

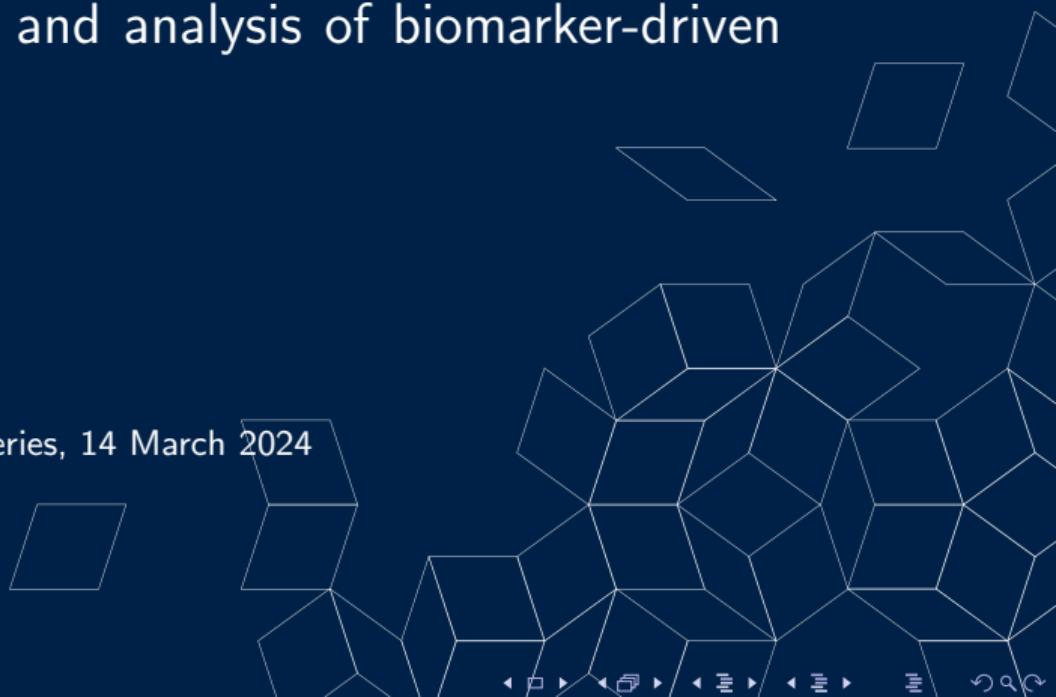


Improving statistical design and analysis of biomarker-driven clinical trials

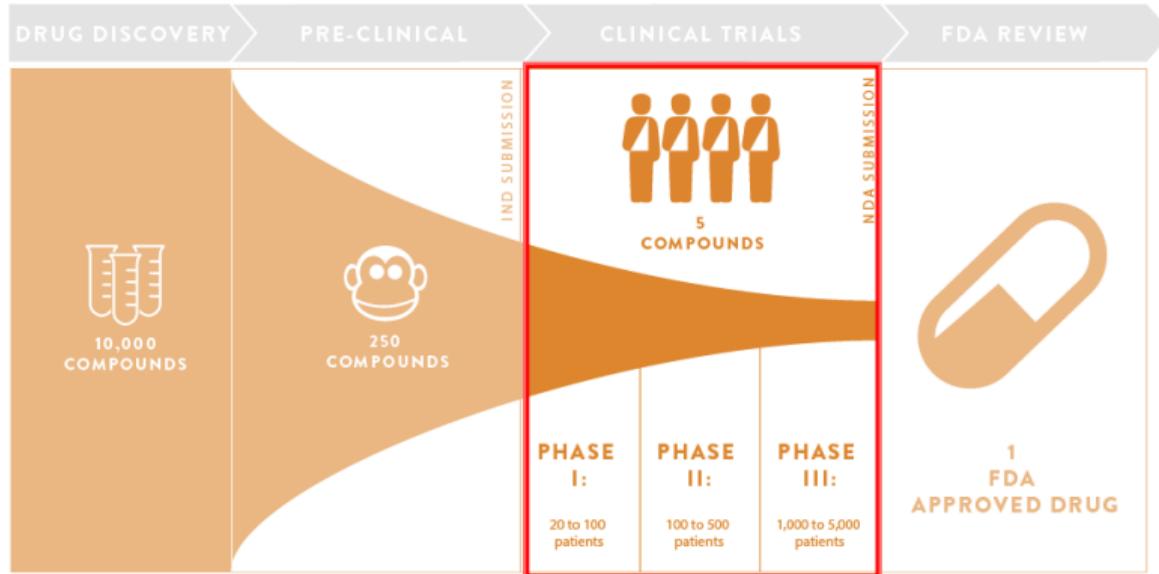
HAIYAN ZHENG

✉ hz2075@bath.ac.uk

Newcastle University Statistics Seminar Series, 14 March 2024



Drug development



Q: Does the drug work better than a placebo or the standard-of-care **on average?**

- ▶ **Biomarker:** e.g., measurable indicator of biological properties/genetic aberration
- ▶ **Molecular profiling** has become feasible and affordable → new biomarker data

Patient ID (i)	Treatment (T_i)	Outcome (Y_i)	Biomarker (B_i)
1	A	29.5	36.9
2	A	33.3	44.3
3	B	28.6	34.9
4	A	41.5	41.6
...
n	B	36.9	27.8

Major use in clinical trials

(i) outcome assessment (surrogate endpoint) **(ii) patient stratification**

- ▶ **Biomarker:** e.g., measurable indicator of biological properties/genetic aberration
- ▶ **Molecular profiling** has become feasible and affordable → new biomarker data

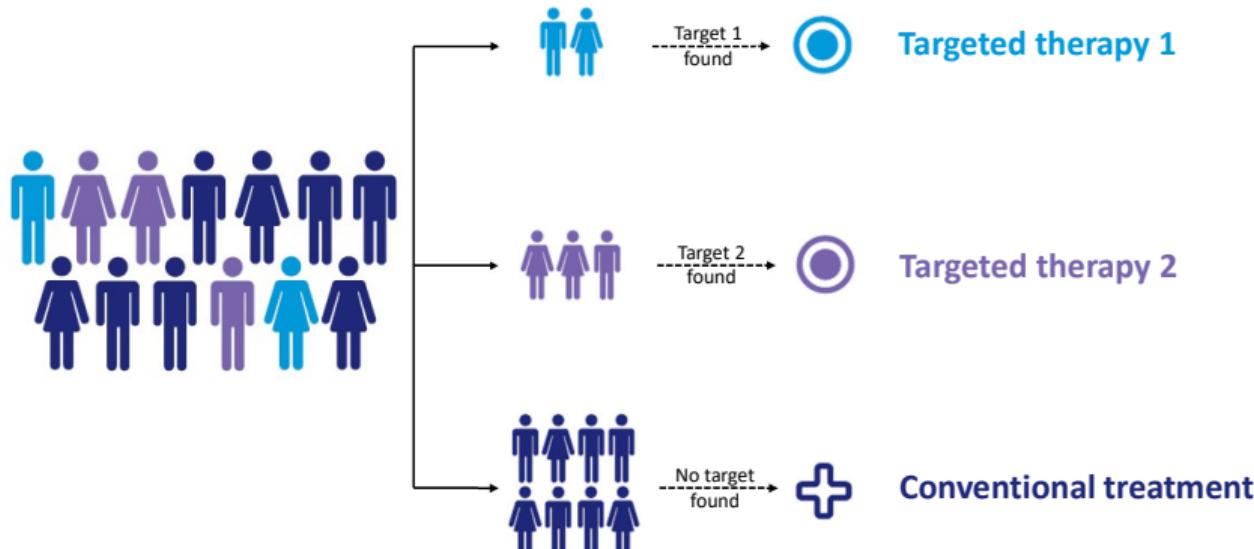
Patient ID (i)	Treatment (T_i)	Outcome (Y_i)	Biomarker (B_i)
1	A	29.5	36.9
2	A	33.3	44.3
3	B	28.6	34.9
4	A	41.5	41.6
...
n	B	36.9	27.8

Major use in clinical trials

(i) outcome assessment (surrogate endpoint) **(ii) patient stratification**

Precision medicine clinical trials

Right treatment for the right patients at the right time

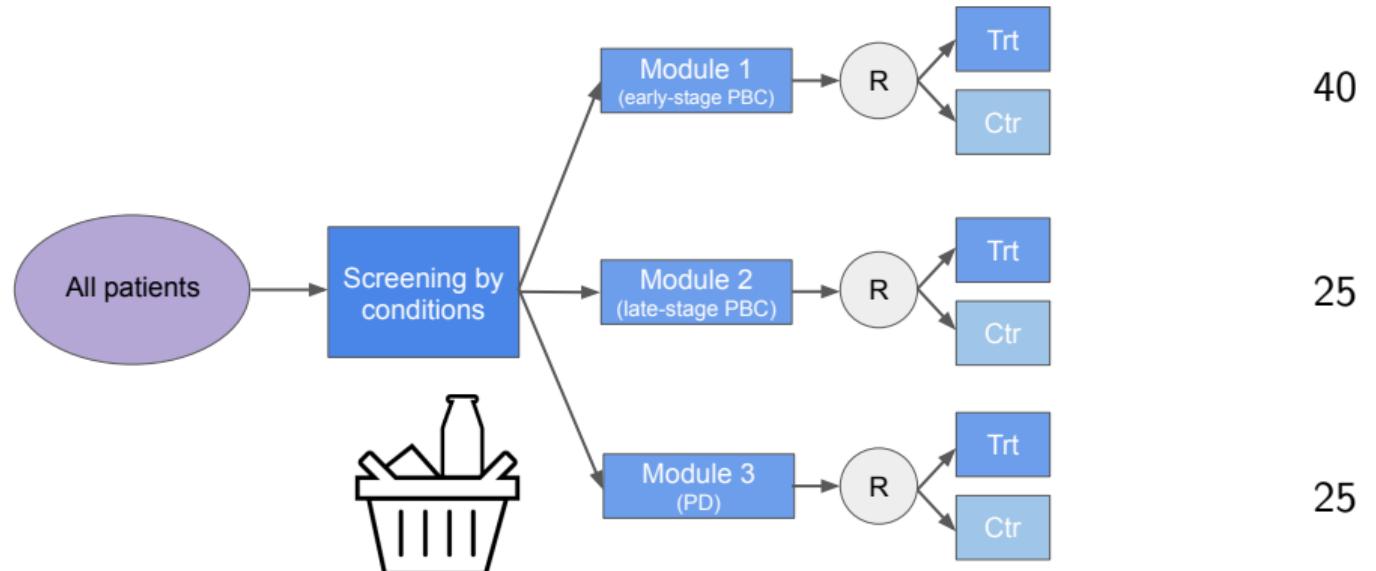


Q: Which subgroup(s) of patients can benefit and to what extent?

The OACS trial (in Newcastle!)

Evaluating an OCA therapy in chronic diseases

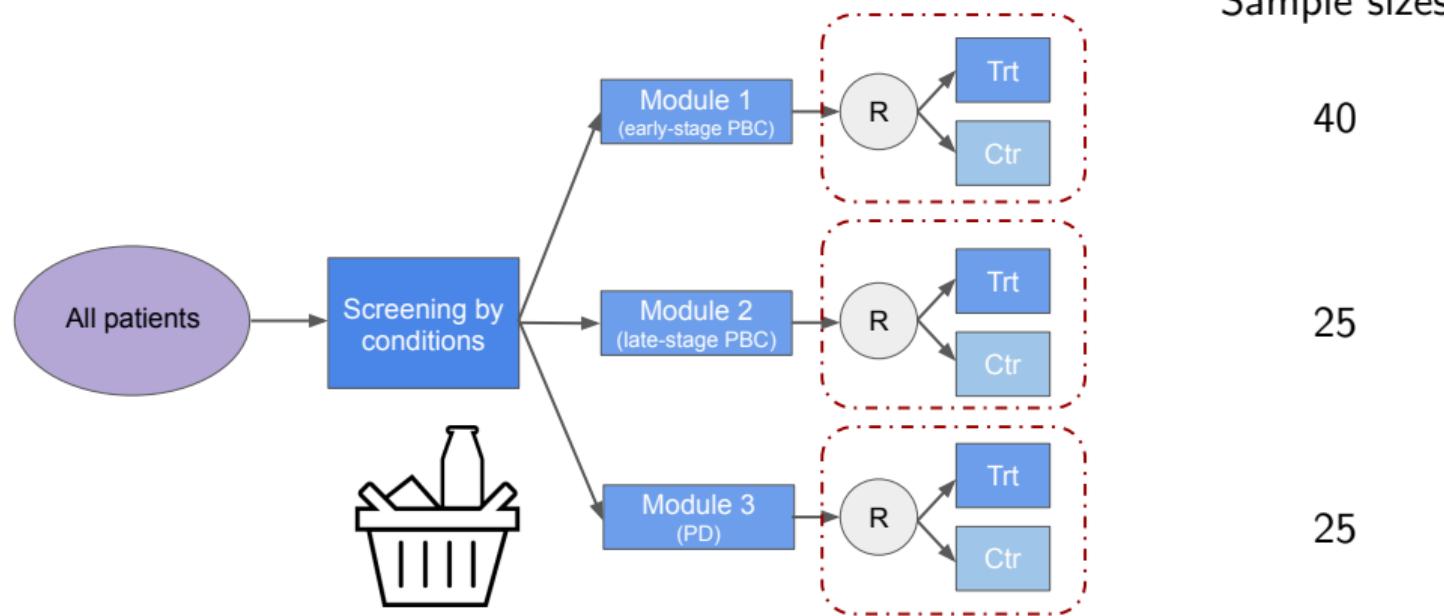
Primary outcome: a **continuous**, composite score to measure cognitive dysfunction
Sample sizes



The OACS trial (in Newcastle!)

Evaluating an OCA therapy in chronic diseases

Primary outcome: a **continuous**, composite score to measure cognitive dysfunction
Sample sizes

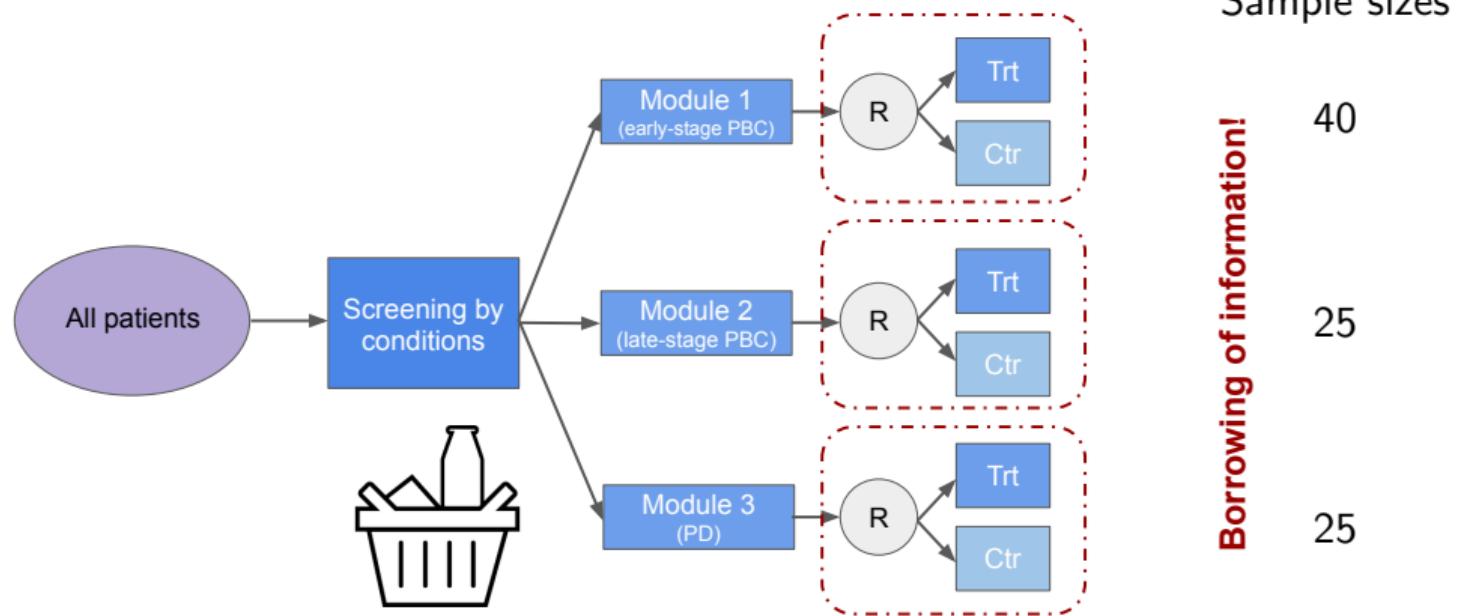


The OACS trial (in Newcastle!)

Evaluating an OCA therapy in chronic diseases

Primary outcome: a **continuous**, composite score to measure cognitive dysfunction

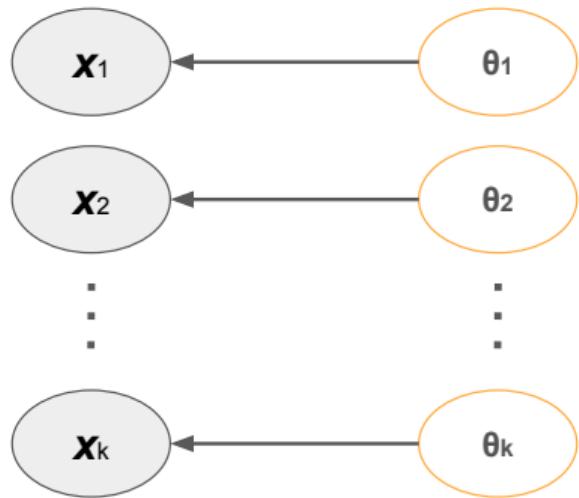
Sample sizes



Borrowing of information

Observable data

Subtrial parameters

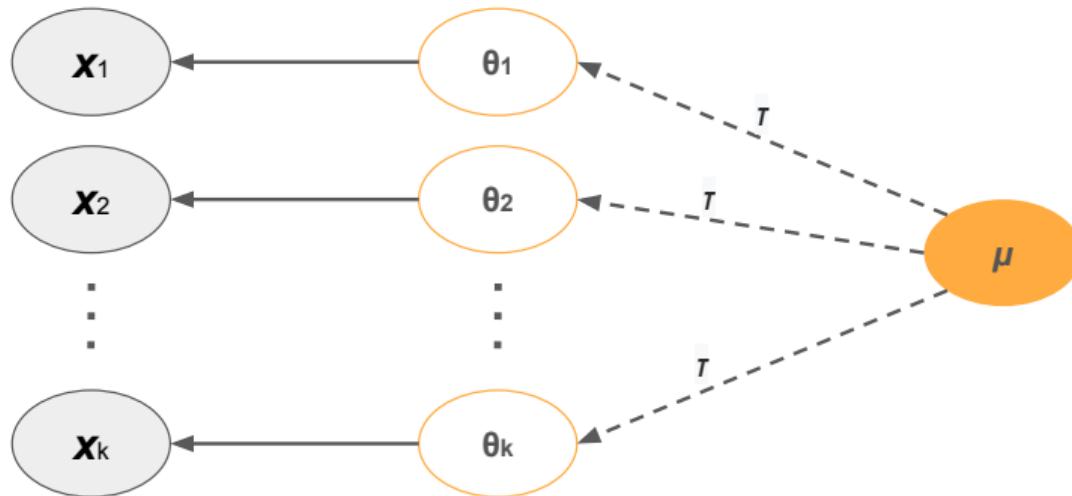


Borrowing of information

Observable data

Subtrial parameters

Population mean
(with shrinkage par.)



The degree of borrowing is determined by τ .

A normal-normal hierarchical model

Assume normally distributed data sorted by K sets



- ▶ Let X_{ijk} be measurements of patient i receiving treatment j within subtrial k .

$$X_{ijk} \mid \gamma_{jk}, \sigma_{jk}^2 \sim N(\gamma_{jk}, \sigma_{jk}^2), \text{ for } i = 1, \dots, n_{jk}; j = A, B,$$

$$\theta_k = \gamma_{Ak} - \gamma_{Bk}$$

$$\theta_k \mid \mu, \tau \sim N(\mu, \tau^2), \forall k = 1, \dots, K$$

- ▶ Assume $\theta_1, \dots, \theta_K$ are exchangeable (similar)
- ▶ The degree of borrowing is determined by τ
 - ▶ $\tau = 0$, complete pooling of data from other modules (identical parameters)
 - ▶ $\tau \rightarrow \infty$, no borrowing (independent parameters)

Robust extension to the parameter model:

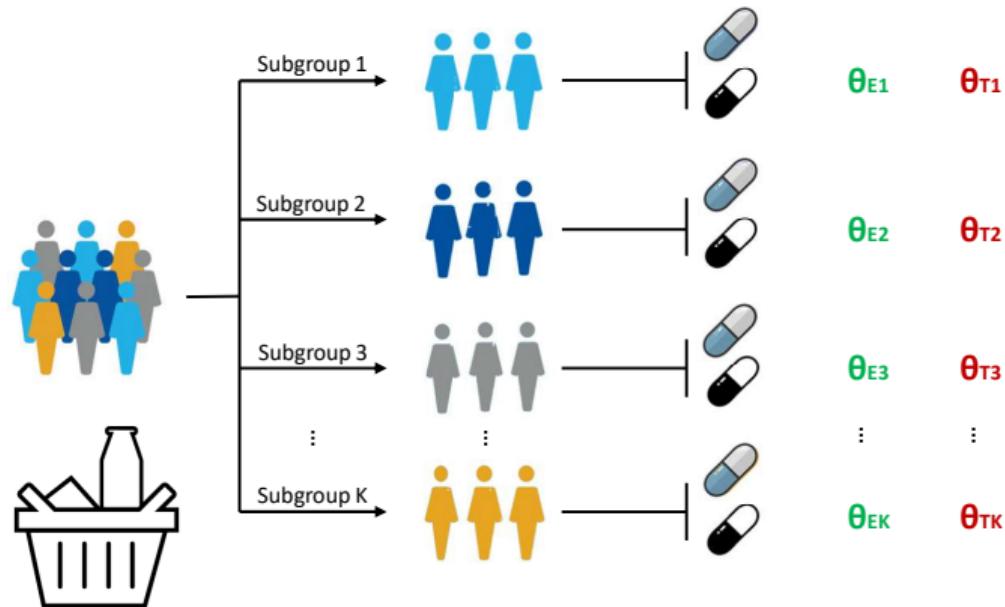
$$\theta_k \mid \mu, \tau \sim N(\mu, \tau^2), \forall k = 1, \dots, K$$

... with probability of 1!

to allow

- ▶ **EX**: $\theta_k \mid \mu, \tau \sim N(\mu, \tau^2)$ with probability of w_k
- ▶ **NEX**: $\theta_k \sim N(m_k, s_k^2)$ with probability of $1 - w_k$

Common mutation
the drug targets



Continuous efficacy + binary toxicity



- ▶ Let X_{ijk} be (continuous) efficacy measurements of patient $i = 1, \dots, n_{jk}$

$$X_{ijk} \mid \gamma_{jk}, \sigma_{jk}^2 \sim N(\gamma_{jk}, \sigma_{jk}^2), \text{ for } j = A, B$$

$$\theta_{E_k} = \gamma_{Ak} - \gamma_{Bk}$$

- ▶ Let Z_{jk} be the number of patients with toxicity out of n_{jk} receiving treatment j

$$Z_{jk} \sim \text{Binomial}(n_{jk}, p_{jk}), \text{ for } j = A, B,$$

$$\theta_{T_k} = \text{logit}(p_{Ak}) - \text{logit}(p_{Bk})$$

- ▶ Handle the subtrial-specific parameter vectors $(\theta_{E_k}, \theta_{T_k})$, $k = 1, \dots, K$

Proposal 1: BiEXNEX

Bivariate version of EXNEX



- **EX**: with probability w_k ,

$$\begin{pmatrix} \theta_{Ek} \\ \theta_{Tk} \end{pmatrix} \left| \begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix}, \begin{pmatrix} \phi_1 \\ \phi_2 \end{pmatrix}, \rho \right. \sim \mathcal{N} \left(\begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix}, \begin{pmatrix} \phi_1^2 & \rho\phi_1\phi_2 \\ \rho\phi_1\phi_2 & \phi_2^2 \end{pmatrix} \right) \quad (1)$$

- **NEX**: with probability $1 - w_k$,

$$\begin{pmatrix} \theta_{Ek} \\ \theta_{Tk} \end{pmatrix} \left| \kappa \right. \sim \mathcal{N} \left(\begin{pmatrix} m_{1k} \\ m_{2k} \end{pmatrix}, \begin{pmatrix} s_{1k}^2 & \kappa s_{1k}s_{2k} \\ \kappa s_{1k}s_{2k} & s_{2k}^2 \end{pmatrix} \right) \quad (2)$$

Proposal 2: E-BiEXNEX

Four-component mixture distributions



To further relax the exchangeability assumption:

- ▶ With probability λ_{1k} , both θ_{Ek} s and θ_{Tk} s are exchangeable,

$$\left(\begin{array}{c} \theta_{Ek} \\ \theta_{Tk} \end{array} \right) \middle| \left(\begin{array}{c} \beta_1 \\ \beta_2 \end{array} \right), \left(\begin{array}{c} \phi_1 \\ \phi_2 \end{array} \right), \rho \sim \mathcal{N} \left(\left(\begin{array}{c} \beta_1 \\ \beta_2 \end{array} \right), \left(\begin{array}{cc} \phi_1^2 & \rho\phi_1\phi_2 \\ \rho\phi_1\phi_2 & \phi_2^2 \end{array} \right) \right) \quad (3)$$

- ▶ With probability λ_{2k} , only θ_{Ek} s are exchangeable,

$$\left(\begin{array}{c} \theta_{Ek} \\ \theta_{Tk} \end{array} \right) \middle| \beta_1, \phi_1 \sim \mathcal{N} \left(\left(\begin{array}{c} \beta_1 \\ m_{2k} \end{array} \right), \left(\begin{array}{cc} \phi_1^2 & 0 \\ 0 & s_{2k}^2 \end{array} \right) \right) \quad (4)$$

Proposal 2: E-BiEXNEX (Cont'd)

Four-component mixture distributions



- With probability λ_{3k} , only θ_{Tk} s are exchangeable,

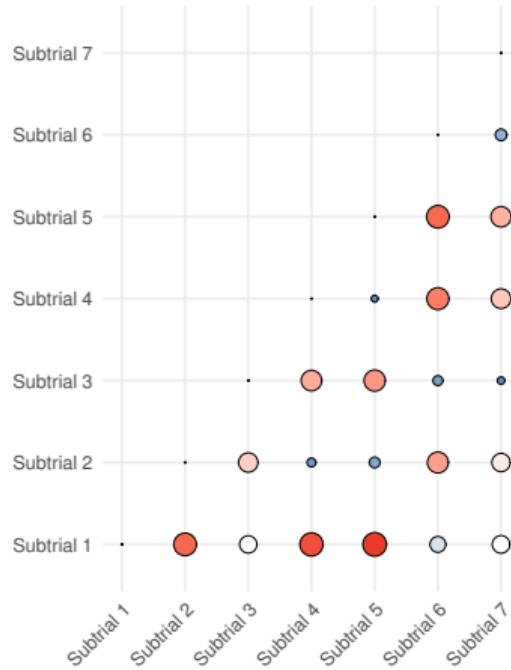
$$\begin{pmatrix} \theta_{Ek} \\ \theta_{Tk} \end{pmatrix} \middle| \beta_2, \phi_2 \sim \mathcal{N} \left(\begin{pmatrix} m_{1k} \\ \beta_2 \end{pmatrix}, \begin{pmatrix} s_{1k}^2 & 0 \\ 0 & \phi_2^2 \end{pmatrix} \right) \quad (5)$$

- With probability λ_{4k} , neither θ_{Ek} s nor θ_{Tk} s are exchangeable,

$$\begin{pmatrix} \theta_{Ek} \\ \theta_{Tk} \end{pmatrix} \middle| \kappa \sim \mathcal{N} \left(\begin{pmatrix} m_{1k} \\ m_{2k} \end{pmatrix}, \begin{pmatrix} s_{1k}^2 & \kappa s_{1k} s_{2k} \\ \kappa s_{1k} s_{2k} & s_{2k}^2 \end{pmatrix} \right) \quad (6)$$

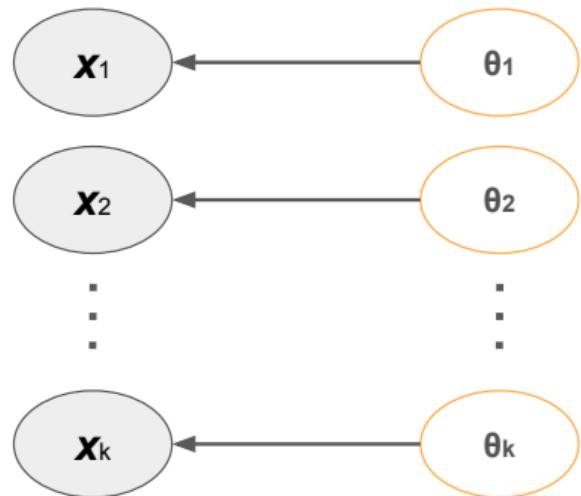
For each subtrial $k = 1, \dots, K$, $\sum_{\ell=1}^4 \lambda_{\ell k} = 1$ and $\lambda_{\ell k} \in (0, 1)$.

Pairwise (dis)similarity

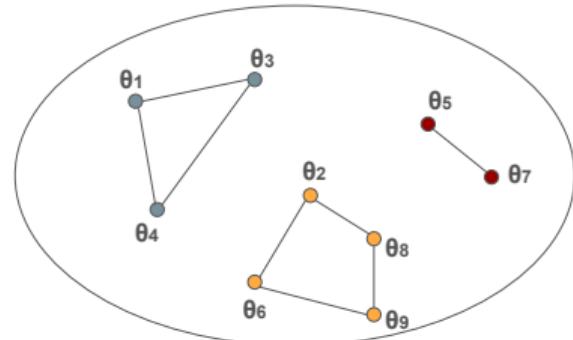


Complex data structure

Observable data

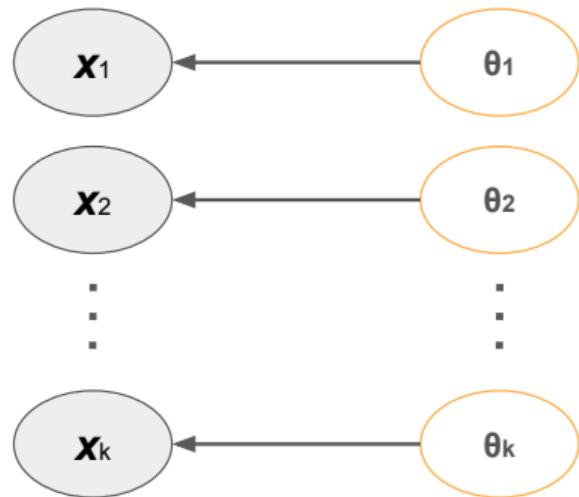


Subtrial parameters

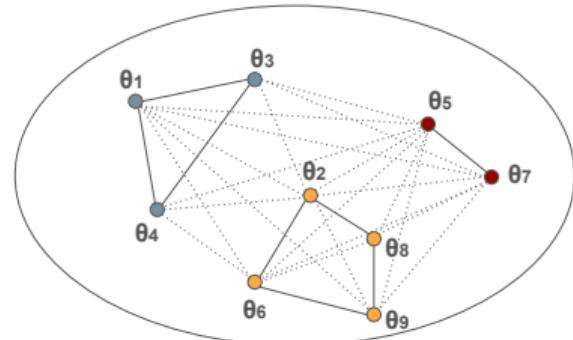


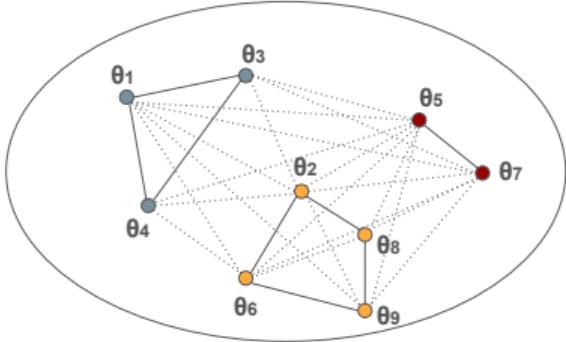
Complex data structure

Observable data



Subtrial parameters





Robust borrowing of information:

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

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

With $a_1/b_1 \ll a_2/b_2$, $w_{qk} \rightarrow 0$ means strong borrowing (small discrepancy)
 $\rightarrow 1$ no borrowing (large discrepancy) *a priori*.

Pairwise borrowing – a closer look

Zheng et al. (2023a, 2023b)



Integrating out ν_{qk} , we obtain

$$f(\theta_k \mid \theta_q) \propto w_{qk} \left(\frac{(\theta_k - \theta_q)^2}{2b_1} + 1 \right)^{-\frac{2a_1+1}{2}} + (1 - w_{qk}) \left(\frac{(\theta_k - \theta_q)^2}{2b_2} + 1 \right)^{-\frac{2a_2+1}{2}}.$$

By matching the first two moments,

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

Note that θ_q comes with uncertainty, and it leads to a predictive prior $\pi(\theta_k \mid \mathbf{x}_q)$.

Obtain a collective prior when $K \geq 3$



Recall that w_{qk} can be regarded as the expected pairwise **discrepancy**:

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

Assign the largest **synthesis weight**, p_{qk} , to a $\pi(\theta_k | \mathbf{x}_q)$ with the smallest discrepancy.

Transform w_{qk} of each column into probability weights that ensure $\sum_q p_{qk} = 1$:

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

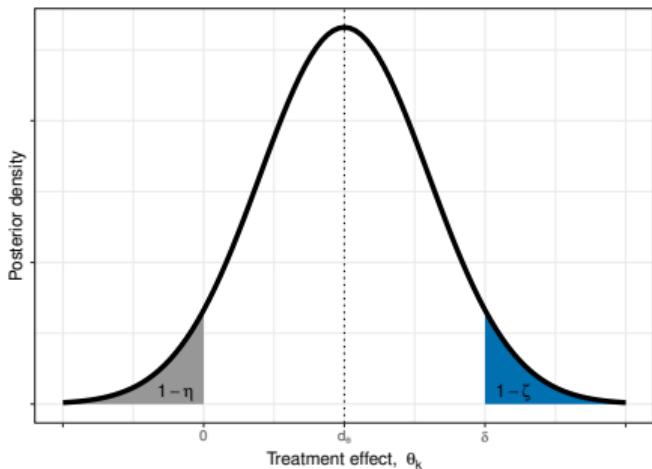
Trial decision criterion

Whitehead et al. (2008)

Data collected to provide convincing evidence

either that E is better than C

or that it fails to improve upon C by some clinically relevant difference, $\delta > 0$.



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

where both η and ζ are values close to 1.

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

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

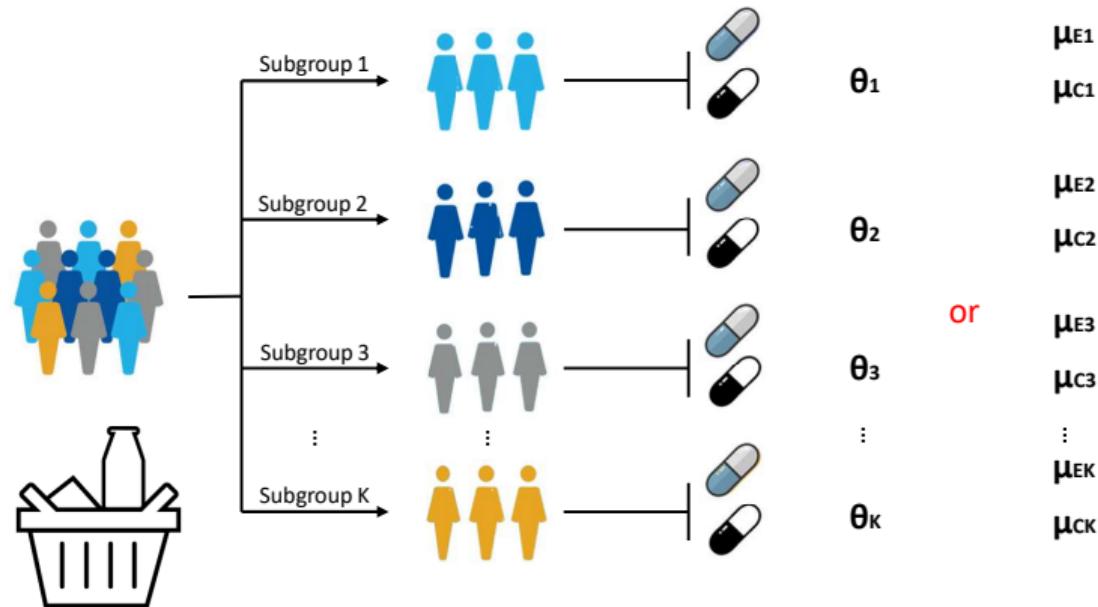
where R_k is the randomisation ratio to E within subtrial $k = 1, \dots, K$.

- * 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.

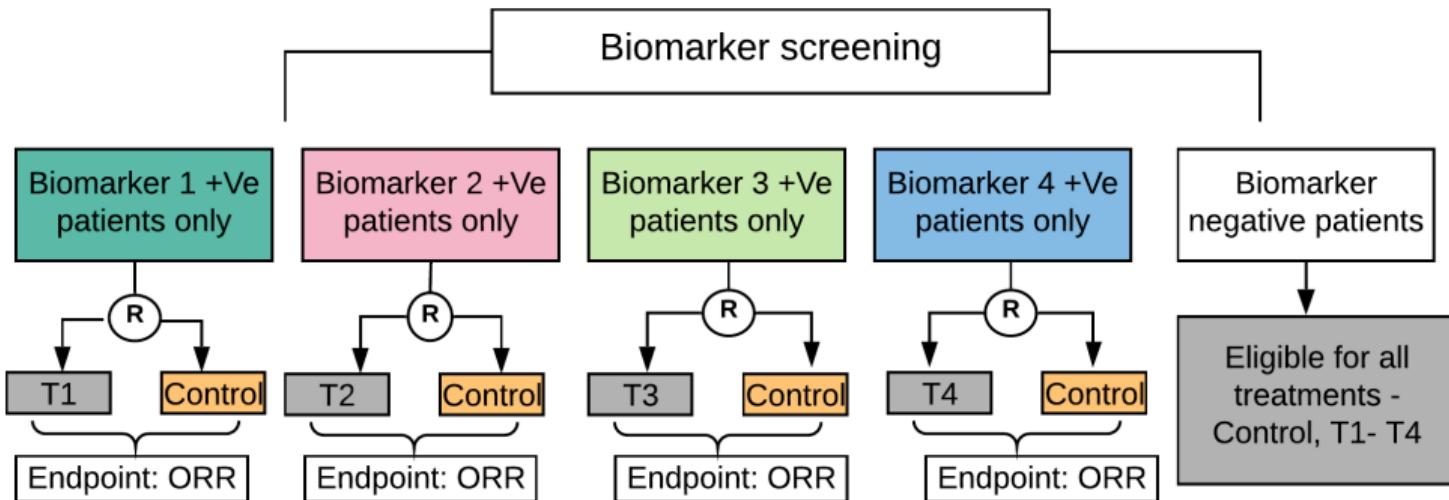
An alternative strategy for pairwise borrowing

Ouma et al. (2022)

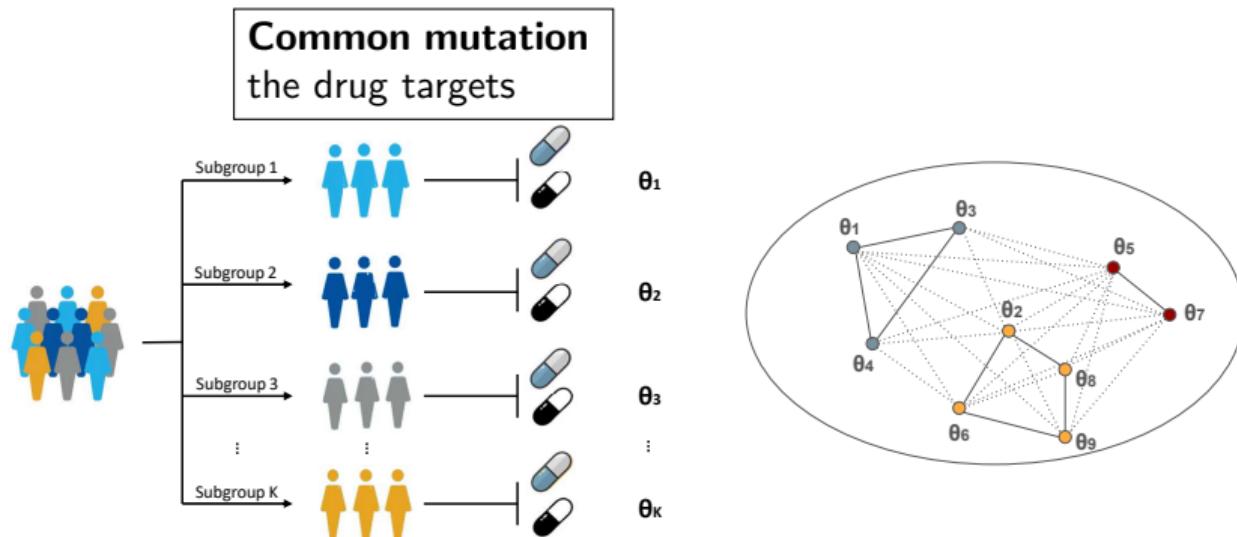


Umbrella trials: borrowing over control

Ouma et al. (2025+)



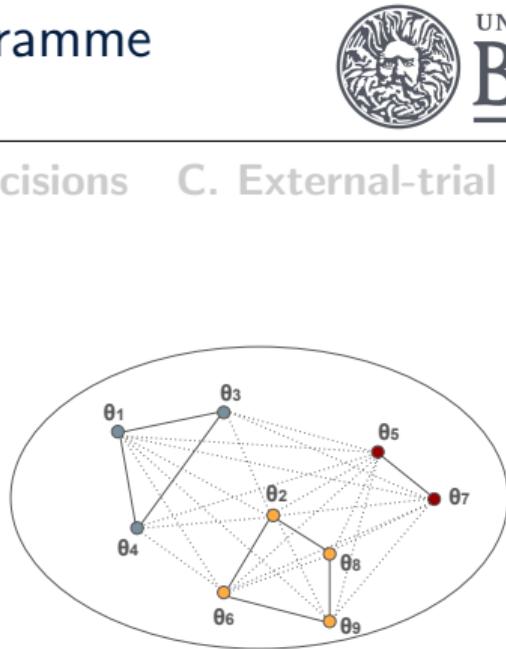
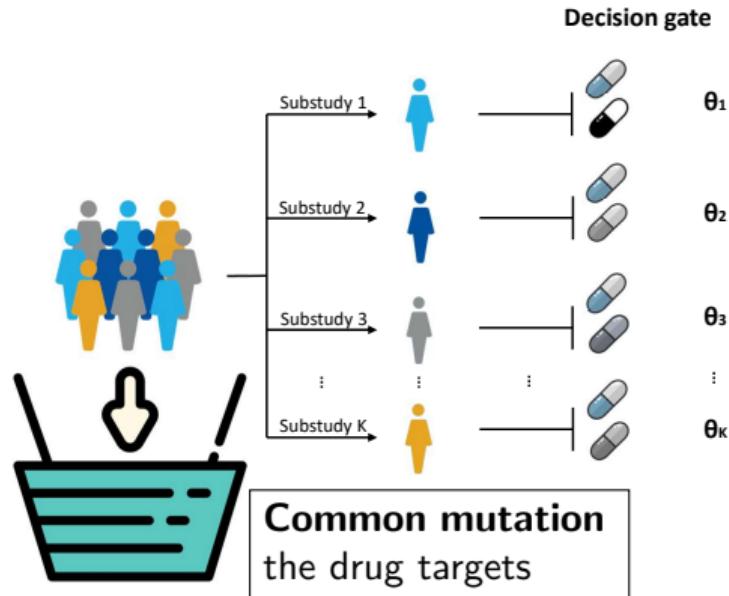
The CRUK-funded research programme IDENT (2021-2024)



- (A) Bayesian hierarchical models enabling pairwise borrowing of information
- (B) Sample size (re-)estimation

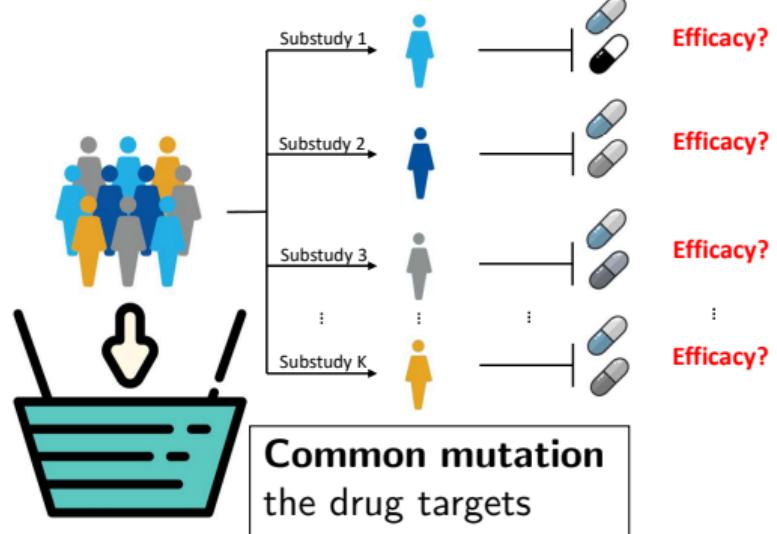
Newish CRUK-funded research programme STEEP (2024-2030)

A. Error rate control B. Sequential decisions C. External-trial data



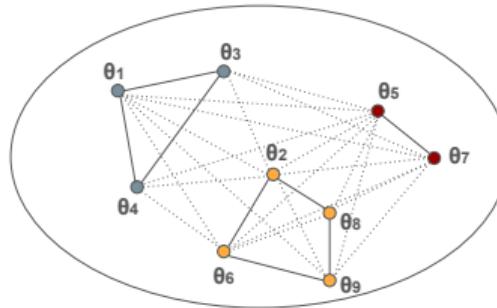
Newish CRUK-funded research programme STEEP (2024-2030)

A. Error rate control

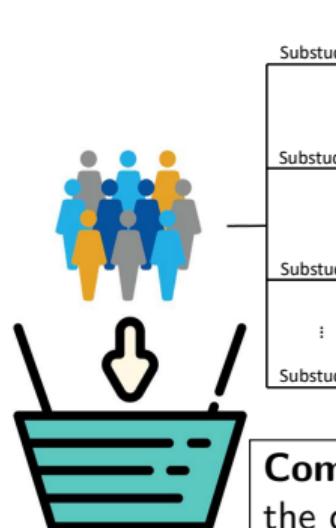


B. Sequential decisions

C. External-trial data

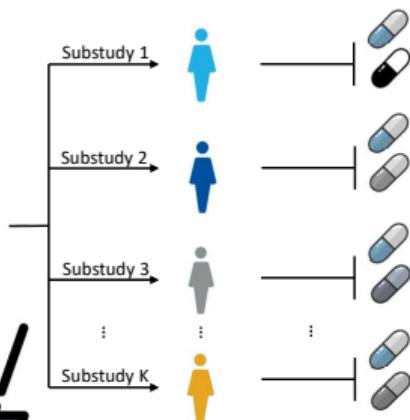


A. Error rate control



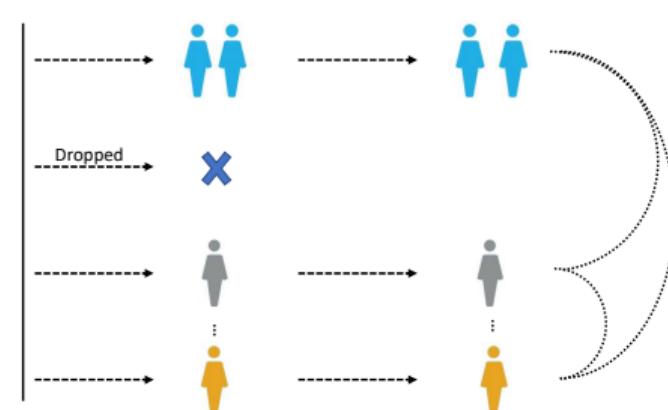
B. Sequential decisions

Decision gate(s)



C. External-trial data

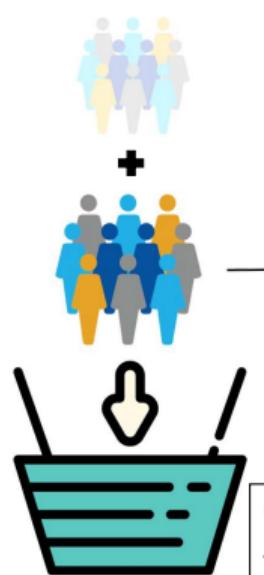
Final analysis



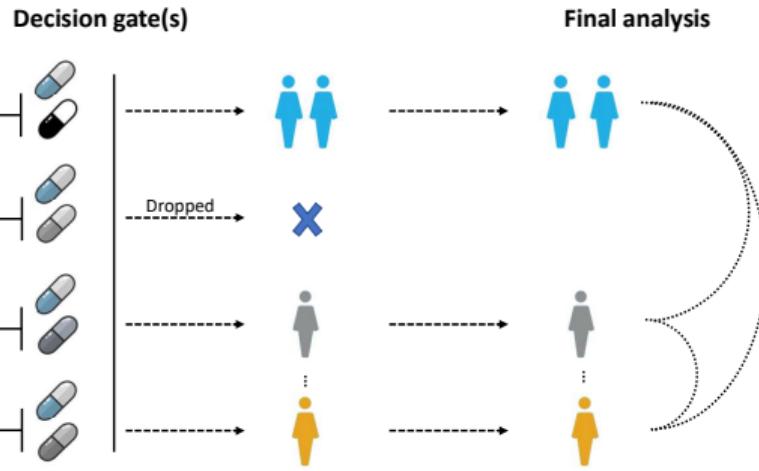
Common mutation
the drug targets

Newish CRUK-funded research programme STEEP (2024-2030)

A. Error rate control



B. Sequential decisions



C. External-trial data

Common mutation
the drug targets

Workshop at Bath, 5 June 2025

In-person & Online



<https://www.zhengh-stats.co.uk/events/m2p-workshop>



A hybrid Workshop on

Improving the Efficiency of Clinical Trials – from Methods to Practice

Theme 1: Master protocols and cluster randomised trials

Theme 2: Optimisation in adaptive designs

Confirmed Speakers:

Chris Jennison, University of Bath

Elias Laurin Meyer, Berry Consultants

Haiyan Zheng, University of Bath

Karim Anaya-Izquierdo, University of Bath

Lizzi Pitt, GlaxoSmithKline plc

Nick Berry, Berry Consultants

Peter Jacko, Berry Consultants

Tom Burnett, University of Bath

Tom Parke, Berry Consultants

Zhi Cao, University of Cambridge

References (I)

-  Neuenschwander B, Wandel S, Roychoudhury S, Bailey S. (2016) Robust exchangeability designs for early phase clinical trials with multiple strata. *Pharmaceut. Statist.*, 15: 123–134.
-  Ouma LO, Wason JMS, Zheng H, Wilson N, Grayling MJ. (2022) Design and analysis of umbrella trials: Where do we stand? *Frontiers in Medicine*, 9: 1037439.
-  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.
-  Whitehead J, Valdés-Márquez E, Johnson P, Graham G. (2008) Bayesian sample size for exploratory clinical trials incorporating historical data. *Statist. Med.*, 27: 2307-2327.
-  Zheng H, Wason JMS. (2022) Borrowing of information across patient subgroups in a basket trial based on distributional discrepancy. *Biostatistics*, 23(1):120-135.

References (II)

-  Zheng H, Jaki T, Wason JMS. (2023a) Bayesian sample size determination using commensurate priors to leverage preexperimental data. *Biometrics*, 79(2): 669-683.
-  Zheng H, Grayling MJ, Mozgunov P, Jaki T, Wason JMS. (2023b) Bayesian sample size determination in basket trials borrowing information between subsets. *Biostatistics*, 24(4): 1000-1016.
-  Whitehead LE, Wason JMS, Sailer O, Zheng H. (2024+) Bayesian sample size determination using robust commensurate priors with interpretable discrepancy weights. arXiv: 2401.10592
-  Cao Z, Mozgunov P, Zheng H. (2025+) Robust Bayesian hierarchical models for basket trials enabling joint evaluation of toxicity and efficacy. To submit.
-  Ouma LO, Zheng H, Grayling MJ, Wason JMS. (2025+) A two-stage Bayesian adaptive umbrella design borrowing information over control data. To submit.