - Defined as the line partitioning the grid into combinations **above** and **below** the target toxicity (30%)

		Drug B		
		1 mg	2 mg	3 mg
Drug A	10 mg	0/3	0/6	2/3
	20 mg	3/6	2/3	
	30 mg			

Contour #2: Highly likely to be the maximum tolerated contour

If our confidence exceeds the MTC threshold, then insert

Our insertion method

- Key idea: Estimate the **maximum tolerated contour**
 - Defined as the line partitioning the grid into combinations **above** and **below** the target toxicity (30%), **with insertions directly linked to the maximum tolerated contour**

New dose

		Drug B			
		1 mg	2 mg	2.5 mg	3 mg
Drug A	10 mg	0/3	0/6		2/3
	15 mg				
	20 mg	3/6	2/3		
	30 mg				

Is the method any good?

MTC = maximum tolerated contour

- Need to run a **simulation study**
- Goal is to test behaviour of insertion method in different scenarios

Scenario A		Drug B		
		1 mg	2 mg	3 mg
Drug A	10 mg	5%	10%	45%
	20 mg	10%	45%	50%
	30 mg	45%	50%	60%

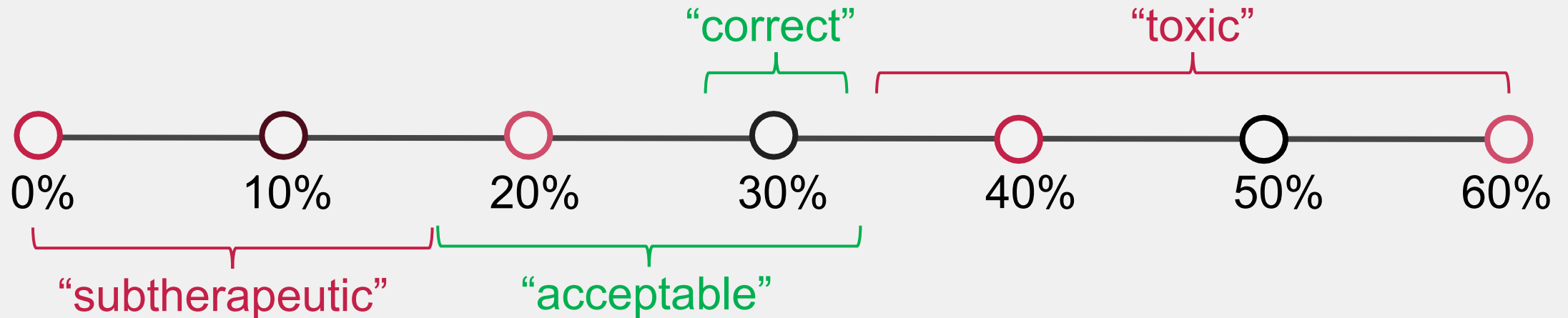
Scenario B		Drug B		
		1 mg	2 mg	3 mg
Drug A	10 mg	5%	5%	10%
	20 mg	5%	10%	30%
	30 mg	10%	30%	45%

- Run 1000 trials in each scenario, at each MTC threshold
 - MTC threshold reflects the confidence needed before making an insertion and takes values in $\{0.5, 0.6, 0.7, 0.8, 0.9, 1\}$
 - Higher MTC threshold means **stricter** insertion rule (1 = no insertions)

Simulation study

For each trial

- sample size = 48 (cohort size = 3)
- target toxicity = 30%
- underlying dose escalation design is PIPE (although can apply to any)
- aim is select one combination for phase II

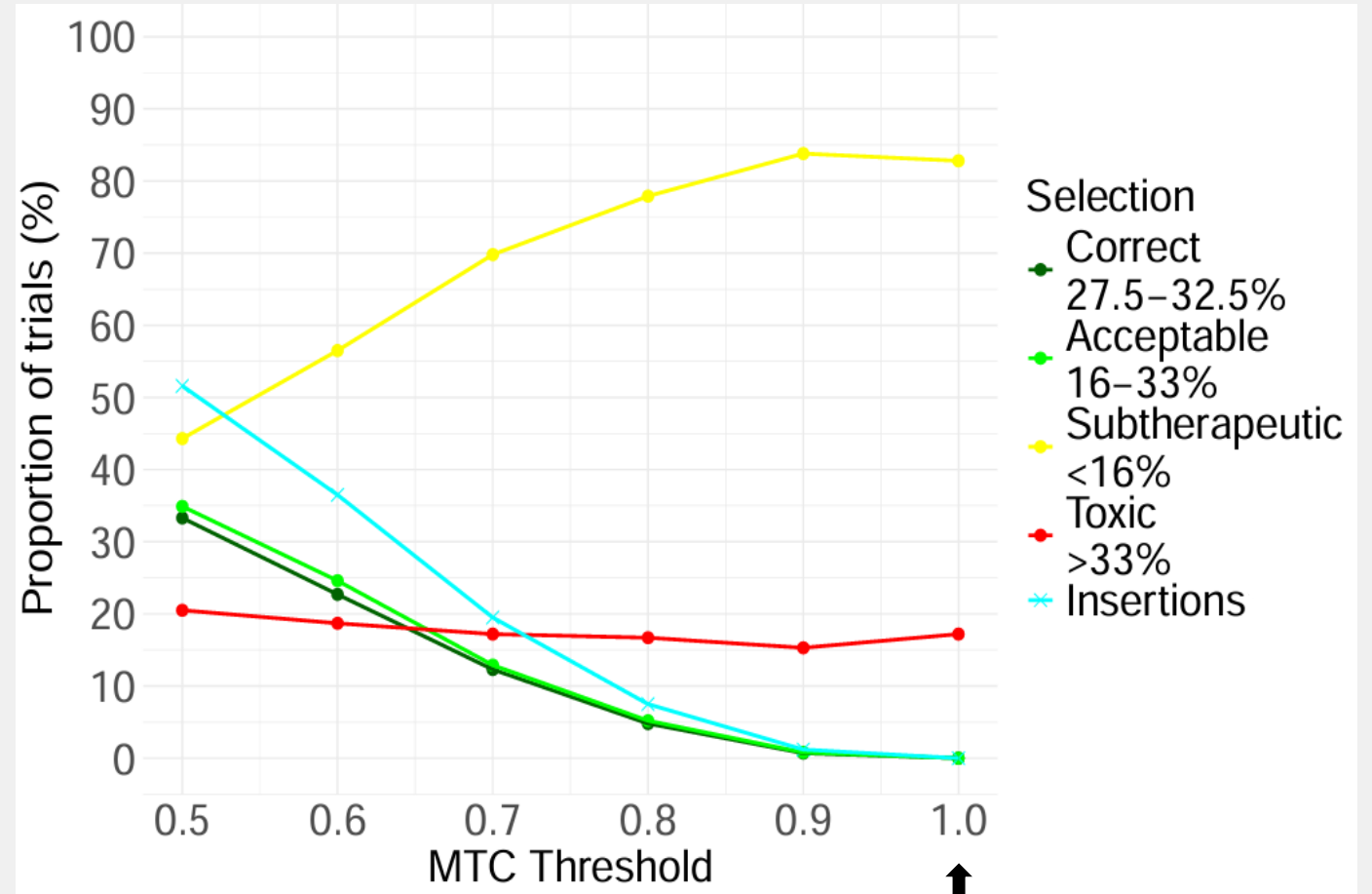


Results: Scenario A

		Drug B		
		1 mg	2 mg	3 mg
Drug A	10 mg	5%	10%	45%
	20 mg	10%	45%	50%
	30 mg	45%	50%	60%

- **Clear merit in inserting dose levels**
- No. of trials with insertions increases
- Proportion of correct selections **increases from 0 to 33%**
- Toxic selections unaffected

MTC = maximum tolerated contour



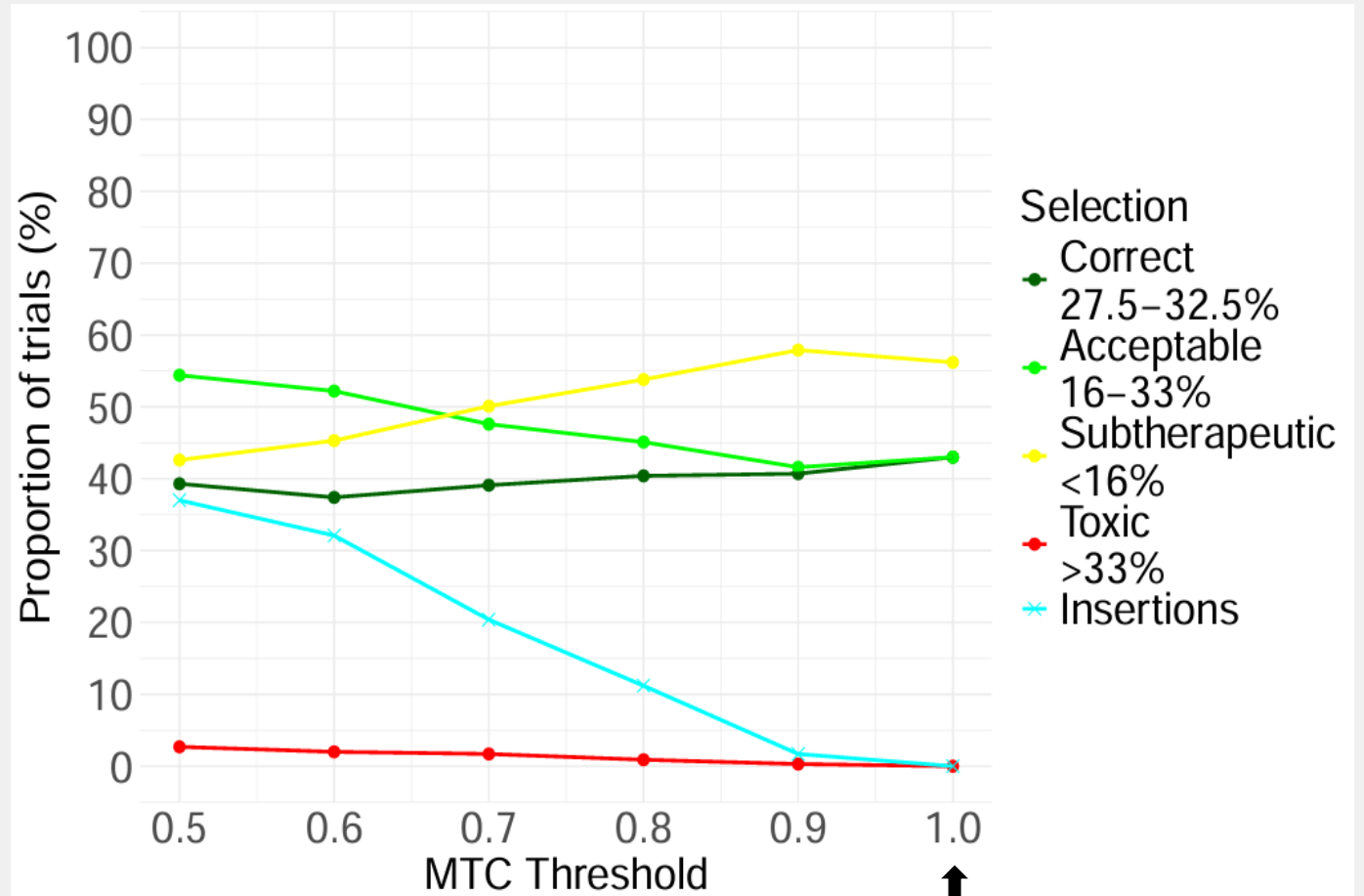
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Insertions turned off

Results: Scenario B

		Drug B		
		1 mg	2 mg	3 mg
Drug A	10 mg	5%	5%	10%
	20 mg	5%	10%	30%
	30 mg	10%	30%	45%

- **Less need to insert dose levels**
- No. of trials with insertions increases
- Correct selections from **43 to 39%**
- Acceptable selections from **43 to 54%**
- Toxic selections unaffected

MTC = maximum tolerated contour



↑
Insertions turned off

Summary

- There is a **risk** of starting an early phase trial with no combinations close to the target toxicity
- Motivates our method for **inserting dose levels** mid-trial
- We can **improve the chance of selecting combinations close to the target toxicity** without compromising on other measures

Thank You

References

[1] George, M., Wadsworth, I. and Mozgunov, P., 2026. A Novel Method for Inserting Dose Levels Mid-Trial in Early-Phase Oncology Combination Studies. *Statistics in Medicine*, 45(3-5), p.e70417.

[2] Mander, A.P. and Sweeting, M.J., 2015. A product of independent beta probabilities dose escalation design for dual-agent phase I trials. *Statistics in medicine*, 34(8), pp.1261-1276.

How to estimate the maximum tolerated contour

- Let π_{ij} be the probability a patient has a toxic event on combination i, j
- Model each π_{ij} independently – gives posteriors as follows
 $\pi_{11} \sim \text{Beta}()$, $\pi_{12} \sim \text{Beta}()$, $\pi_{21} \sim \text{Beta}()$, $\pi_{22} \sim \text{Beta}()$
- For the contour 1 below
 $P(\pi_{11} \leq 0.30) \times P(\pi_{12} \leq 0.30) \times P(\pi_{21} \leq 0.30) \times (1 - P(\pi_{22} \leq 0.30))$
- Gives us probability that contour 1 is the maximum tolerated contour

If data suggests this is far below 30% toxicity, this quantity will be higher

		Drug B	
		1 mg	2 mg
Drug A	10 mg	π_{11}	π_{12}
	20 mg	π_{21}	π_{22}

Contour #1

How to estimate the maximum tolerated contour

- Let π_{ij} be the probability a patient has a toxic event on combination i,j
- Model each π_{ij} independently – gives posteriors as follows
 $\pi_{11} \sim \text{Beta}()$, $\pi_{12} \sim \text{Beta}()$, $\pi_{21} \sim \text{Beta}()$, $\pi_{22} \sim \text{Beta}()$
- For the **contour 2** below
 $P(\pi_{11} \leq 0.30) \times (1 - P(\pi_{12} \leq 0.30)) \times P(\pi_{21} \leq 0.30) \times (1 - P(\pi_{22} \leq 0.30))$
- Gives us probability that **contour 2** is the maximum tolerated contour

If data suggests this is far below 30% toxicity, this quantity will be higher

		Drug B	
		1 mg	2 mg
Drug A	10 mg	π_{11}	π_{12}
	20 mg	π_{21}	π_{22}

Contour #2