

# Innovative study designs for precision medicine trials

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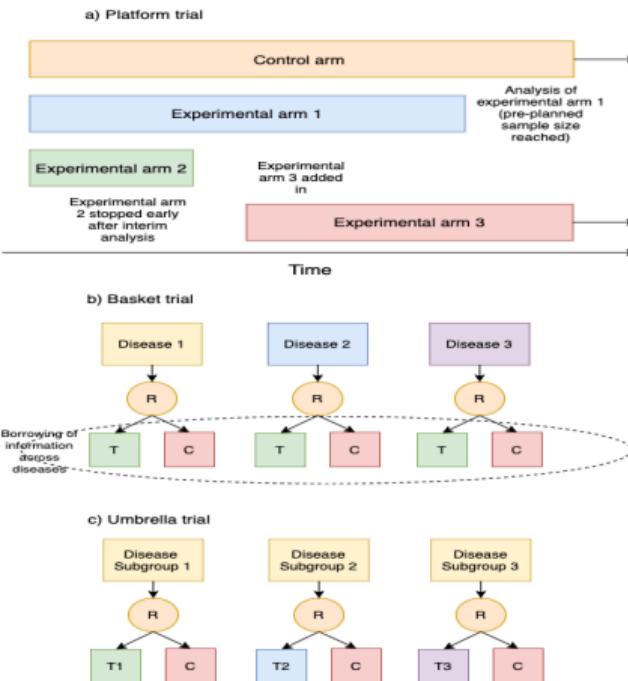
## Overview

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- What are master protocols?
- Basket trials
- Umbrella trials
- Platform trials
- Bayesian analysis models

# Master protocols

- Several types of master protocols exist.
- They combine what would have been multiple trials into one.
- Each has different advantages and may be suitable in different settings.



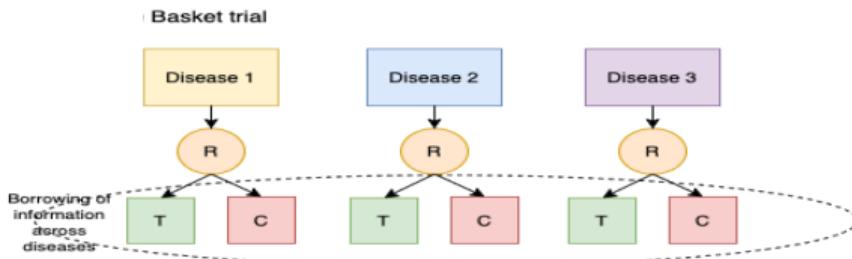
## Benefits

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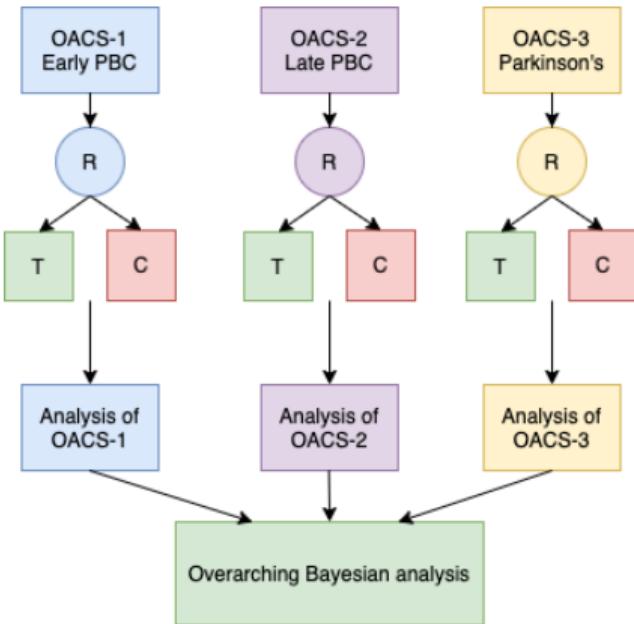
- Operational
  - running several trials within a single protocol should be more efficient than separate trials.
- Statistical
  - allows application of innovative statistical methods than can increase power/efficiency.
- Patients
  - may offer benefits to trial patients;
  - may provide more information for tailoring treatment for future patients.

## Basket trials

- Originated from oncology trials for drugs that targeted a tumour mutation present in different tumour types.
- Each ‘sub-trial’ was testing the drug in a different tumour type.
- Can also be used in other settings:
  - e.g. when intervention may work well for multiple diseases that share a cause or symptom.



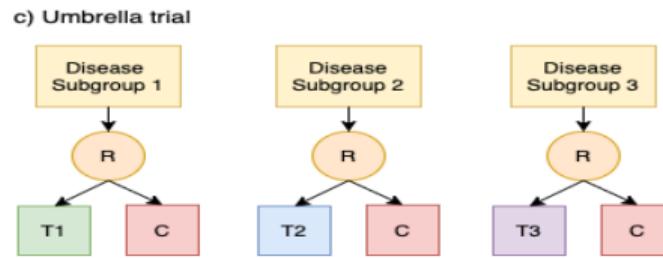
## Example 1 – OACS trial (basket)



- Three small randomised controlled trials.
- Each tests a common treatment (Obeticholic Acid) against placebo for three conditions with cognitive dysfunction as a symptom.
- Each trial analysed separately, but with an overarching Bayesian analysis.

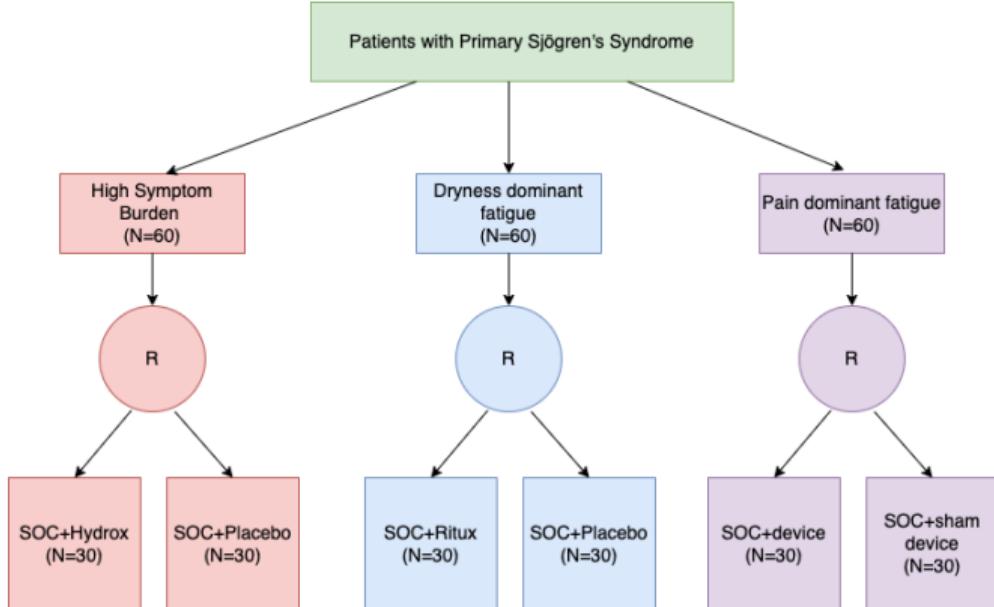
## Umbrella trials

- Again, originated in oncology trials for testing multiple targeted drugs in one tumour type.
- Allocation to treatment depends on the tumour mutation(s) the trial participant has.
- Can be more complex than the schematic.
- This approach could also be used in complex diseases with different manifestations/symptoms.



## Example 2 – umbrella design for Sjögren's syndrome

- Sjögren's syndrome is heterogeneous disease.
- Research in Newcastle has developed a tool that can stratify patients into distinct groups that experience different symptoms.
- Proposed trial will stratify patients and use symptom-targeted treatment.



## Platform trials

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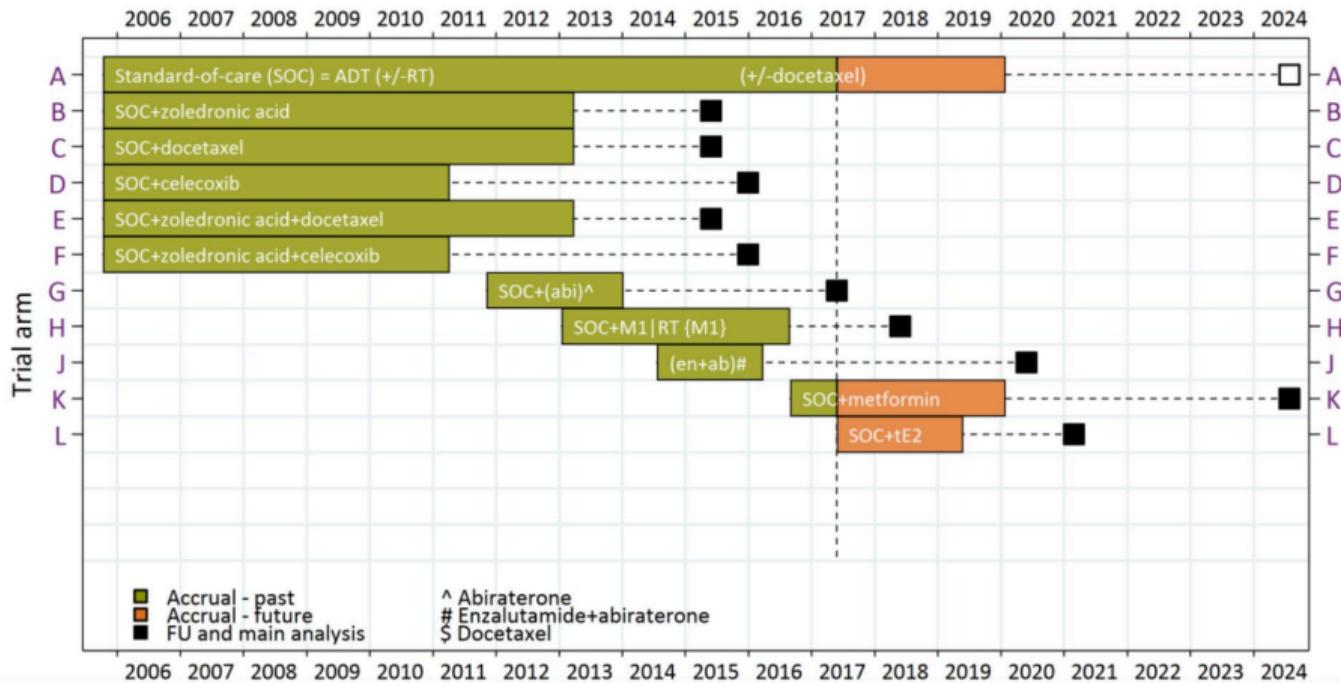
- A platform trial is a type of master protocol that usually consists of the following elements:
  1. Multiple experimental arms compared against a shared control group
  2. Adaptive design allows dropping of less promising arms
  3. Opportunity to add in new arms as they become available.

## Platform trials

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- **Advantages:**
- Shared control group means lower sample size overall
- Allows early stopping of ineffective interventions
- Adding new arms means momentum from opening sites can be maintained rather than starting again in a new trial.
- **Disadvantages**
- Will be bigger/more expensive than one two-arm trial
- Raises several statistical and operational complexities.

## Example: STAMPEDE trial



## Statistical issues in master protocols

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- Master protocols are potentially very efficient...
  - but more complex as well!
- 
- An important aspect of basket and umbrella designs is the potential to borrow information between different parts of the trial.

## Borrowing of information

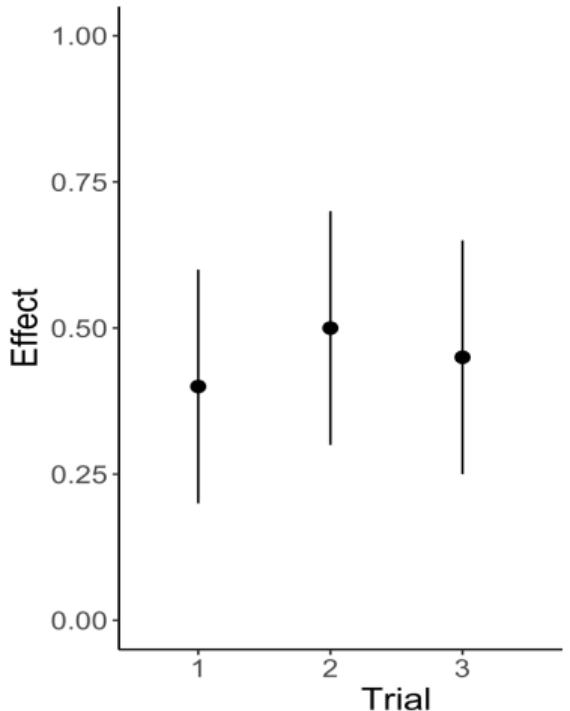
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- In different master protocols it is possible to ‘borrow information’, i.e use data from elsewhere in the trial to test a specific hypothesis.

Design	Borrowing information
Basket	When estimating treatment effect in one subtrial, borrow information on the treatment effect from another subtrial, e.g. using a hierarchical model.
Umbrella	If control treatment is consistent, could borrow information from one subtrial to another.
Platform	When testing a new treatment, could use non-concurrent controls, i.e. control patients enrolled before the new treatment was added

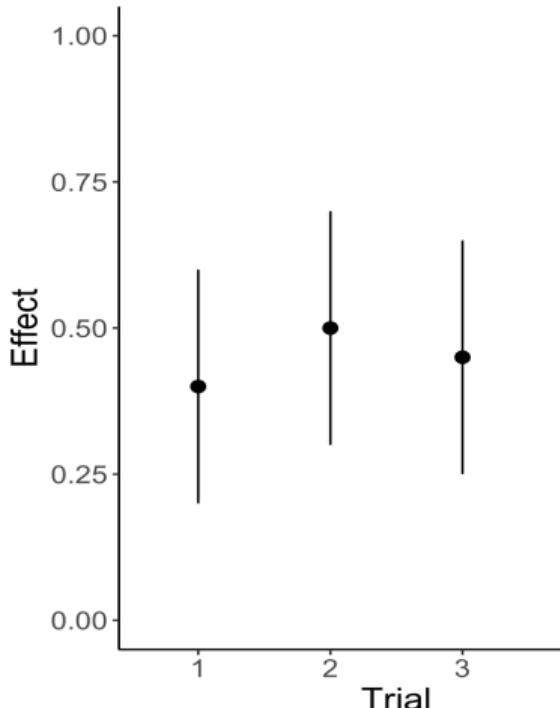
- Generally borrowing information is a classic ‘bias-variance’ trade off.

# Borrowing information



- In a basket trial like OACS we'd want to estimate the treatment effect in each separate part of the trial.

# Borrowing information



- In a basket trial like OACS we'd want to estimate the treatment effect in each separate part of the trial.
- Two potential ways :
  1. **Separate analysis**: just use data from the respective trial.
  2. **Complete pooling**: estimate the overall treatment effect across all trials.

- Separate analysis assumes each trial has a distinct (unrelated) treatment effect;
- Complete pooling assumes all trials have identical treatment effect.
- The latter will be highly efficient if the assumption is correct, but may be misleading if not.
- The former will be robust, but least efficient.
  
- Alternative approaches allow ‘borrowing of information’ across trials.

- A common approach to borrowing information is using a Bayesian hierarchical model.
- An example would be to assume a prior distribution for the treatment effects (e.g. Normal with mean  $m$  and variance  $T^2$ ):
- Small values of  $T^2$  mean the treatment effects are very similar -> more information is borrowed.
- Large values of  $T^2$  mean the treatment effects can be very different -> less information is borrowed.

# Borrowing information

- Several alternative methods have been proposed to allow more flexibility.
- One example is using a Bayesian discrepancy approach, e.g. Zheng and Wason<sup>1</sup>

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## Borrowing of information across patient subgroups in a basket trial based on distributional discrepancy

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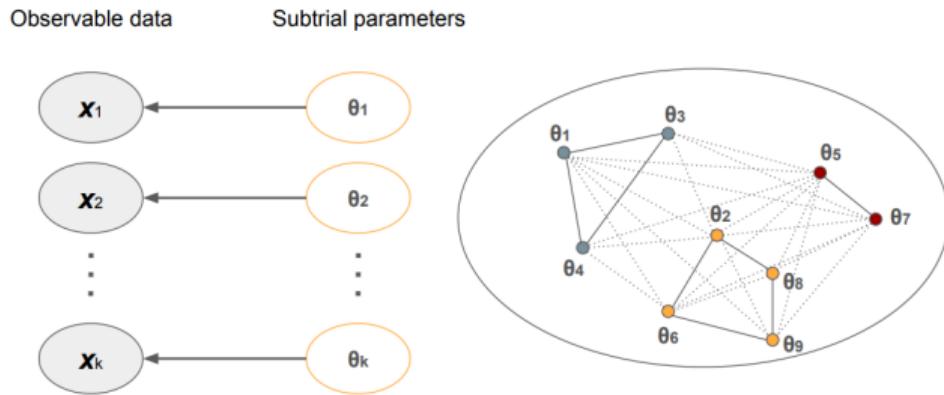
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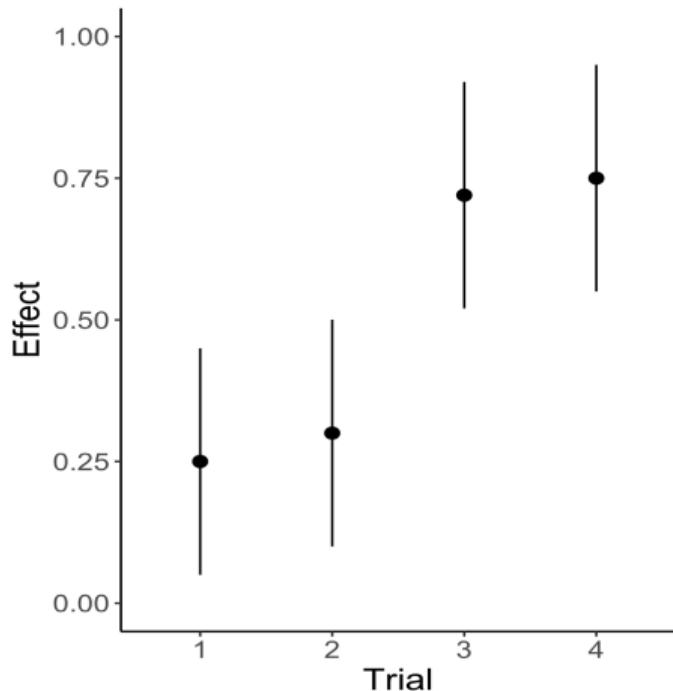
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1. Zheng H and Wason J (2022) Borrowing of information across patient subgroups in a basket trial based on distributional discrepancy. *Biostatistics* 22(1):120-135.

# Bayesian discrepancy approach



# Borrowing information



- Trials form two clusters with similar treatment effects.
- HM approach will not cope well with this.
- Bayesian discrepancy approach will do better – information shared between trial 1 and 2 and between 3 and 4.



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## Design and analysis of umbrella trials: Where do we stand?

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# Limitations of borrowing information

- However borrowing information has the downside that it is not possible to strictly control the type I error rate whilst benefiting.

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**Power gains by using external information in clinical trials are typically not possible when requiring strict type I error control**

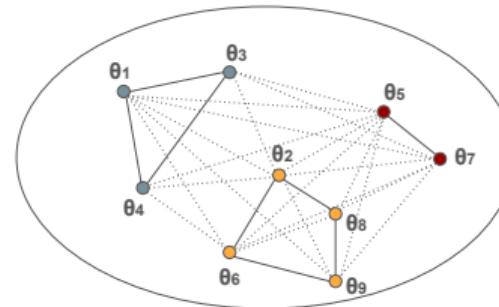
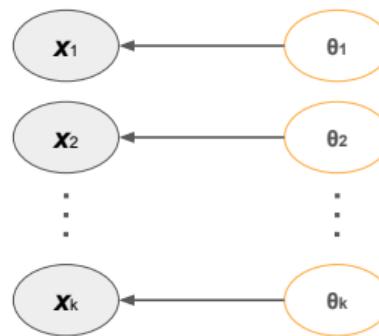
Annette Kopp-Schneider  | Silvia Calderazzo | Manuel Wiesenfarth

- Funder and regulatory views evolving but generally not going to be seen as acceptable as primary analysis for confirmatory trials in non-rare disease.

# Sample size determination

# Borrowing with pairwise (dis)similarity

Observable data      Subtrial parameters



**Aim:** to estimate the treatment effects,  $\theta_k$ , using entire trial data.

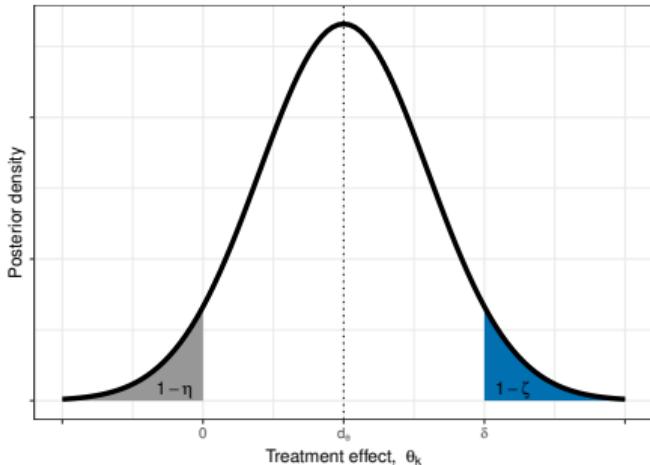
**Robust borrowing of information:**

$$\theta_k \mid \theta_q, \nu_{qk} \sim N(\theta_q, \nu_{qk}^{-1}), \forall k = 1, \dots, K$$

$$\nu_{qk} \sim w_{qk} \text{Gamma}(a_1, b_1) + (1 - w_{qk}) \text{Gamma}(a_2, b_2), \text{ with } q \neq k$$

Setting  $w_{qk} \rightarrow 0$  means strong borrowing and 1 means no borrowing *a priori*.

# Trial decision making



- ★ Compute two posterior interval probabilities:
  - (a)  $\mathbb{P}(\theta_k > 0 | \mathbf{x}_k, \mathbf{x}_{(-k)}) \geq \eta$ , or
  - (b)  $\mathbb{P}(\theta_k < \delta | \mathbf{x}_k, \mathbf{x}_{(-k)}) \geq \zeta$ ,where both  $\eta$  and  $\zeta$  are values close to 1.

The trial data collected will provide convincing evidence  
either that  $E$  is better than  $C$   
or that it fails to improve upon  $C$  by some clinically relevant difference,  $\delta > 0$ .

# Bayesian sample size formulae (Zheng et al., 2022a; 2022b)

For cases of known  $\sigma_k^2$ , the subtrial sample sizes  $n_1, \dots, n_k$  satisfy:

$$\frac{R_k(1 - R_k)n_k}{\sigma_k^2} + \left[ \sum_q p_{qk}^2 \left( \left( \frac{1}{s_{0q}^2} + \frac{R_q(1 - R_q)n_q}{\sigma_q^2} \right)^{-1} + \frac{w_{qk} b_1}{a_1 - 1} + \frac{(1 - w_{qk})b_2}{a_2 - 1} \right) \right]^{-1} \geq \frac{(z_\eta + z_\zeta)^2}{\delta^2}, \quad \forall q \neq k.$$

where  $R_k$  is the randomisation ratio to  $E$  within subtrial  $k = 1, \dots, K$ .

- With  $0 \leq w_{qk} < 1$  (borrowing), sample size saving can be expected.

Apply Newton's method for systems of nonlinear equations to find  $n_1, \dots, n_K$ , simultaneously.

# Application - evaluating a new inhibitor in 7 cancer subtypes

The SUMMIT basket trial (NCT01953926) adopted a single-arm design using binary outcome.

The change in tumour volume on a continuous scale of -100% to 100% was a secondary outcome.

Suppose we were to design a new randomised basket trial with  $K = 7$  using this continuous outcome.

# Prerequisites

Based on the published results, we assume the outcome distributions

$$\begin{cases} \mu_{Ek} = -0.489, 0.226, -0.181, 0.293, 0.329, -0.275, -0.136 \\ \sigma_k^2 = 0.587^2, 0.345^2, 0.380^2, 0.347^2, 0.344^2, 0.392^2, 0.392^2 \end{cases}$$

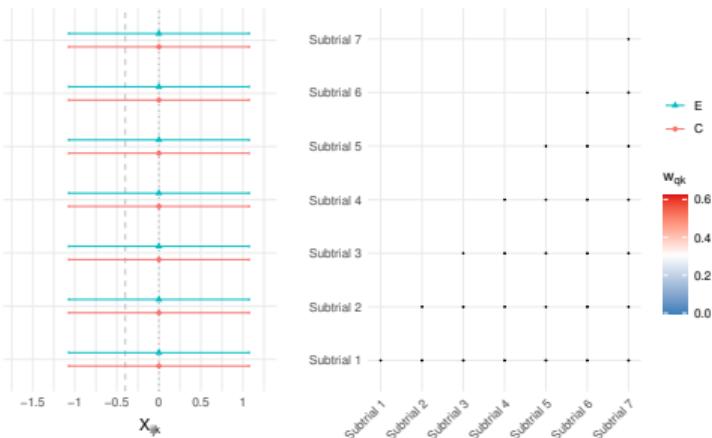
Compute  $w_{qk}$  as the pairwise Hellinger distance between  $N(\mu_{Ek}, \sigma_k^2)$  and the synthesis weights  $p_{qk}$ .

Set  $\eta = 95\%$ ,  $\zeta = 80\%$  and  $\delta = -0.4$ :

Proposed	$n_k = 52.0, 17.3, 20.5, 17.0, 17.1, 22.5, 22.0$
No borrowing	$n_k^0 = 53.3, 18.4, 22.3, 18.6, 18.3, 23.8, 23.8$

# Simulation study (I)

## Scenario 1



$$n_k^0 \quad n_k$$

46.4 8.9

46.4 8.9

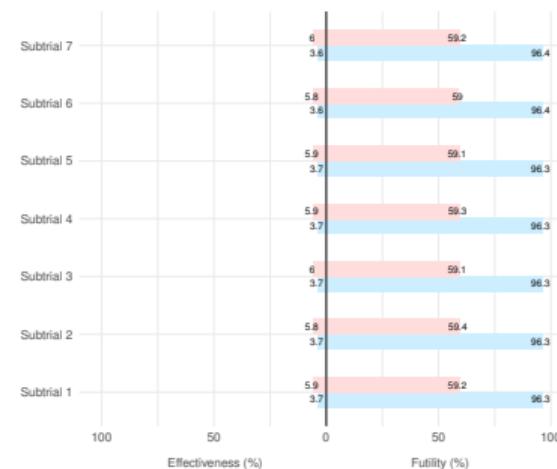
46.4 8.9

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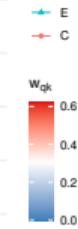
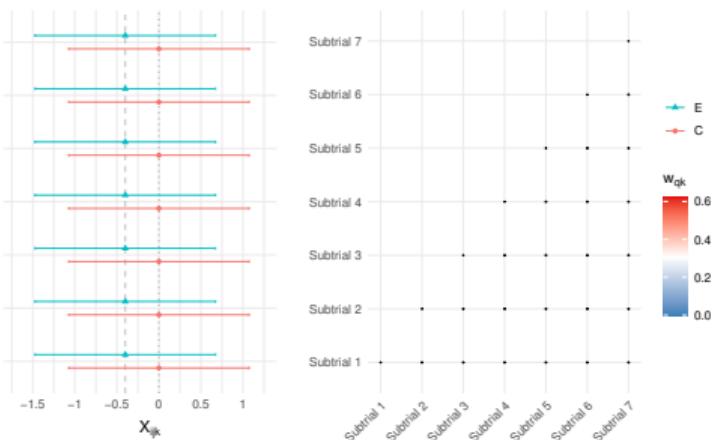
46.4 8.9

324.8 62.3



# Simulation study (II)

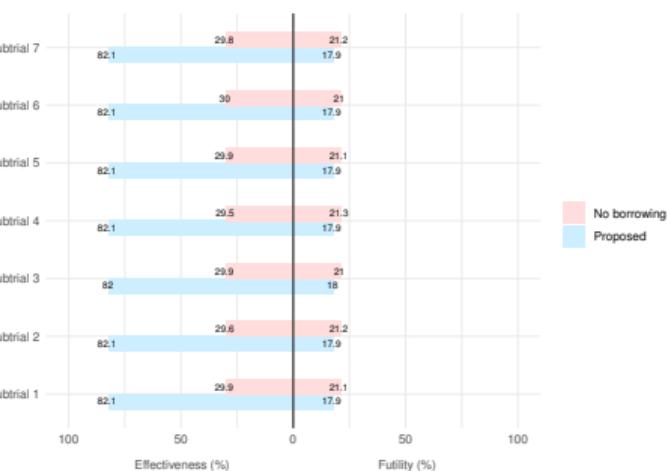
## Scenario 2



$$n_k^0 \quad n_k$$

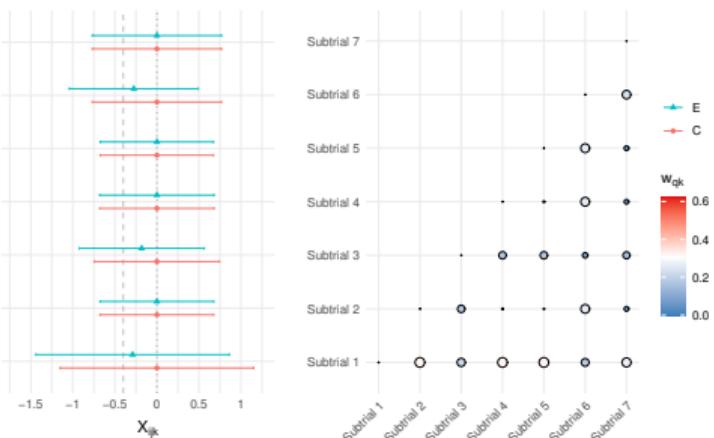
$$\begin{array}{ll} 46.4 & 8.9 \\ 46.4 & 8.9 \\ 46.4 & 8.9 \\ 46.4 & 8.9 \\ 46.4 & 8.9 \\ 46.4 & 8.9 \\ 46.4 & 8.9 \end{array}$$

**324.8    62.3**



# Simulation study (III)

## Scenario 3



$$n_k^0 \quad n_k$$

23.7 20.7

23.7 22.1

18.3 14.2

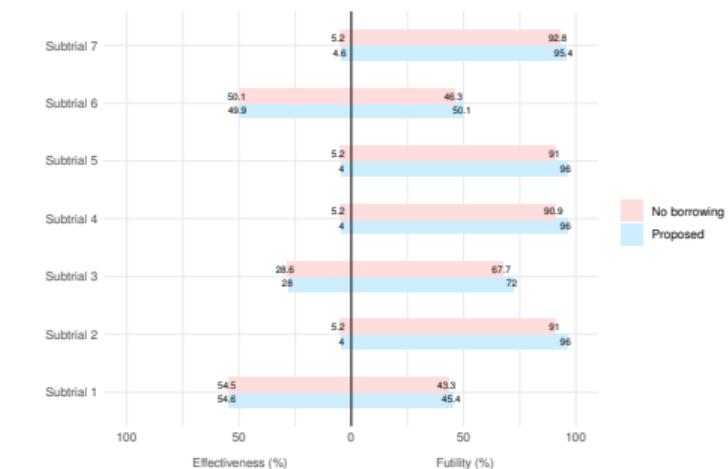
18.6 14.5

22.3 20.4

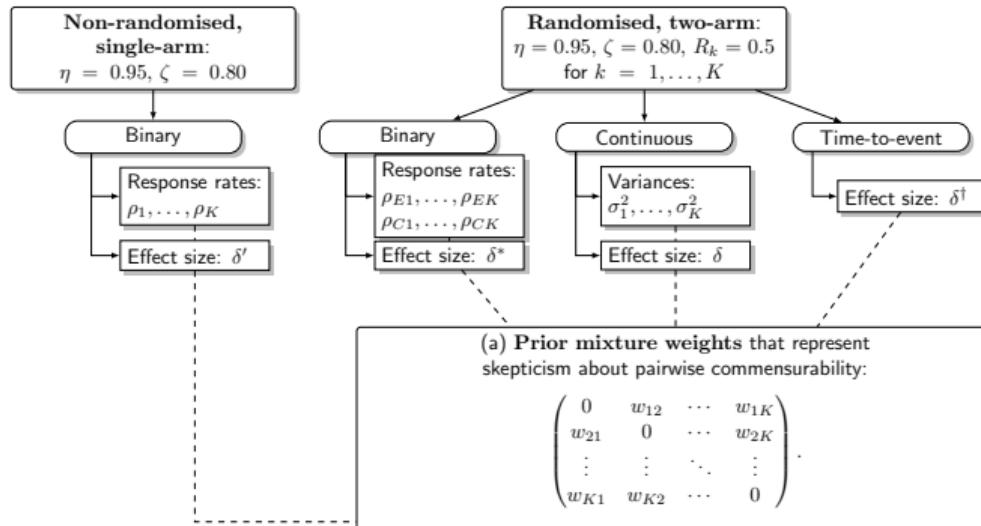
18.4 14.3

53.2 50.8

**178.2 157.0**



# A roadmap for parameter specification



(b) Synthesis weights: transformed from the columnwise non-zero  $w_{qks}$  by

$$p_{qk} = \frac{\exp(-w_{qk}^2/c_0)}{\sum_q \exp(-w_{qk}^2/c_0)}, \quad \forall k = 1, \dots, K,$$

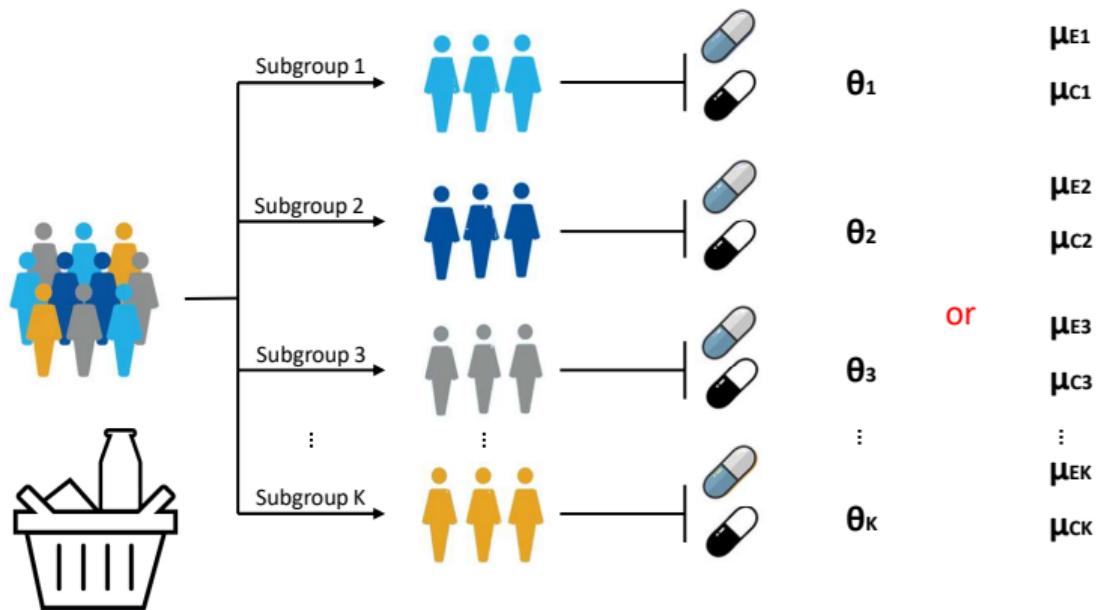
where we recommend setting  $c_0$  to a value close to  $0^+$ .

(c) Other parameters:  
 $a_1 > 1, b_1 \geq a_1, a_2 \geq 54, b_2 = 3$  and  $s_{0k}^2 = 100$ .

Solve the equations to find subtrial sample/event sizes:  
 $n_1, \dots, n_K$  or  $D_1, \dots, D_K$ .

# An alternative strategy for borrowing (Ouma et al., 2022)

**Common mutation**  
the drug targets



# An R shiny app (Zheng et al., 2023)

## No borrowing

http://127.0.0.1:7176 | Open in Browser

# of Trials	$s^2_{0k}$	$\sigma_1$
5	100	0.587
$\eta$	$\sigma_2$	
0.95	0.345	
$\zeta$	$\sigma_3$	
0.8	0.380	
$\delta$	$\sigma_4$	
0.4	0.347	
$\sigma_5$		0.344

Use Equal Allocation Ratios (True/False)

Are you using borrowing? (True/False)

k	$s_k$	$n_R$	$n_T$	$n_C$
1	0.59	92	46	46
2	0.34	54	27	27
3	0.38	60	30	30
4	0.35	54	27	27
5	0.34	54	27	27

Results calculated with  $d=0.4$ ,  $\eta=0.95$ ,  $\zeta=0.8$

## Borrowing with pairwise commensurability

http://127.0.0.1:7176 | Open in Browser

# of Trials	$a_1$	$s^2_{0k}$	$\sigma_1$
5	2	100	0.587
$b_1$	$\eta$	$\sigma_2$	
2	0.95	0.345	
$a_2$	$\zeta$	$\sigma_3$	
54	0.8	0.380	
$b_2$	$\delta$	$\sigma_4$	
3	0.4	0.347	
$\sigma_5$		0.344	

Use Equal Allocation Ratios (True/False)

Are you using borrowing? (True/False)

Extra Table Detail? (True/False)

Level of Borrowing  
Moderate Strong

k	$s_k$	$n_R$	$n_T$	$n_C$
1	0.59	60	30	30
2	0.34	36	18	18
3	0.38	38	19	19
4	0.35	36	18	18
5	0.34	36	18	18

Results calculated with  $d=0.4$ ,  $\eta=0.95$ ,  $\zeta=0.8$

# Roundtable Discussion

# Roundtable discussion

Q1: What are funders' and regulators' opinions?

# Roundtable discussion

Q2: How to write the statistical analysis plans?

# Roundtable discussion

Q3: Barriers experienced in the uptake of master protocol designs? Any recommendations to facilitate the use?

# Roundtable discussion

Q4: Need for better resources to support the implementation?

# Roundtable discussion

Q5: How to better communicate the associated statistical complexities and the need for advanced methods?

# References (I)

-  Woodcock J and LaVange LM. (2017) Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *New England Journal of Medicine*, 377(1):62-70.
-  Hyman DM, Puzanov I, Subbiah V, et al. (2015) Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *New England Journal of Medicine*, 373(8):726-736.
-  Hobbs BP, Pestana RC, Zabor EC, Kaizer AM, Hong DS. (2022) Basket Trials: Review of Current Practice and Innovations for Future Trials. *J Clin Oncol*. Epub ahead of print.
-  Kopp-Schneider A, Calderazzo S, Wiesenfarth M. (2020) Power gains by using external information in clinical trials are typically not possible when requiring strict type I error control. *Biom J*;62(2):361-74.
-  'OACS' trial (ISRCTN15223158). A study to evaluate the effect of Obeticholic Acid to treat patients with Primary Biliary Cholangitis (PBC) who also experience issues with cognitive function around memory and problem solving.

## References (II)

-  Ouma LO, Grayling MJ, Wason JMS, Zheng H. (2022) Bayesian modelling strategies for borrowing of information in randomised basket trials *JRSS: Series C*, 71(5):2014-2037.
-  Ouma LO, Wason JMS, Zheng H, Wilson N, Grayling MJ. (2022) Design and analysis of umbrella trials: Where do we stand? *Front Med (Lausanne)*. 2022;9:1037439.
-  Zheng H, Crout P, Starr C. (2023) An R Shiny for designing Bayesian basket trials. To appear.
-  Zheng H, Grayling MJ, Mozgunov P, Jaki T, Wason JMS. (2022a) Bayesian sample size determination in basket trials borrowing information between subsets. *Biostatistics*, epub ahead of print.
-  Zheng H, Jaki T, Wason JMS. (2022b) Bayesian sample size determination using commensurate priors to leverage preexperimental data. *Biometrics*, epub ahead of print.
-  Zheng H, Wason JMS. (2022) Borrowing of information across patient subgroups in a basket trial based on distributional discrepancy. *Biostatistics*, 23(1):120-135.