A multi-arm multi-stage design for trials with no control arm and all pairwise testing

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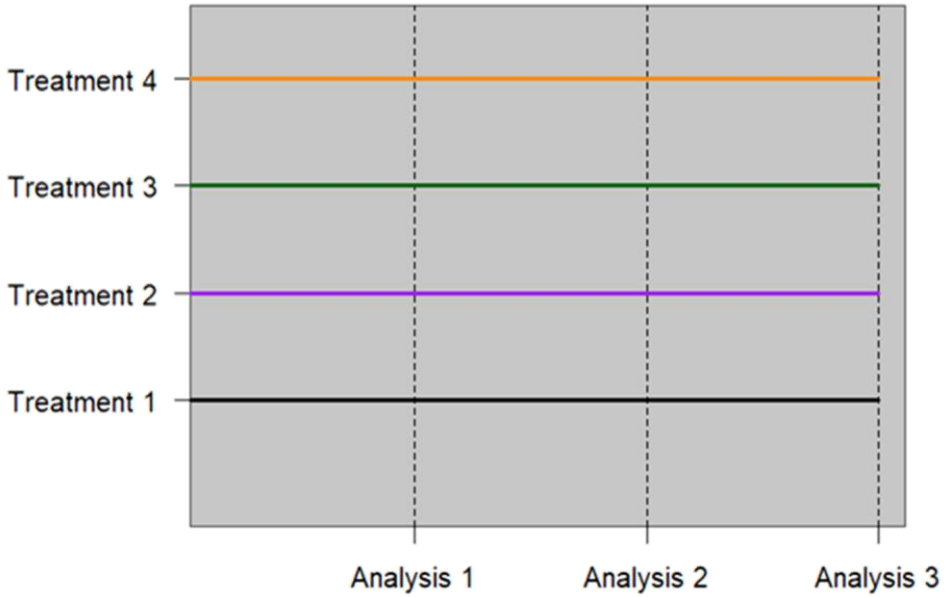
Why multi-arm multi-stage all pairwise (MAMSAP) trials

We are motivated by a trial studying treatments for sepsis. In this setting no treatment exists for this severe disease due to a lack of resources. The motivating example is a 4 arm 3 stage trial.

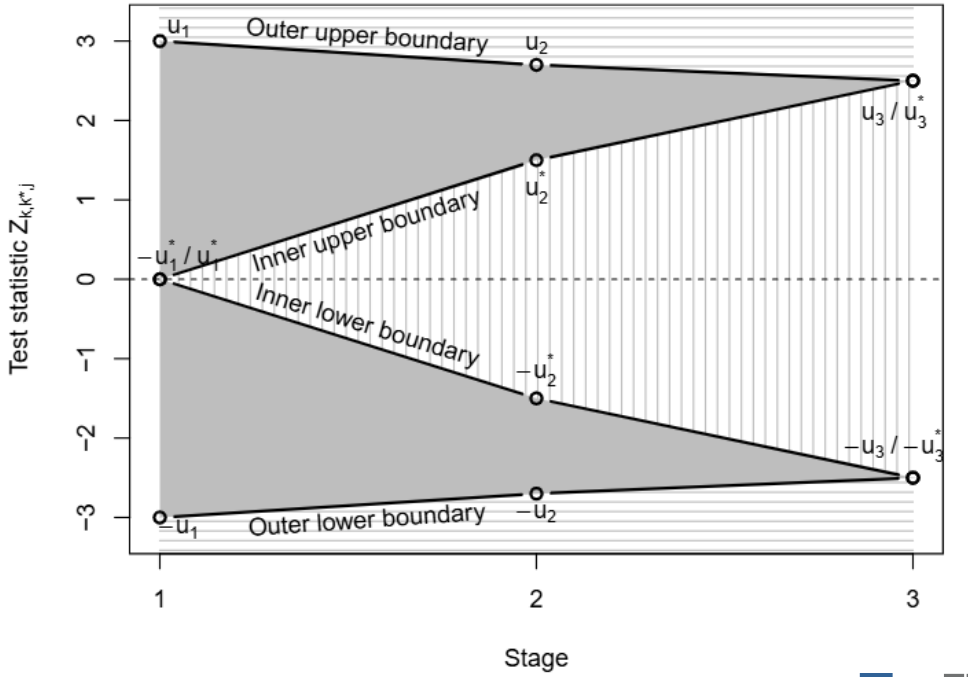
Other scenarios:

- When multiple treatments are already established as the standard of care for a condition.
- No treatment currently exists for a severe emerging infectious disease.
- The current standard of care has a small effect and has tolerability issues.

MAMSAP Design



Boundaries



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Finding boundaries and sample size

- The boundaries are found to ensure control of the type I error across the entire trial at level α, specifically we control the familywise error rate (FWER).
- The sample size is found to ensure the power under the least favourable configuration (LFC) of finding the clinically relevant treatment is greater than 1-β.

Results

Design	FWER	Power	$Max(N)$ $E(N\|\text{Null})$
MAMSAP	5.0%	90.0%	972 749.9
Whitehead approach	21.3%	81.1%	600 488.8
Bonferroni adjusted Whitehead approach	4.5%	92.9%	1068 820.1
Separate Trials	26.5%	73.6%	1800 1284.5
FWER controlled separate trials	5.0%	90.5%	3204 2223.8

Conclusion

- For the trial studied, the MAMSAP design yields the lowest required maximum and expected sample size whilst controlling the FWER and power.

References:

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