Why keeping previous data can be detrimental in platform trials with a change in standard of care

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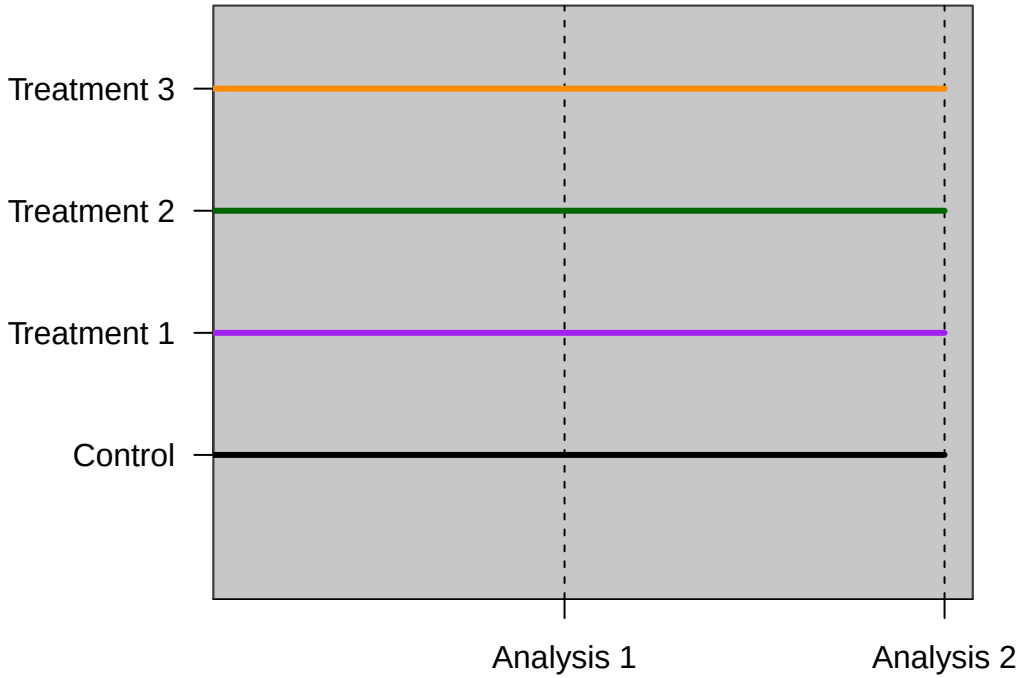
Trial of interest: Multi-Arm Multi-Stage (MAMS) trial



Stopping boundaries at each stage for treatment k

- $Z_{k,0,j} > u_j$.
- $Z_{k,0,j} < l_j$.
- $l_j \leq Z_{k,0,j} \leq u_j$.

Assumptions of the trial

Our assumptions and notation:

- Equal allocation ratio.
- Primary outcome of the i^{th} patient on treatment k, $X_{k,i} \sim \mathcal{N}(\mu_k, \sigma^2)$.
- n_j the number of patients recruited on each treatment by the end of stage j.
- Pre-defined stopping boundaries.

Motivation of this trial

Advantages to including multiple treatments:

- Shared trial infrastructure.
- Shared control group.
- Less administrative and logistical effort.
- Enhanced recruitment.
- Reduced cost and time.

But what if a treatment is found superior after the first stage

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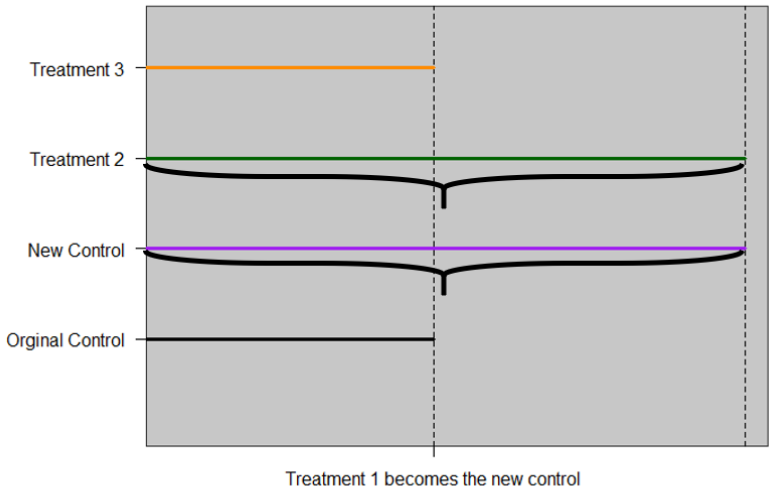
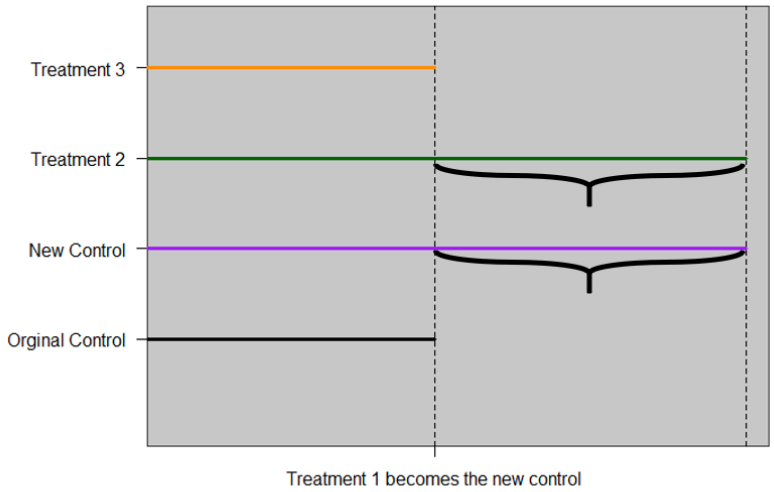
Should this treatment become our new control for the rest of the trial if it is becoming the new standard of care?
Assuming we stay with the predefined boundaries and sample size then a question for powering the study is should we:

- Use all the data?
- Use only the data post the change?





What is going to be tested

Test the null hypotheses $H_{k'k}$ of $\mu_k \leq \mu_{k'}$.
All the data is used:

$$Z_{k,k',j} = \frac{\sum_{i=1}^{n_j} X_{k,i} - \sum_{i=1}^{n_j} X_{k',i}}{\sigma\sqrt{2(n_j)}}.$$

Only the data post the change is used:

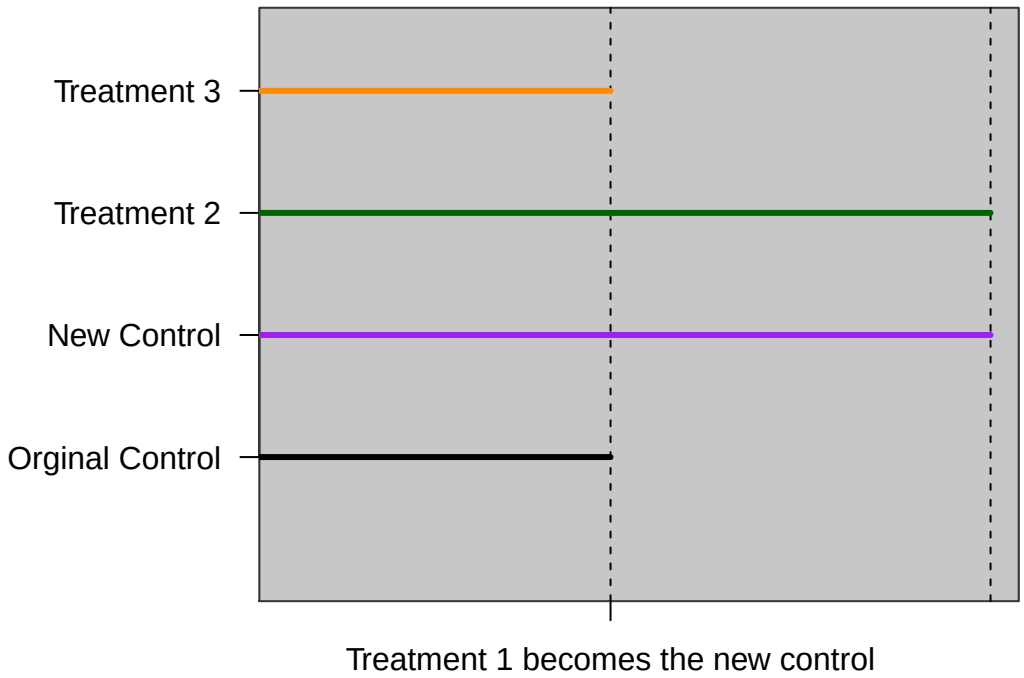
$$Z^{\star}_{k,k',j,j'} = \frac{\sum_{i=n_{j'}+1}^{n_j} X_{k,i} - \sum_{i=n_{j'}+1}^{n_j} X_{k',i}}{\sigma\sqrt{2(n_j - n_{j'})}}$$

where j' defines the stage at which k' became the new control.

Conditional Power

Definition

$P(\text{reject } H_{k'k} | k' \text{ is the current control from stage } j' \text{ and } k \text{ is still being tested})$.



Conditional power theorem

Theorem

If a treatment k' become the control at stage 1 and $u_2 \geq 0$ then keeping the historic data is detrimental to the conditional power of treatment $k^\star$.

It is worth keeping the historic data if:

$$Z_{k^\star,k',j'} > \frac{u_j[\sqrt{n_j} - \sqrt{n_j - n_{j'}}]}{\sqrt{n_{j'}}} \geq 0 \tag{1}$$

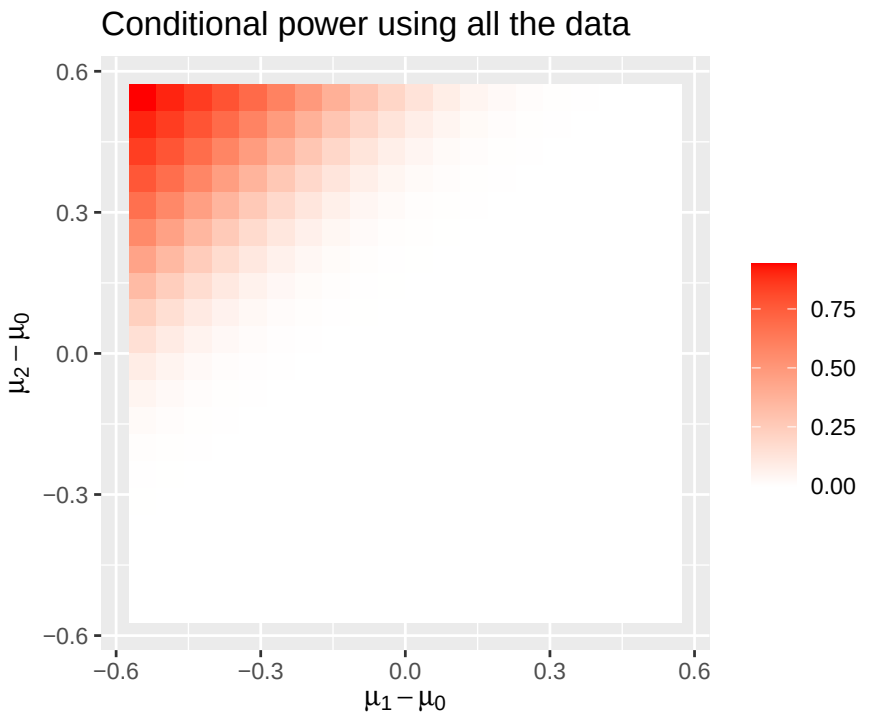
However $Z_{k^\star,k',j'} < 0$ as treatment k' is the new control not treatment $k^\star$.

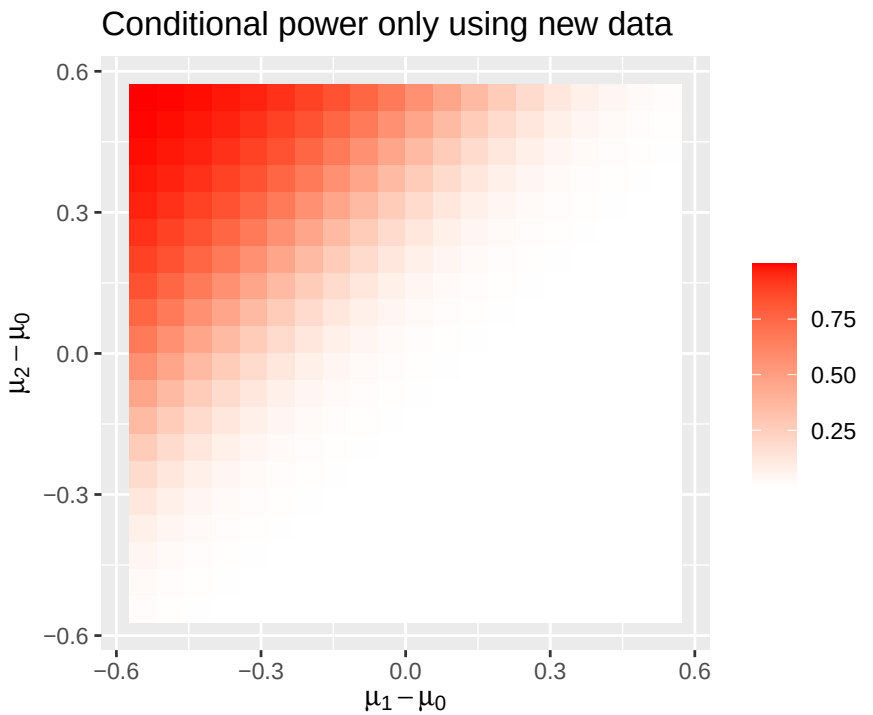
Motivating example

We consider the design of the TAILoR study (Pushpakom et al., 2015):

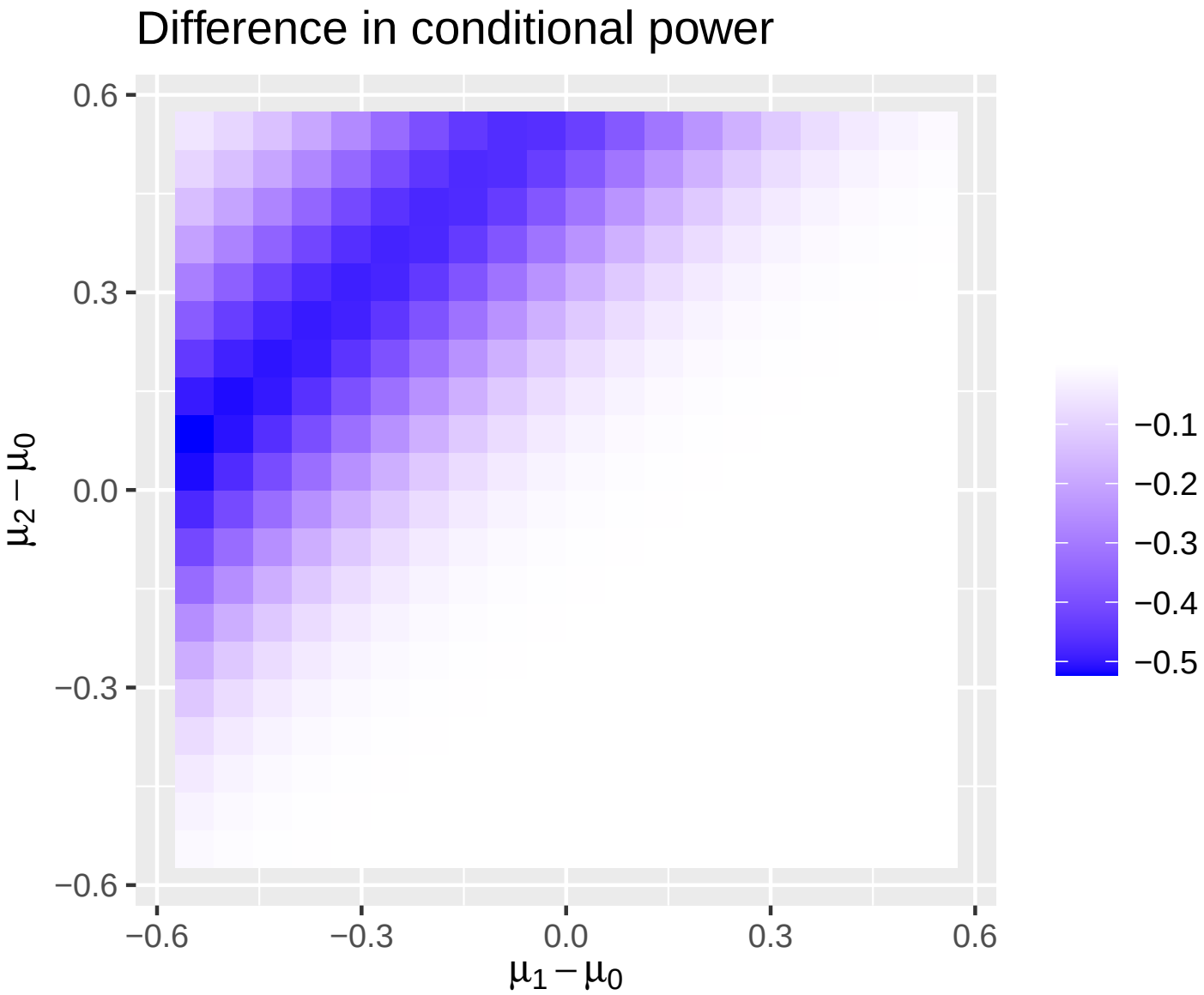
- Family wise error control: 5%
- 3 active arms and 1 control arm
- 2 stages for each arm
- Number of patients per arm per stage: 42
- Clinically relevant effect if $\sigma = 1$ is: 0.545
- We choose the triangular stopping boundaries (Whitehead, 1997) found using Magirr et al. (2012)

Conditional power example





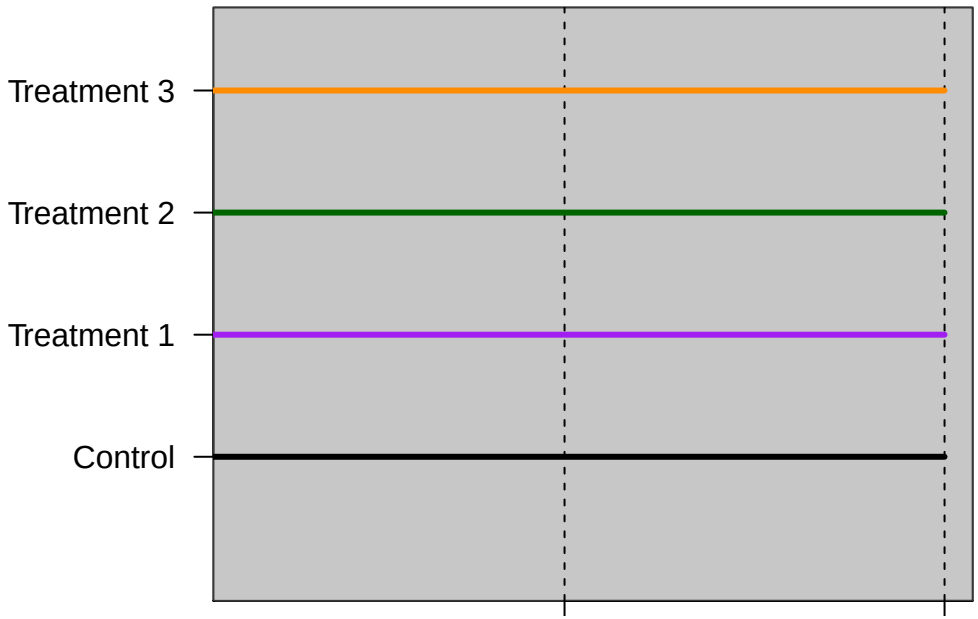
Difference in conditional power example



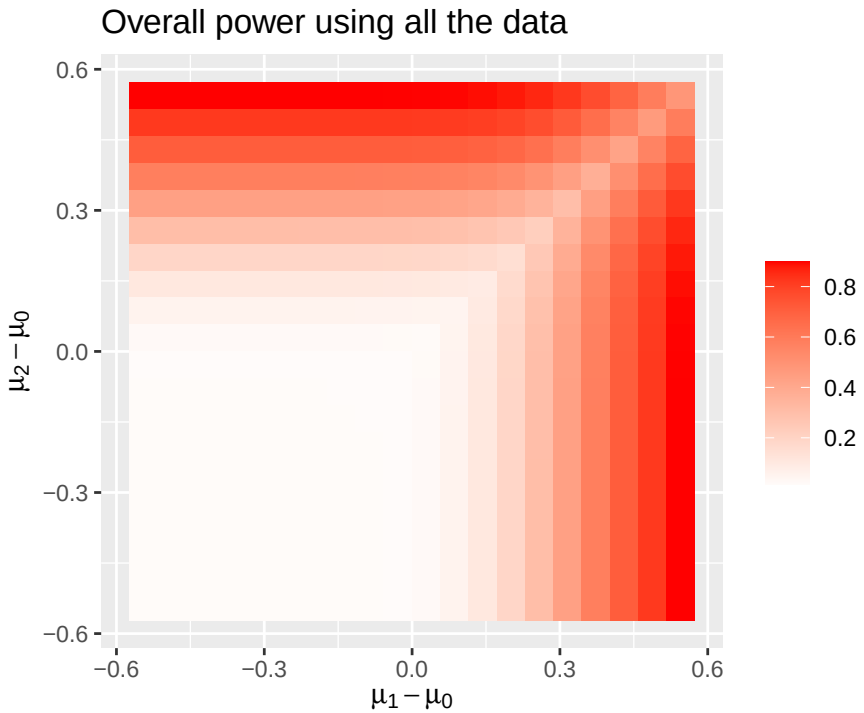
Overall power

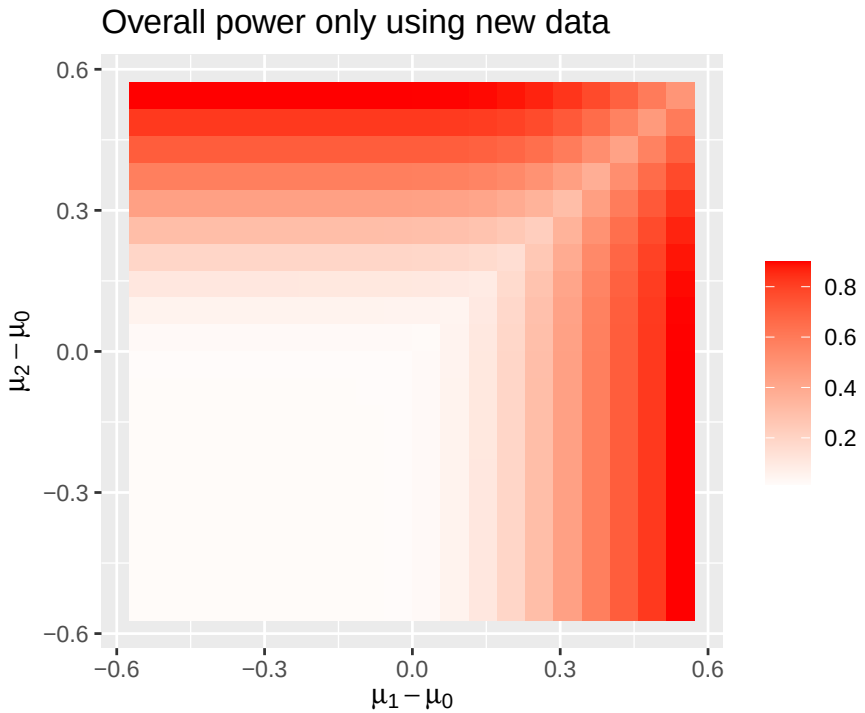
Definition

$P($The treatment $k^\star$ with the greatest treatment effect, $\mu_{k^\star} \geq \mu_k \forall k = 1, \ldots, K,$ is taken forward when compared to the original control or is found superior to a new control k').

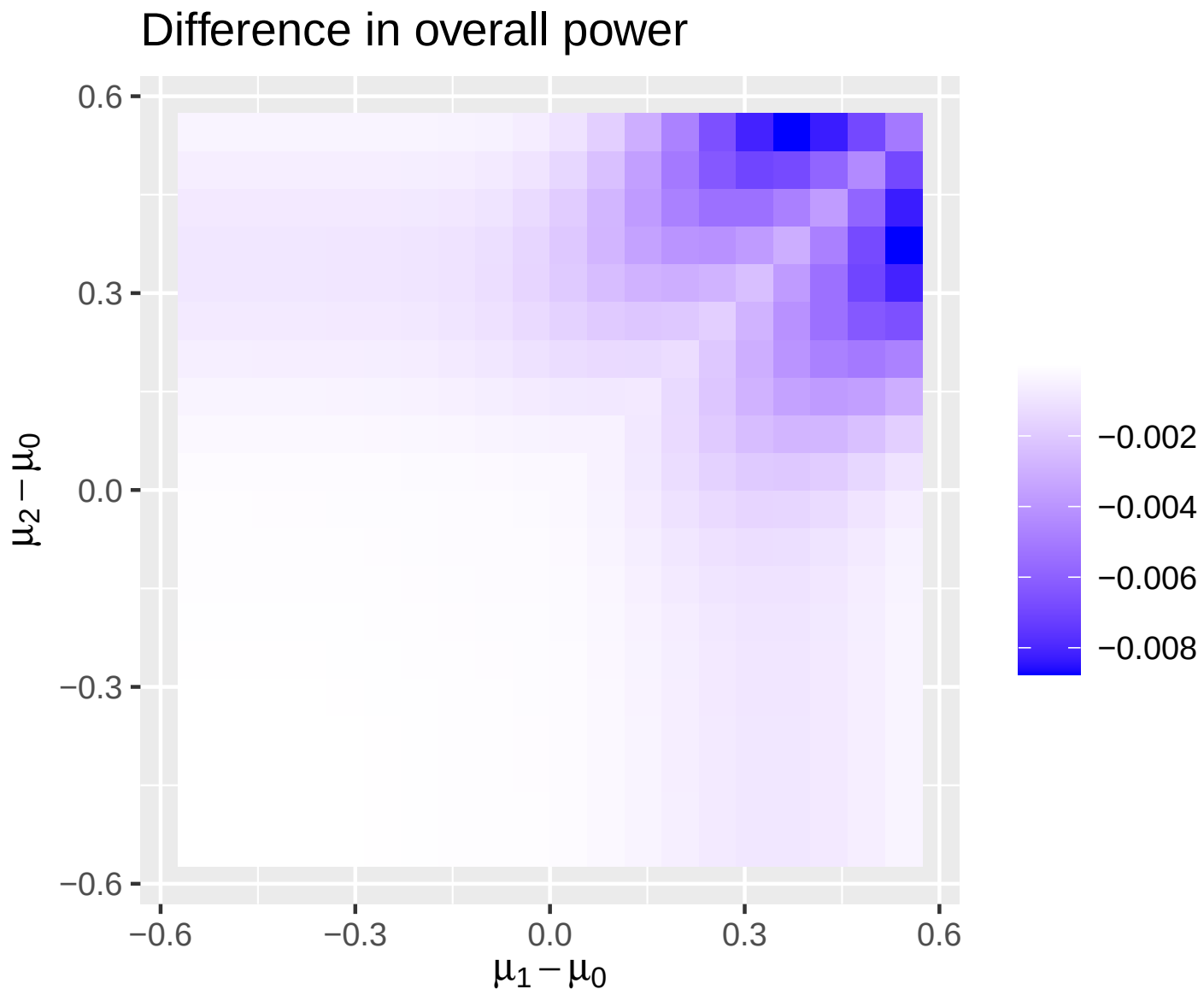


Overall power example





Difference in overall power example



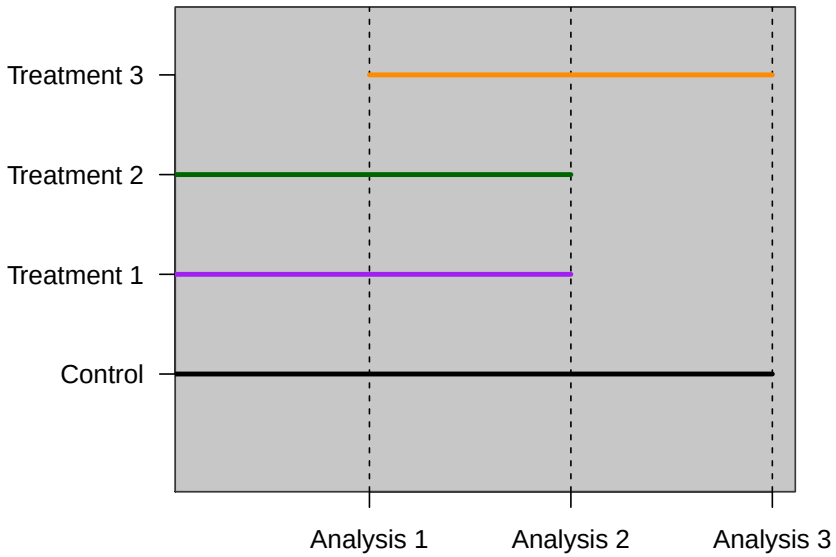
Adding a treatment later

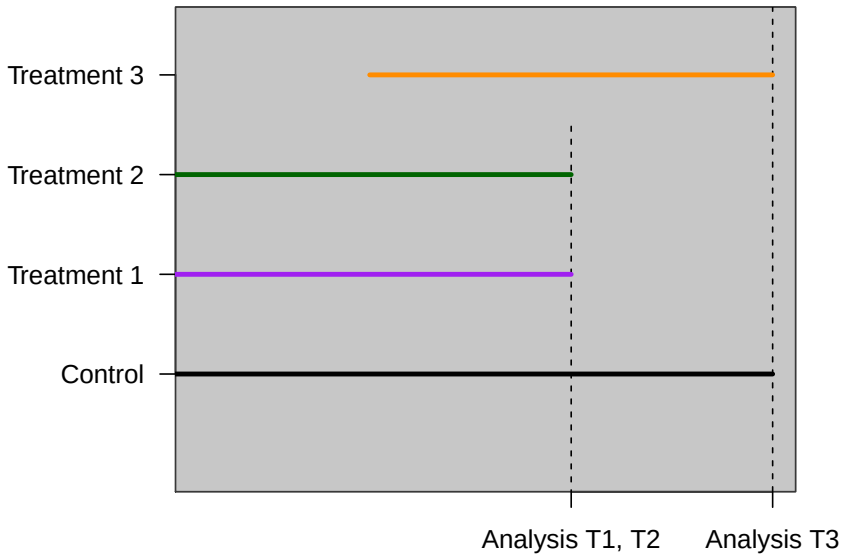
2 cases when a treatment is planned to be added halfway through:

(i) 2 analyses per treatment.

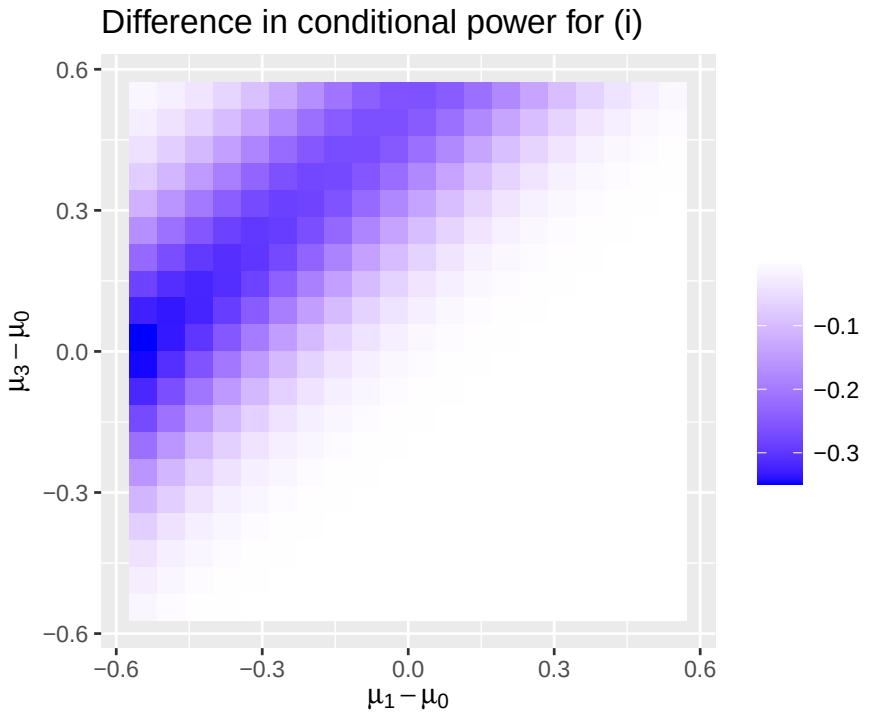
(ii) Only one analysis per treatment.

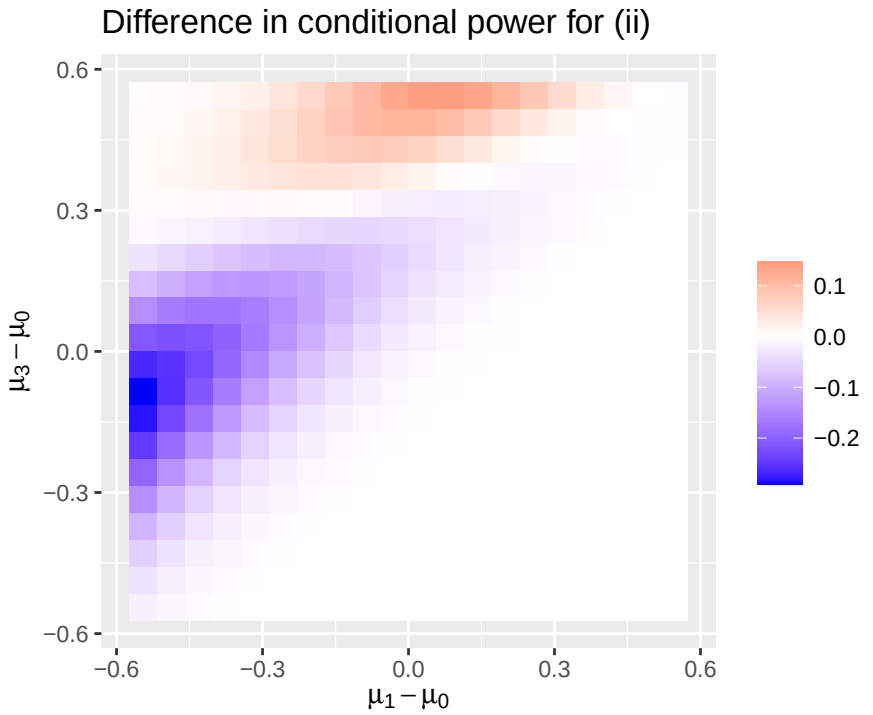
We choose triangular stopping boundaries found using Greenstreet et al. (2021).



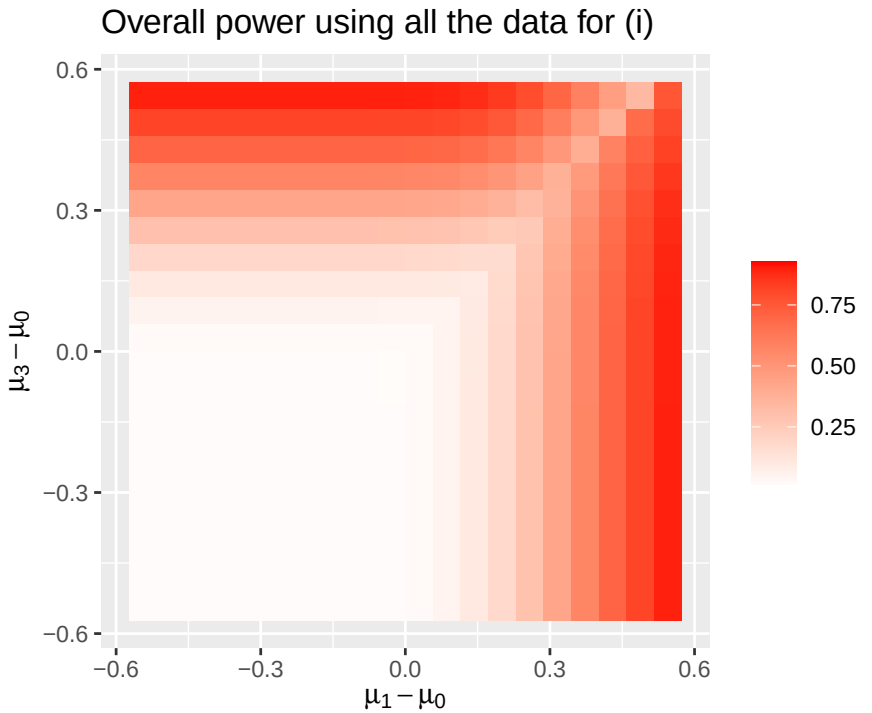


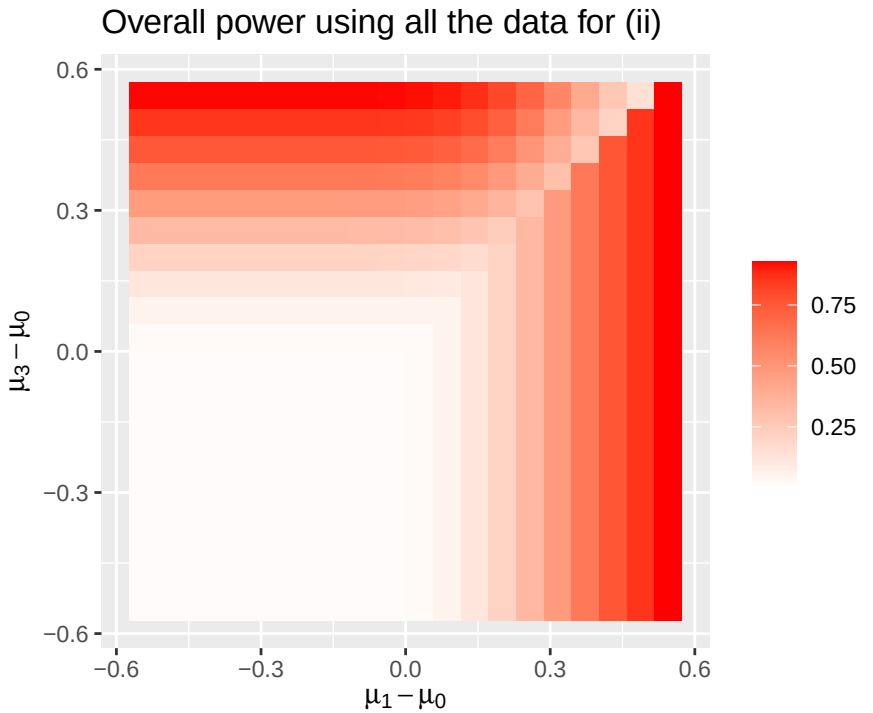
Conditional power difference for treatment 3



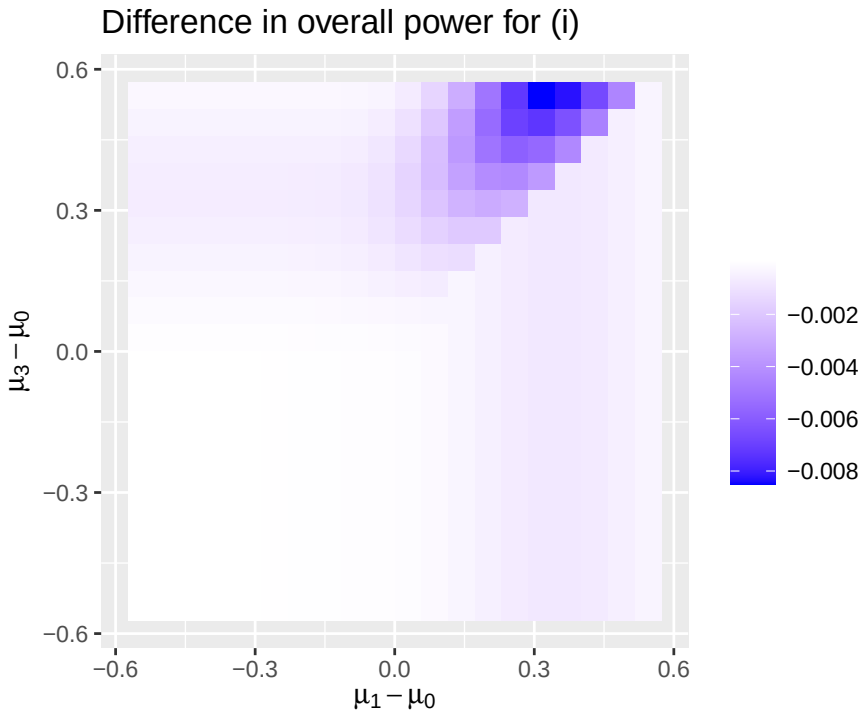


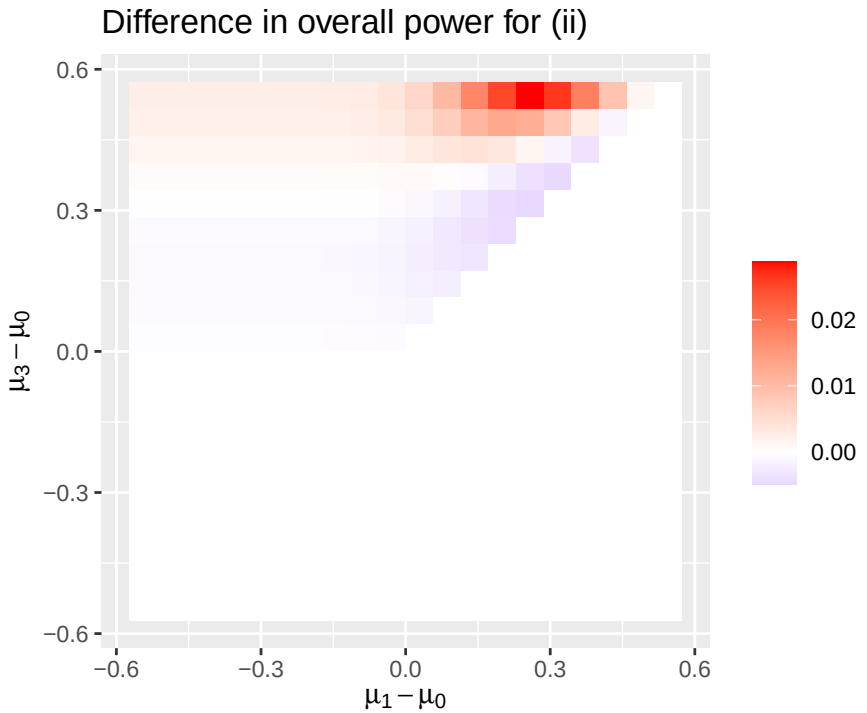
Overall power using all the data





Overall power difference





Conclusion

All treatments start at the same time

- In most cases conditional power is lower when the pre change data is retained.
- In most cases overall power is lower when the pre change data is retained.

When adding later

- In most cases treatments added at the start have lower conditional power and overall power when the pre change data is retained.
- Even for the later treatments there is no guarantee that keeping the old data will increase the conditional power or overall power.

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