An order restricted multi-arm multi-stage clinical trial design

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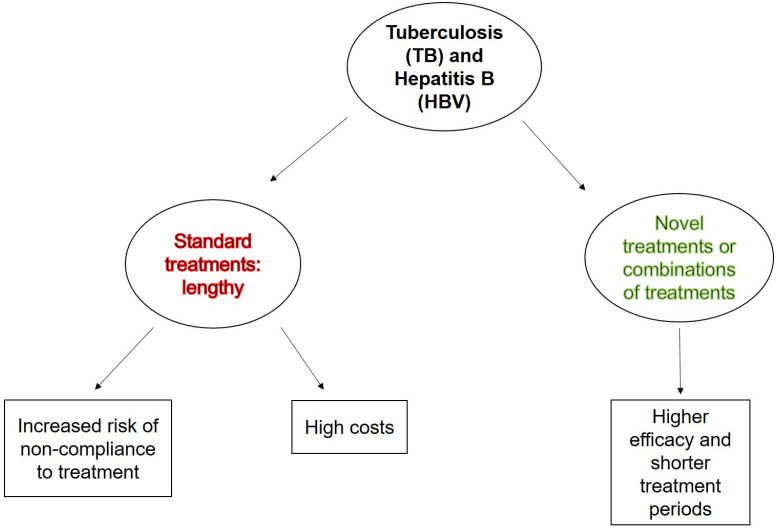
Background


Tuberculosis (TB) and Hepatitis B (HBV)
Standard treatments: lengthy
Novel treatments or combinations of treatments
Increased risk of non-compliance to treatment
High costs
Higher efficacy and shorter treatment periods

Objective

Objective: develop a MAMS design that can identify the shortest promising treatment duration with high probability while maintaining a strong control of the overall errors in the study.

Notations

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- **equal allocation** of patients to all arms

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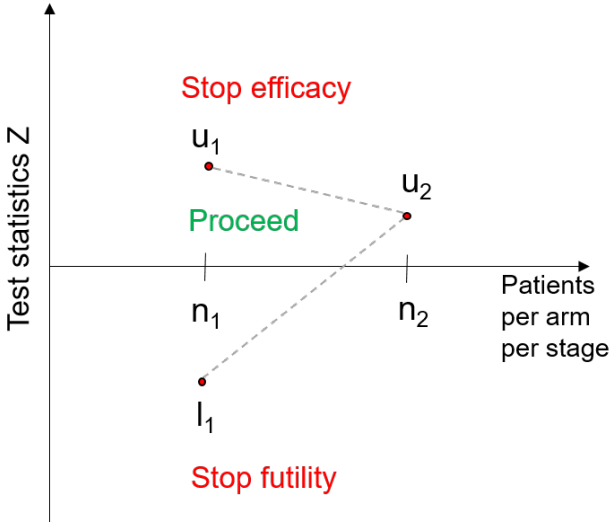
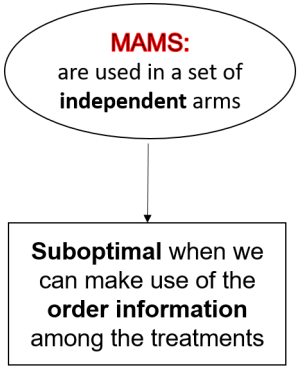
- the correlation structure among the $Z_j^{(k)}$ statistics is known

Two-stage design



Limitations of MAMS

Aim of the study: select all the promising treatment arms.



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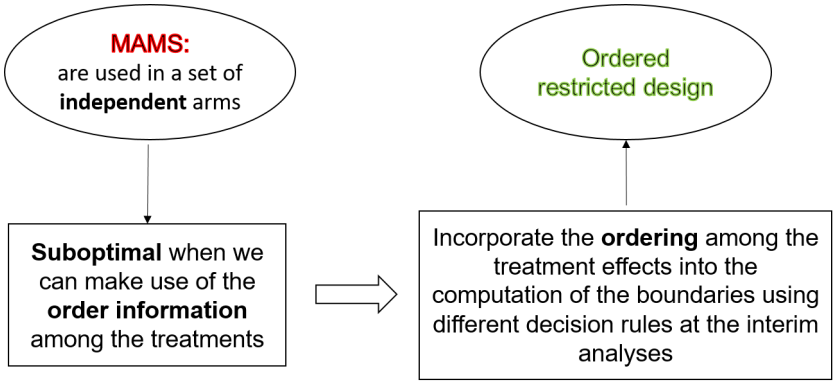

Ordered Restricted Design

Let consider:

- $Z_1^{(k)}$ the test statistic relative to the arm k at the first stage
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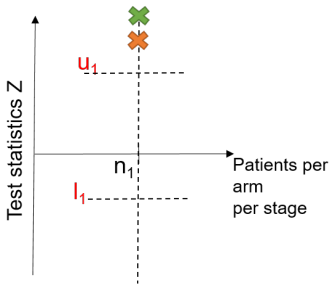
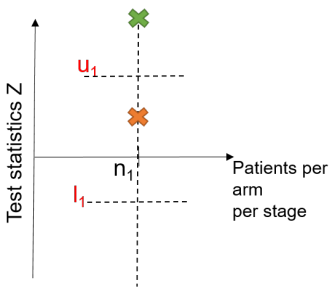
- $\theta^{(L)} \geq \theta^{(S)}$
- $\theta^{(L)}$ and $\theta^{(S)}$ are the effects at the longest and shortest treatment durations, respectively

Decision rules when $\theta^{(L)} \geq \theta^{(S)}$, $Z_1^{(L)} \geq u_1$

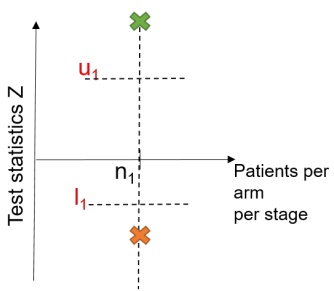
Treatments: L and S



Stop the trial: select L and S



Continue with S



Stop the trial: select L

Decision rules when $\theta^{(L)} \geq \theta^{(S)},\ l_1 < Z_1^{(L)} < u_1$

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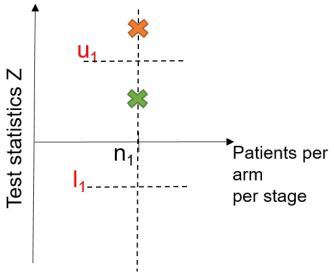

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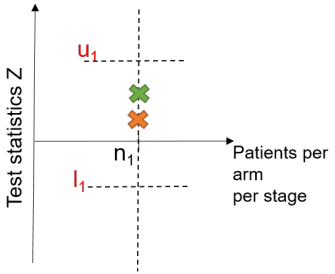

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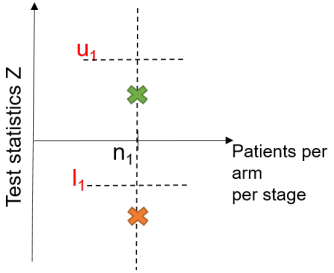

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Decision rules when $\theta^{(L)} \geq \theta^{(S)}$, $Z_1^{(L)} \leq l_1$

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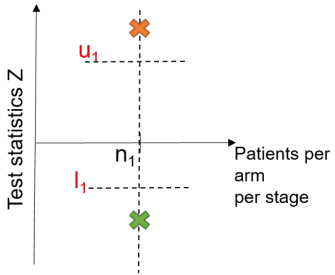

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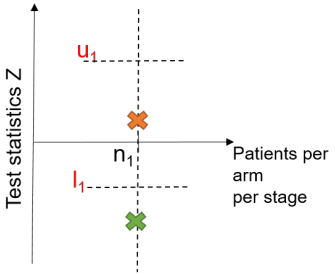

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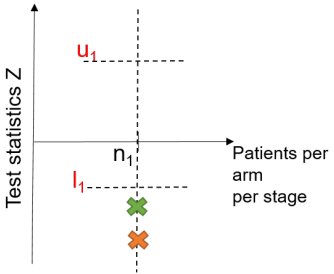

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Family-wise Error Rate and Power requirement

- **Family-wise Error Rate (FWER)**

  Strong control of the FWER at level α:

$$P(\text{rejecting at least one true } H_{0k},\ k \in \{L, S\} | H_0) \leq \alpha$$

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- **Power requirement**

  Power the study at $(1 - \beta)$ to reject both hypotheses under $\boldsymbol{\theta} = (\theta^{(L)}, \theta^{(S)})$, where $\theta^{(L)} \geq \theta^{(S)} \geq \delta_0 > 0$ and δ_0 the minimum clinically relevant difference.

Simulations

Simulations were run to compare the 3-arm 2-stage Ordered Restricted Design (ORD) with:

a) Fixed Sample Design (FSD)

b) Fixed Sample Design with hierarchical test (FSD(h)): that is the 3-arm 1-stage ORD

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The **measure of performance** is the probability of rejecting both hypotheses.
The **efficiency** of the proposed design is measured by its expected sample size (ESS).

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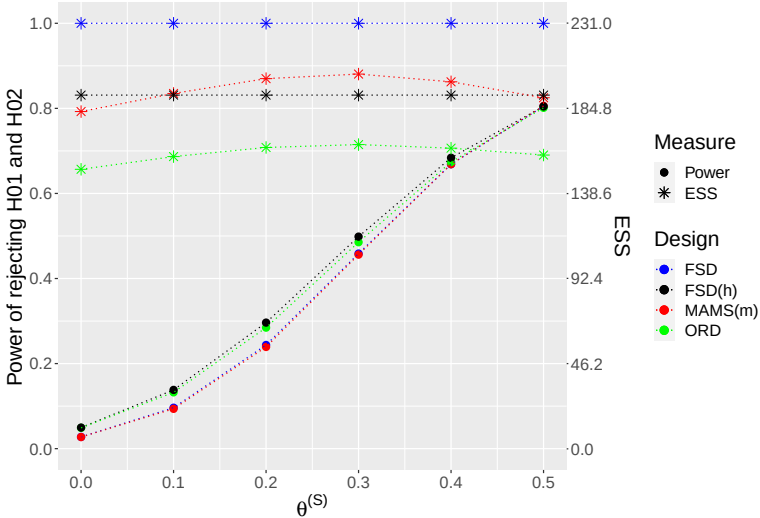
- different scenarios of $\boldsymbol{\theta} = (0.5, \theta^{(S)})$, $\theta^{(L)} \geq \theta^{(S)}$
- use of triangular bounds for the 3-arm 2-stage ORD and MAMS(m) designs

Numerical results under null treatment effect

Design	u_1, u_2, l_1	Max. SS	ESS	Reject at least one H_{0k}
FSD	1.917, -, 1.917	231	231.0	0.05
FSD(h)	1.644, -, 1.644	192	192.0	0.05
ORD	1.898, 1.789, 0.633	222	134.4	0.05
MAMS(m)	2.179, 2.055, 0.726	264	166.6	0.05

Probability to reject both hypotheses



Conclusion

- The inclusion of the information about the ordered treatments can inform better decision-making and requires fewer patients in the trial.

Serra, A., Mozgunov, P., & Jaki, T. (2022). An order restricted multi-arm multi-stage clinical trial design. Statistics in medicine, 41(9), 1613-1626.

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Conclusion

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- The ORD can be generalized to K-arm J-stage design.
- Potential increase in power if different critical bounds are used for each treatment.

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Thank you

Limitations and future work

- In the TB setting, the **non–inferiority** designs are usually adopted.
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- We assumed that **information time is the same** for all treatments.
  Further work will consider optimal designs when information accumulates a different times.
- We assumed that there is **no uncertainty** about the order of the treatment effects.
  The use of a Bayesian framework can allow to account for uncertainty about the order of the treatment effects.

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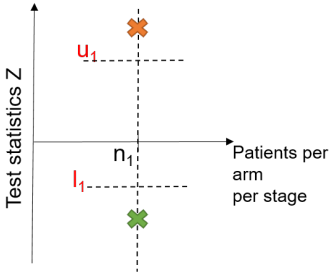

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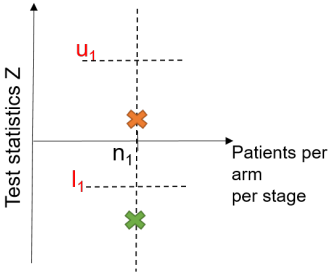

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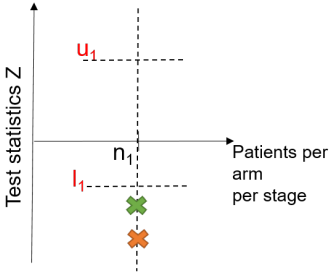

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