Design and analysis of basket trials to enable added efficiency

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Motivation

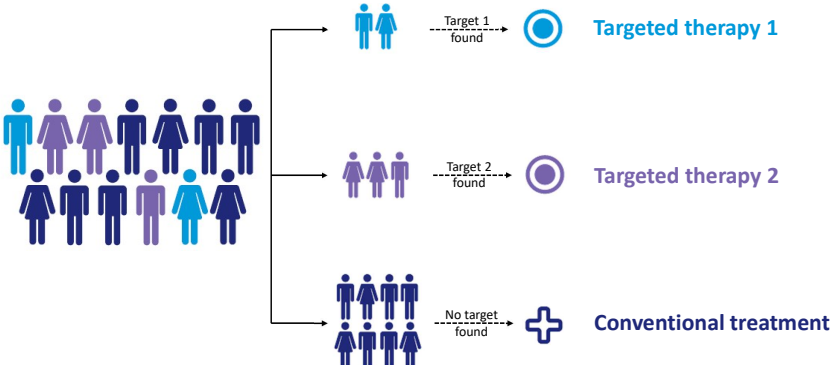


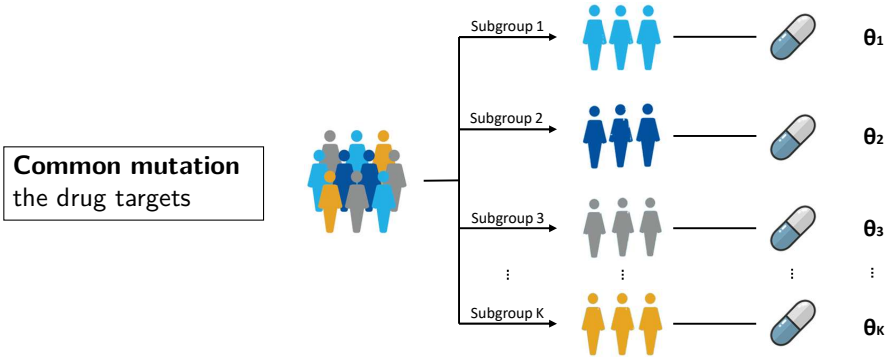
Figure: Precision medicine – right treatments for right patients at the right time

Biomarker-driven designs

Revolution of molecular profiling → common mutations may be present in multiple tumour histologies

Expectation: develop **targeted therapies** that would show activity when the mutation is present

One approach: use certain biomarker for screening and recruit patients harbouring a common mutation



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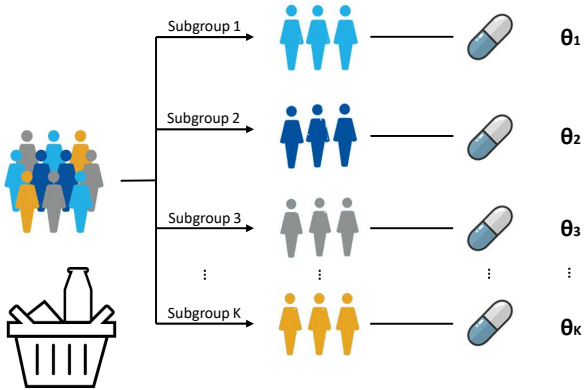
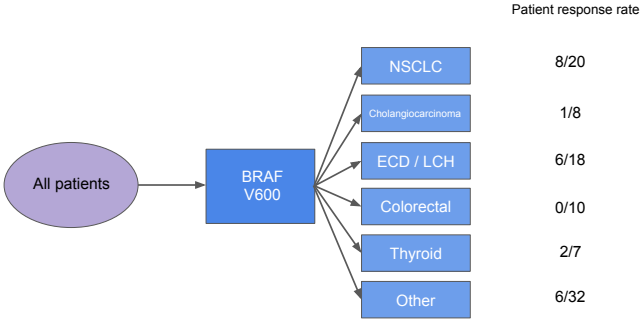
Common mutation
the drug targets



Basket trials in oncology – an example

Hyman *et al.* (2015) reported a basket trial for evaluating the efficacy of vemurafenib in BRAF-V600.

A total of 122 patients with BRAF-V600 mutations were enrolled, of which 95 entered six subtrials.



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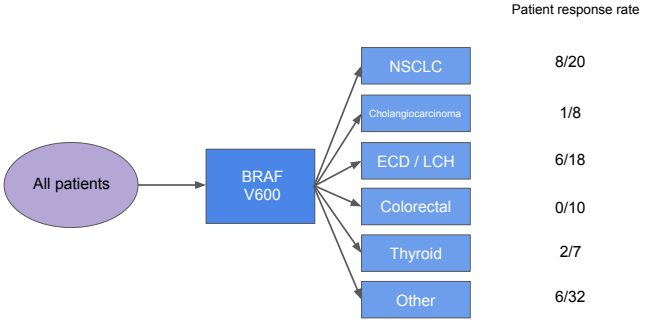
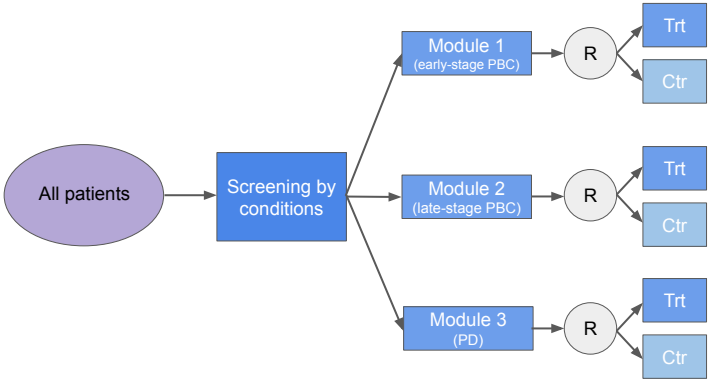


Potential analysis strategies:

- ⋆ Complete pooling
  (... fine if highly homogeneous)
- ⋆ Stand-alone analyses
- ⋆ Borrowing of information

Basket trials in chronic diseases – an example

The OACS trial in Newcastle upon Tyne (UK)



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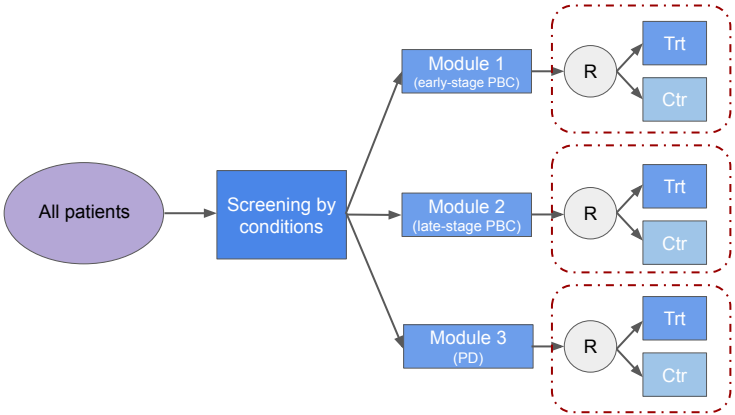

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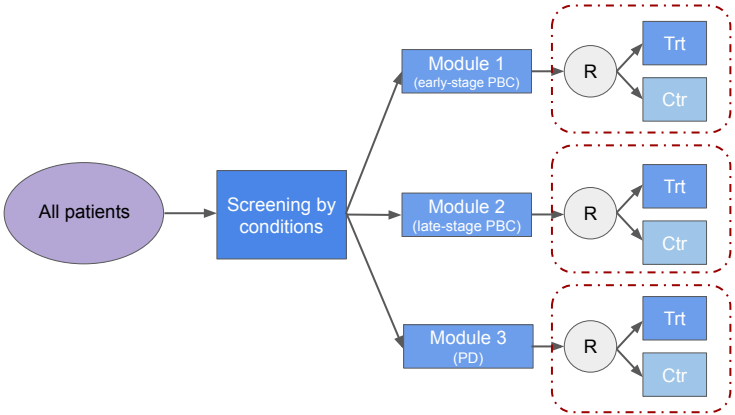
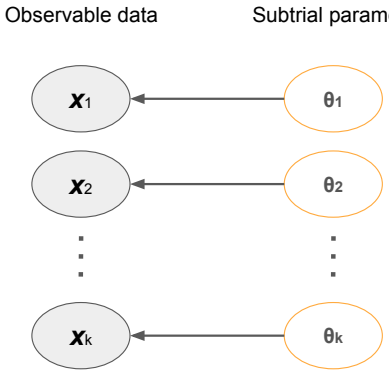


Complex data structure of basket trials



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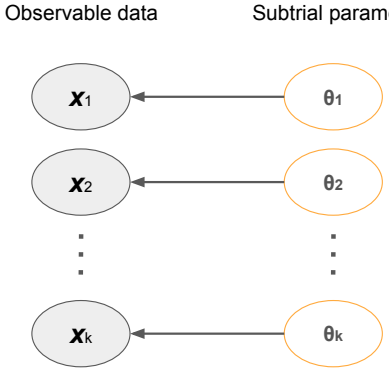

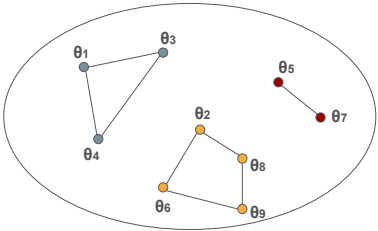

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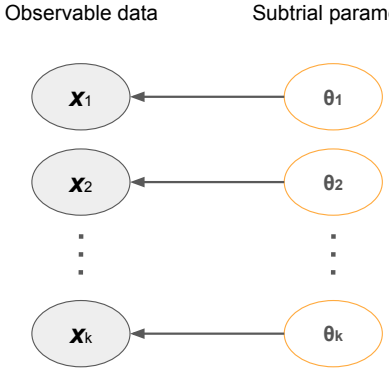
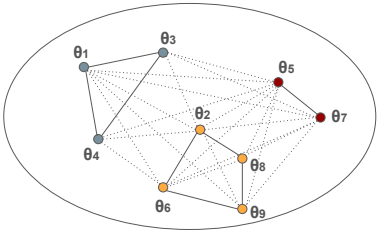
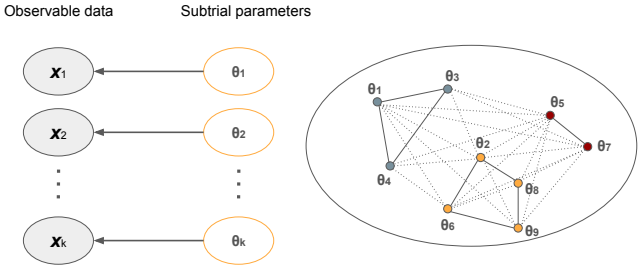




Accounting for pairwise commensurability (Zheng & Wason, 2022)



Robust borrowing of information:

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

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

$$\implies \theta_k \mid \theta_q \dot{\sim} N\left(\theta_q, \frac{w_{qk} b_1}{a_1 - 1} + \frac{(1 - w_{qk}) b_2}{a_2 - 1}\right), \quad \text{with } a_1, a_2 > 1.$$

With $b_1/a_1 \ll b_2/a_2$, setting $w_{qk} \to 0$ means strong borrowing and 1 means no borrowing *a priori* .

Obtain a collective prior, $\pi(\theta_k \mid \boldsymbol{x}_{(-k)})$

When $K \geq 3$, we **synthesise** the $(K-1)$ commensurate predictive priors $\pi(\theta_k \mid \boldsymbol{x}_q)$, $\forall q \neq k$.

Recall that w_{qk} can be regarded as the expected pairwise **discrepancy** and our approach features

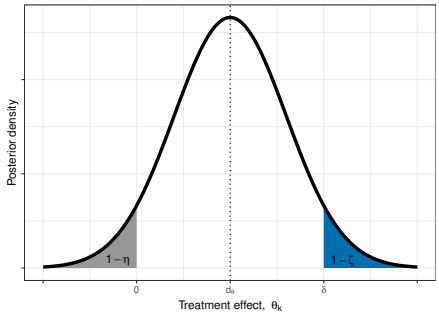
$$\begin{pmatrix} 0 & w_{12} & \cdots & w_{1K} \\ w_{21} & 0 & \cdots & w_{2K} \\ \vdots & \vdots & \ddots & \vdots \\ w_{K1} & w_{K2} & \cdots & 0 \end{pmatrix}.$$

We expect to assign the largest **synthesis weights**, p_{qk}, to one that has the smallest discrepancy.

A decreasing function can transform w_{qk} of each column into probability weights, with $\sum_q p_{qk} = 1$:

$$p_{qk} = \frac{\exp(-w_{qk}^2/r_0)}{\sum_q \exp(-w_{qk}^2/r_0)}, \qquad \forall k = 1, \ldots, K.$$

Decision making & sample size formulae (Zheng et al., 2022)



- ⋆ Compute two posterior interval probabilities:
  - (a) $\mathbb{P}(\theta_k > 0 \mid \boldsymbol{x}_k, \boldsymbol{x}_{(-k)}) \geq \eta$, and
  - (b) $\mathbb{P}(\theta_k < \delta \mid \boldsymbol{x}_k, \boldsymbol{x}_{(-k)}) \geq \zeta$,

  where both η and ζ are values close to 1.

The subtrial sample sizes $n_1, \ldots, n_k$ satisfy:

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

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

Evaluating a new inhibitor in $K = 7$ cancer subtypes

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

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

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

Based on the published results, we assume the outcome distributions

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

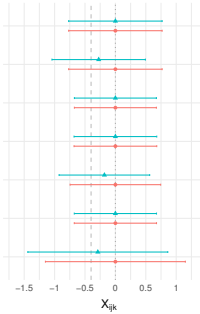
Compute w_{qk} as the pairwise Hellinger distance between $N(\mu_{Ek}, \sigma_k^2)$ and the synthesis weights p_{qk}.

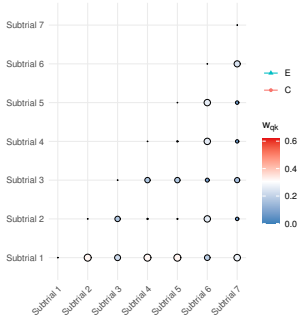
Set $\eta = 95\%, \zeta = 80\%$ and $\delta = -0.4$:

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

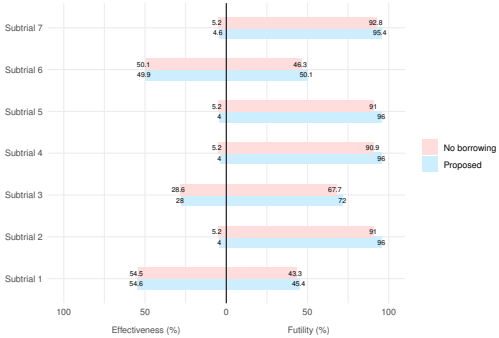
Simulation study (I)

Scenario 1



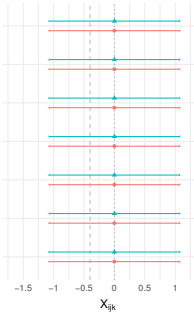


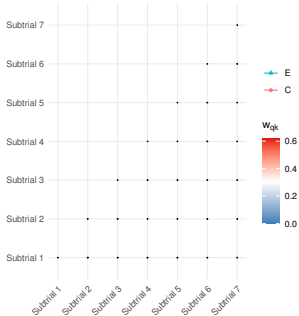
	n_k^0	n_k
	23.7	20.7
	23.7	22.1
	18.3	14.2
	18.6	14.5
	22.3	20.4
	18.4	14.3
	53.2	50.8
	178.2	**157.0**



Simulation study (II)

Scenario 2





	n_k^0	n_k
	46.4	8.9
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	46.4	8.9
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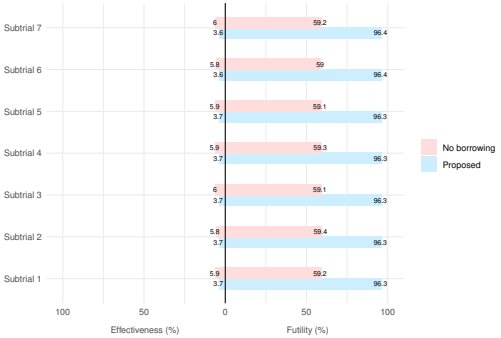
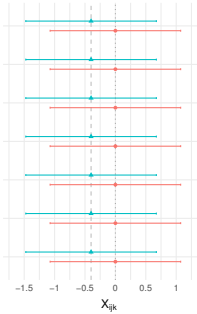
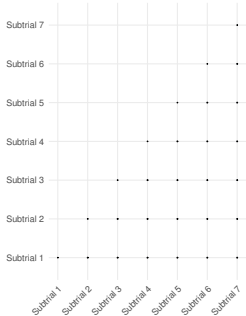
	324.8	**62.3**



Simulation study (III)

Scenario 3





	n_k^0	n_k
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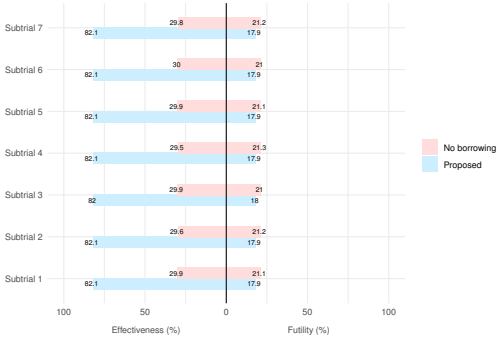
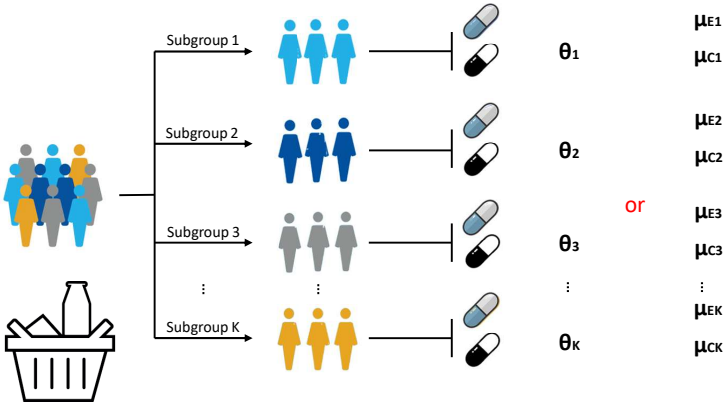


An alternative strategy for borrowing (Ouma et al., 2022)

Common mutation
the drug targets



The ongoing CRUK Fellowship Programme – IDENT

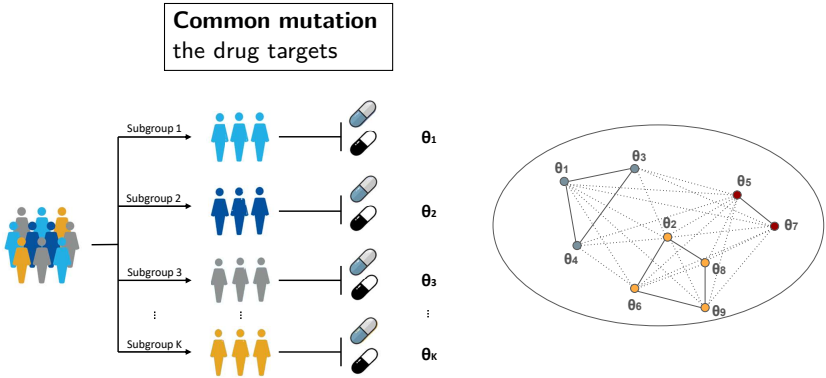


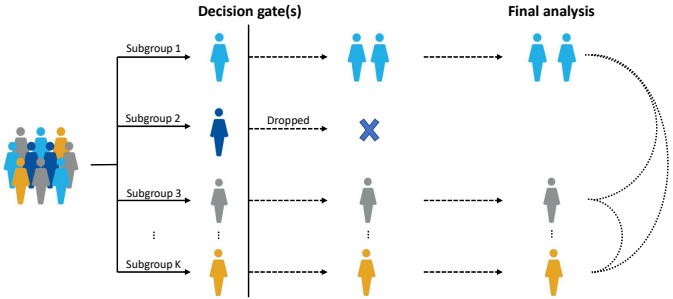
Figure: Basket trials that can establish a new treatment *faster* and at a *lower cost*

(A) Bayesian hierarchical models considering pairwise commensurability

(B) Sample size (re-)estimation

Next step: adaptive methods for multi-stage basket trials

- Sample size reassessment + early stopping for futility or efficacy (ongoing)
- Enrichment strategies
- Multiplicity considerations



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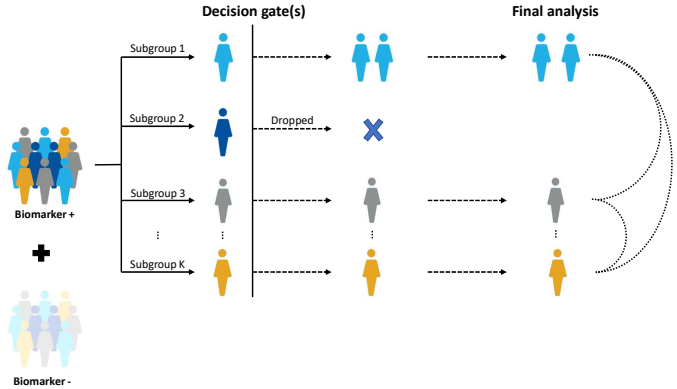

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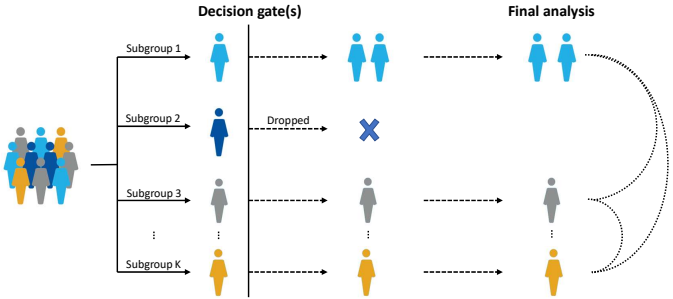

Key references

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.

'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.

Ouma LO, Grayling MJ, Wason JMS, Zheng H. (2022) Bayesian modelling strategies for borrowing of information in randomised basket trials *JRSS: Series C*. To appear.

Zheng H, Grayling MJ, Mozgunov P, Jaki T, Wason JMS. (2022) Bayesian sample size determination in basket trials borrowing information between subsets. *Biostatistics*. Epub ahead of print.

Zheng H, Jaki T, Wason JMS. (2022) 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.