

# Adaptive Enrichment Designs for Clinical Trials

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# Overview

What is Adaptive Enrichment

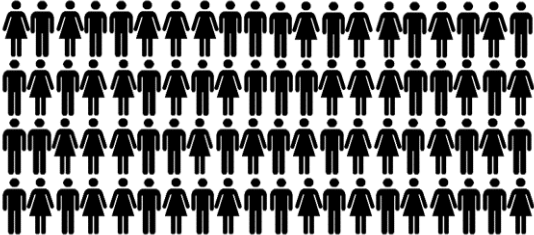
Familywise Error Rate (FWER)

Hypothesis testing

Bayes optimal decisions

# What is Adaptive Enrichment

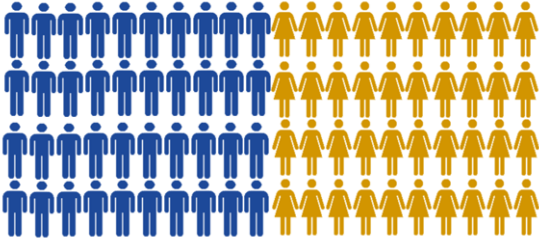
# Pre-identified sub-populations



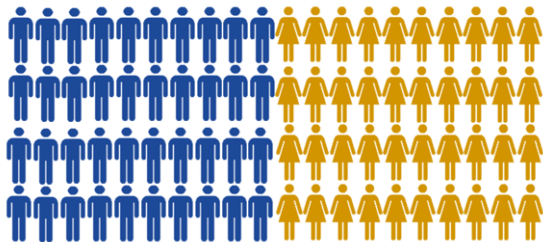
## Pre-identified sub-populations



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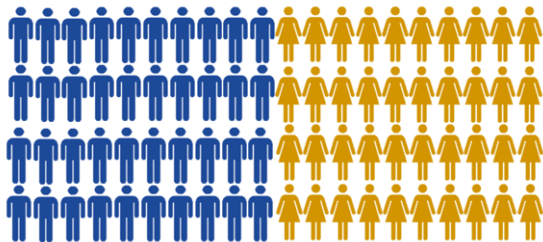
## Pre-identified sub-populations



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

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

## Pre-identified sub-populations



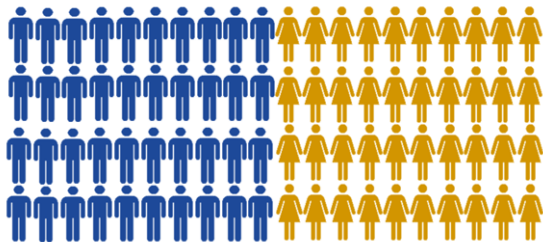
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$$H_{03} : \theta_3 \leq 0 \text{ where } \theta_3 = \lambda\theta_1 + (1 - \lambda)\theta_2$$



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# Conducting Adaptive Enrichment

Pre-interim recruitment

Post-interim recruitment

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# Conducting Adaptive Enrichment

Pre-interim recruitment



Post-interim recruitment



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

Familywise Error Rate (FWER)

## Defining FWER

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



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

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

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

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- ▶ 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.

# Hypothesis testing

## Closed testing procedures

For testing  $H_{01}$  and  $H_{02}$  we construct level  $\alpha$  tests for

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

Then:

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

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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.

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

With  $w_1$  and  $w_2$  such that  $w_1^2 + w_2^2 = 1$

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

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



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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	$p_1^{(c)}$	$p_2^{(c)}$	$p_{12}^{(c)}$

## Bayes optimal decisions

# Optimisation components

Prior distribution:

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

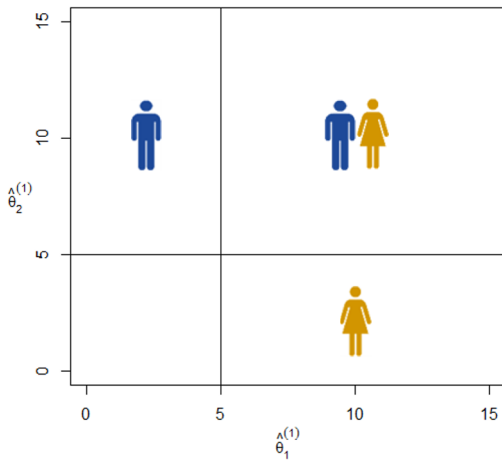
Utility function (gain):

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

# Simple optimisation

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

**Simple decision rule**



# Bayes optimal decision

Data available at the interim analysis:

$$X$$

Bayes expected gain:

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



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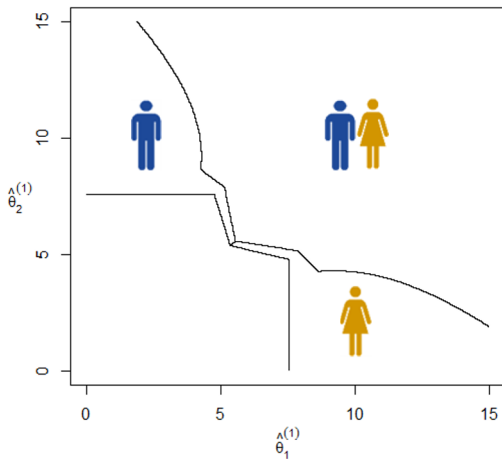


Choose sub-population that maximises  $\mathbb{E}_{\pi(\theta), X}(G(\theta))$

# Bayes optimal rule

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

**Bayes optimal decision**





## Key points

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

Any questions?