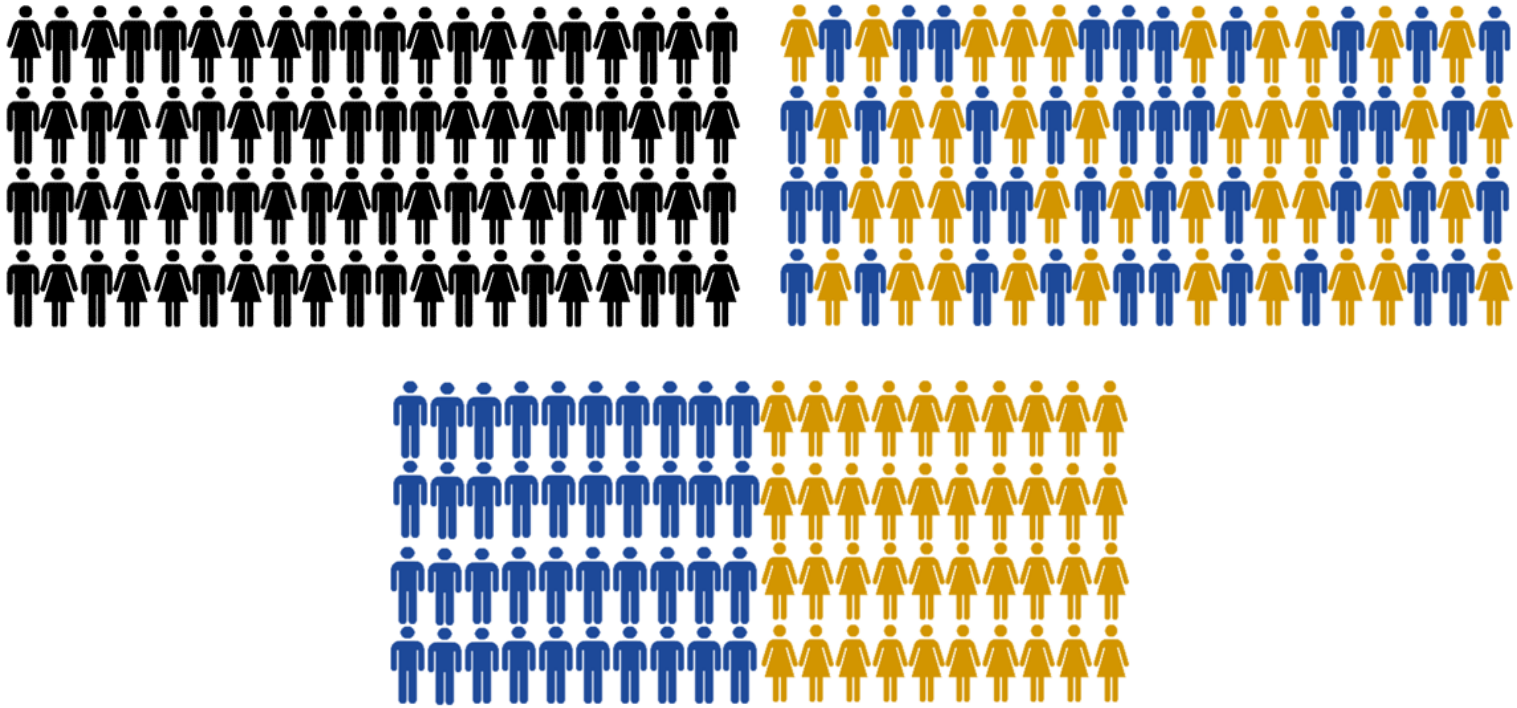
Adaptive Enrichment Designs for Clinical Trials

Thomas Burnett
University of Bath

30/1/2017

Pre-identified sub-populations



$H_{01} : \theta_1 \leq 0$ $H_{02} : \theta_2 \leq 0$

$H_{03} : \theta_3 \leq 0$ where $\theta_3 = \lambda\theta_1 + (1 - \lambda)\theta_2$

Conducting Adaptive Enrichment

Pre-interim recruitment

Post-interim recruitment

$H_{01} : \theta_1 \leq 0$

$H_{02} : \theta_2 \leq 0$

$H_{01} : \theta_1 \leq 0$

$H_{02} : \theta_2 \leq 0$

Defining FWER

$\mathbb{P}_{\boldsymbol{\theta}}$(Reject any combination of true null hypotheses) for all $\boldsymbol{\theta}$

True null hypotheses	Familywise error to reject
H_{01}	H_{01}
H_{02}	H_{02}
H_{01} and H_{02}	H_{01}, H_{02} or both

Achieving strong control of FWER

$\mathbb{P}_{\boldsymbol{\theta}}(\text{Reject any combination of true null hypotheses}) \leq \alpha$ for all $\boldsymbol{\theta}$

To achieve this we require:

- If H_{01} true, $\mathbb{P}(\text{Reject } H_{01}) \leq \alpha$
- If H_{02} true, $\mathbb{P}(\text{Reject } H_{02}) \leq \alpha$
- If H_{01} and H_{02} true, $\mathbb{P}(\text{Reject both } H_{01} \text{ and } H_{02}) \leq \alpha$

The Bonferroni correction where both H_{01} and H_{02} are tested at $\alpha/2$ is the simplest procedure that ensures strong control of the FWER.

Closed testing procedures

For testing H_{01} and H_{02} we construct level α tests for

- $H_{01} : \theta_1 \leq 0$,
- $H_{02} : \theta_2 \leq 0$,
- $H_{01} \cap H_{02} : \theta_1 \leq 0$ and $\theta_2 \leq 0$.

Then:

- Reject H_{01} globally if H_{01} and $H_{01} \cap H_{02}$ are both rejected.
- Reject H_{01} globally if H_{01} and $H_{01} \cap H_{02}$ are both rejected.

Simes rule and the method proposed by Dunnett provide two methods for testing the intersection hypothesis that are suitable for Adaptive Enrichment designs.

Combination tests

Suppose $P^{(1)}$ and $P^{(2)}$ are the p-values from the first and second stages of the trial. Using the weighted inverse Normal we find $P^{(c)}$ the p-value for the whole trial.

$$Z^{(1)} = \phi^{-1}(1 - P^{(1)}) \text{ and } Z^{(2)} = \phi^{-1}(1 - P^{(2)})$$

$$\text{With } w_1 \text{ and } w_2 \text{ such that } w_1^2 + w_2^2 = 1$$

$$Z^{(c)} = w_1 Z^{(1)} + w_2 Z^{(2)}$$

$$P^{(c)} = 1 - \phi(Z^{(c)})$$

Choosing w_1 and w_2 in proportion to the sample size from each stage gives the optimal procedure.

Overall testing procedure

	H_{01}	H_{02}	$H_{01} \cap H_{02}$
Pre-interim recruitment cohort	$p_1^{(1)}$	$p_2^{(1)}$	$p_{12}^{(1)}$
Post-interim recruitment cohort	$p_1^{(2)}$	$p_2^{(2)}$	$p_{12}^{(2)}$
Overall	$p_1^{(c)}$	$p_2^{(c)}$	$p_{12}^{(c)}$

Optimisation components

Prior distribution:

$$\pi(\boldsymbol{\theta})$$

Utility function (gain):

$$G(\boldsymbol{\theta}) = \gamma_1(\theta_1)\mathbb{I}(\text{Reject } H_{01}) + \gamma_2(\theta_2)\mathbb{I}(\text{Reject } H_{02})$$

Simple optimisation

$$\mathbb{E}_{\pi(\boldsymbol{\theta})}(G(\boldsymbol{\theta}))$$

Bayes optimal decision

Data available at the interim analysis:

$$X$$

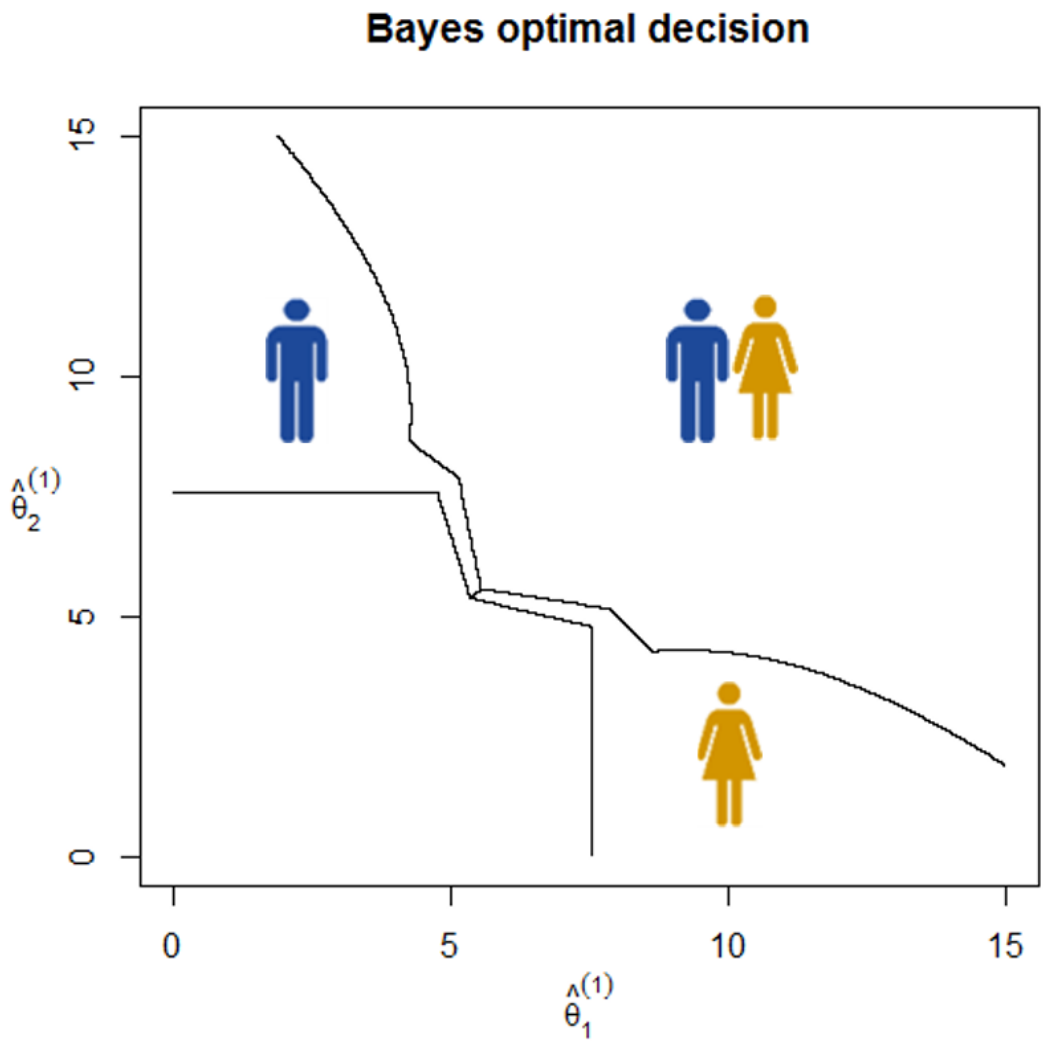
Bayes expected gain:

$$\mathbb{E}_{\pi(\theta),X}(G(\theta))$$

Choose sub-population that maximises $\mathbb{E}_{\pi(\theta),X}(G(\theta))$

Bayes optimal rule

$$\mathbb{E}_{\pi(\theta),X}(G(\theta))$$



Key points

- Strong control of FWER
- Prior distribution
- Gain function
- $\mathbb{E}_{\pi(\boldsymbol{\theta}),X}(G(\boldsymbol{\theta}))$ for optimisation
- $\mathbb{E}_{\pi(\boldsymbol{\theta})}(G(\boldsymbol{\theta}))$ for overall behaviour