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# Case Studies and Exemplars of Efficient Study Designs in Clinical Trials

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# Introduction

- Definition of an Efficient Design
- Case studies
  - Replication
  - PLEASANT
  - Using early data
  - RATPAC (Re-analysis)
  - Adaptive Designs
  - Futility
- Discussion and Conclusions



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**What is an Efficient Design?**

- An umbrella term for smarter ways of doing trials
- Using routine data
- Early data
- Being adaptive
- Simple design enhancements

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# Replication in Cross-over trials



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# Replication in Cross-over studies

- A two treatment cross-over study may be done in a two period study of two sequences AB BA
- Is the AB BA design out of tune with what is required?
  - A three period replicate design would require 25% less patients
  - A four period replicated design 50% less

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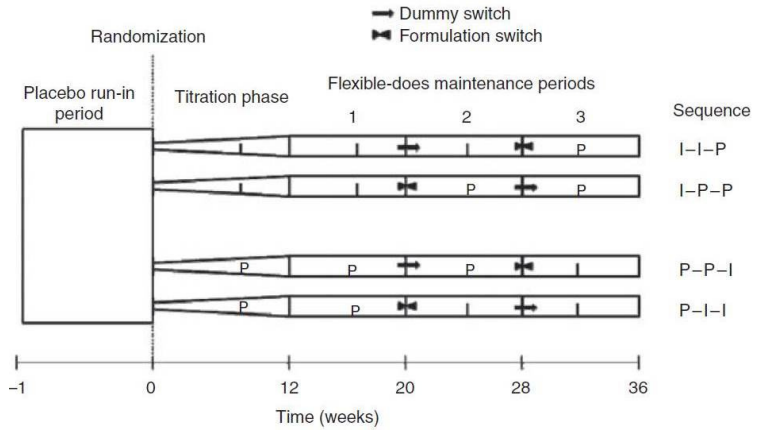
# Comparison or two formulations of Ropinerole



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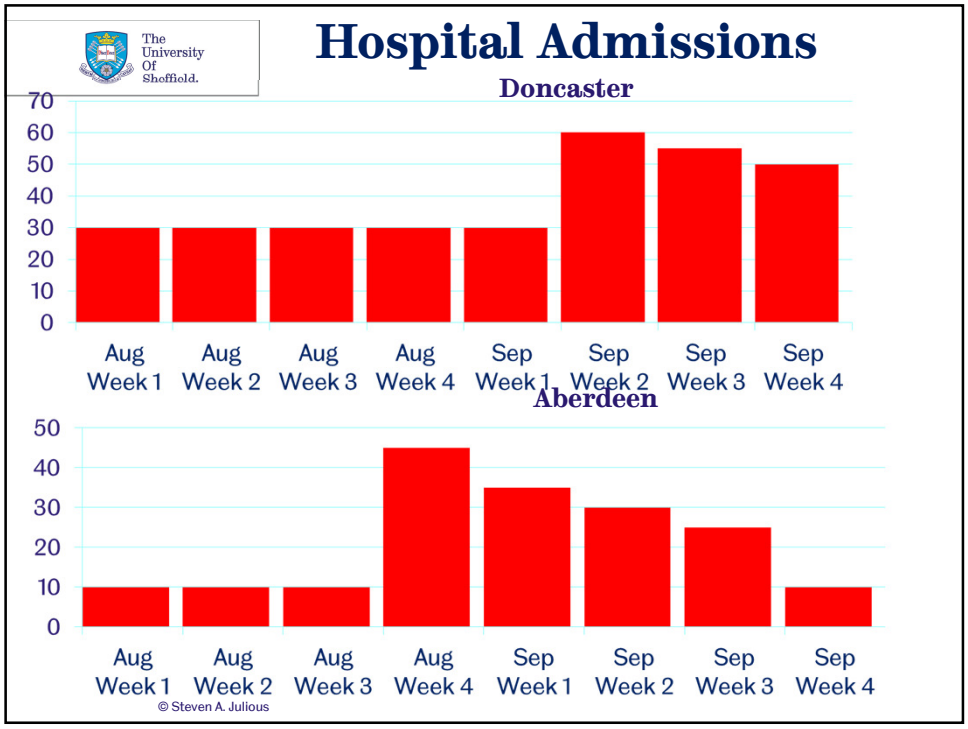
# Using Routine Data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Hospital Admissions
Doncaster
70
60
50
40
30
20
10
0
Aug Week 1
Aug Week 2
Aug Week 3
Aug Week 4
Sep Week 1
Sep Week 2
Sep Week 3
Sep Week 4
Aberdeen
50
40
30
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Aug Week 1
Aug Week 2
Aug Week 3
Aug Week 4
Sep Week 1
Sep Week 2
Sep Week 3
Sep Week 4
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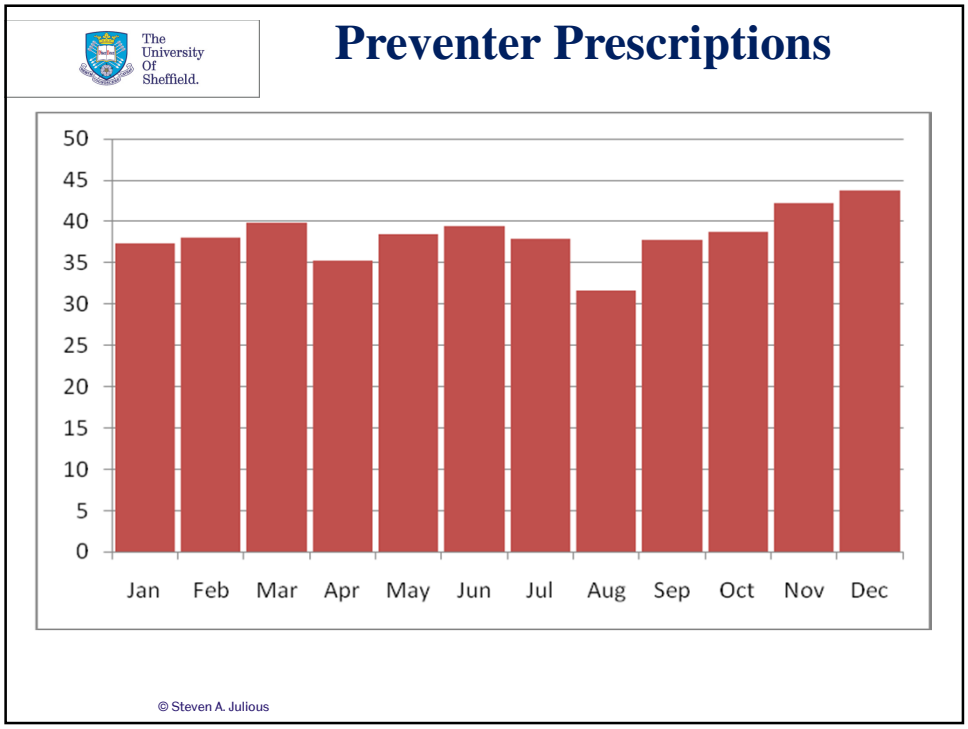
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Preventer Prescriptions
50
45
40
35
30
25
20
15
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Jan
Feb
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May
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Jul
Aug
Sep
Oct
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Dec
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# **P**reventing and **L**essening **E**xacerbations of **A**sthma in **S**chool-age children **A**ssociated with a **N**ew **T**erm



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PLEASANT

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# The PLEASANT Trial

- It is a National Health Service (NHS) delivered public health intervention in a primary care setting in 142 GP practices
- Used routine data and the Clinical Practice Research Datalink (CPRD) to collect the data
- More efficient than need to contact individual practices to collect data



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# Adaptive Design Case Study

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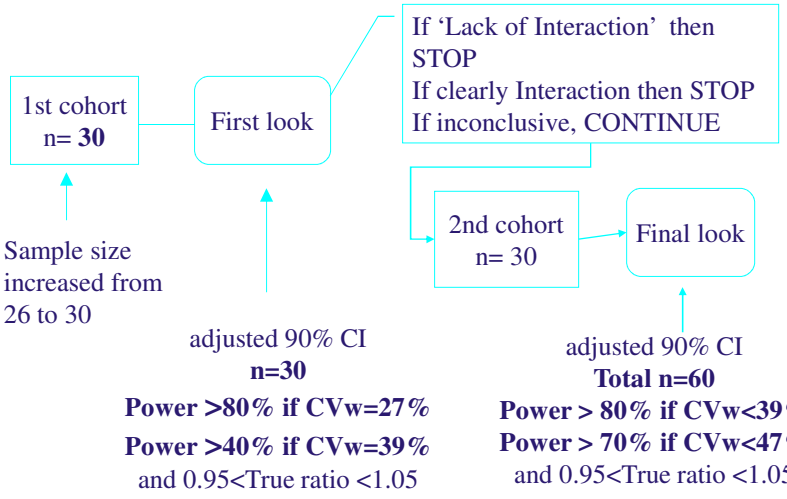
# Group Sequential Design - Concept



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# What was Good About this Study?

## Recruitment was Controlled by the Sponsor

- Subjects were recruited and enrolled into a single centre and a rate fixed by sponsor
  - Planning for the analysis was straightforward
  - Time lines preset
- How much more time consuming if this is not the case?
- What if recruitment continued whilst interim taking place?



## Endpoint in the Interim Analysis was the Same as in the Final Analysis

- Could be using a surrogate
  - For example an imaging endpoint for interim analysis
  - Or the main outcome measured at an earlier time point...

•Could analyse a primary endpoint but assessed at an earlier time point

•How predictive is this of response?

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# A Cohort Randomised Trial



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# Example Dosing Cohorts

Cohort 1

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D1 | D1 | D1 | D1 | D1 | D1 | D1 | D1 | D1 | D1 | D1 | D1 | P | P | P | P | P | P |

Cohort 2

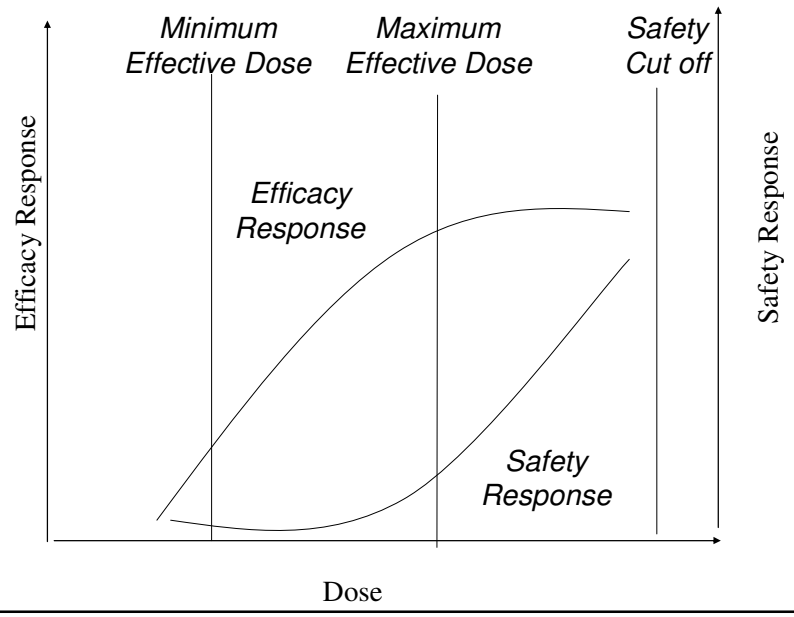
| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D2 | D2 | D2 | D2 | D2 | D2 | D2 | D2 | D2 | D2 | D2 | D2 | P | P | P | P | P | P |

Cohort 3

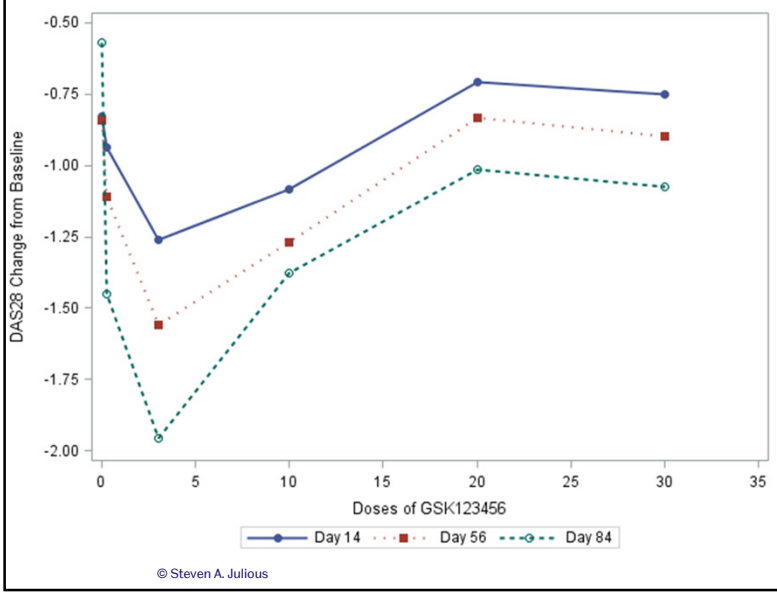
| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D3 | D3 | D3 | D3 | D3 | D3 | D3 | D3 | D3 | D3 | D3 | D3 | P | P | P | P | P | P |

etc

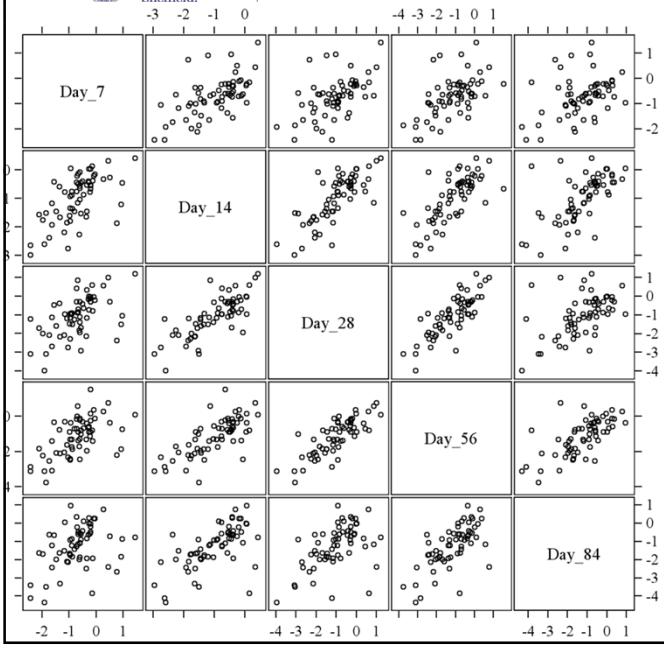
## Schematic of Dose Response



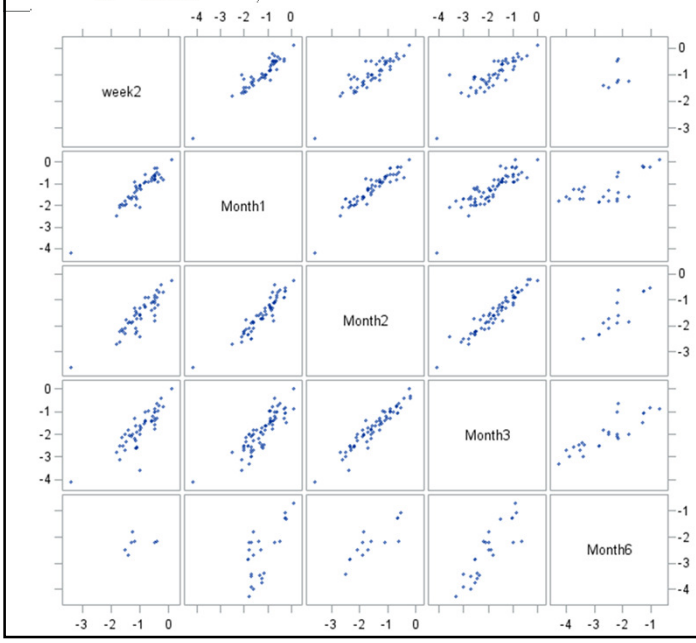

## Dose Response by Day



# Individual Data Analysis




# Meta Analysis of 20 Studies



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# The RATPAC Trial



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# The RATPAC Trial

- Randomised Assessment of Treatment Using Panel Assay of Cardiac Markers (RATPAC) trial was in an Emergency Care setting
- Primary endpoint was successful discharge within 4 hours with no re-admission within 3 months

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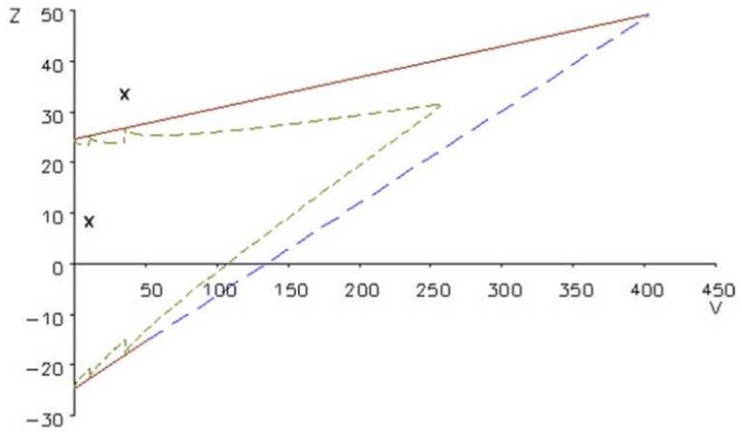
# Re-analysis or RATPAC



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# RATPAC Results

| | Original RATPAC | Group Sequential RATPAC* |
|---|---|---|
| Estimated POC success, % | 32 | 32 |
| Estimated SC success, % | 13 | 16 |
| Pearson $\chi^2$ statistic | 112.25, $P<.001$ | 29.69, $P<.001$ |
| Odds ratio (95% CI) | 3.11 (2.59–3.72) | 2.48 (1.80–3.42) |
| Sample size at termination | 2,243 | 772 |
| Duration, mo | 18 | 6 |

*POC*, Point-of-care; *SC*, standard care.
*Group sequential results shown for the final (updated) endpoint.

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# The ESETT Trial



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# The ESETT Trial

Established status epilepticus treatment trial (ESETT): A pragmatic randomised controlled comparison of phenytoin, valproate or levetiracetam in established status epilepticus where initial benzodiazepine treatment has failed

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## Comparisons of Interest

- Comparison 1: Valproate vs. Phenytonin
- Comparison 2: Levetircetam vs. Phenytonin
- Comparison 3: Levetircetam vs. Valproate



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## Testing Procedure

- Statistical significance to be declared if both comparisons 1 and 2 are significant at the 5% level or if either comparison is significant at the 2.618% level.
- Comparison 3 will be tested at a 5% level of significanceif both Comparison 1 and Comparison 2 are statistically significant at 5%

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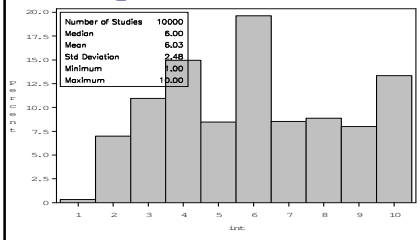
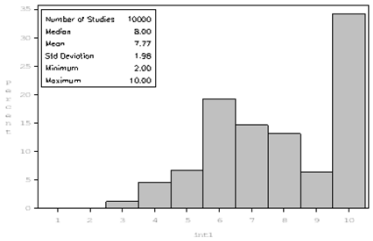
# Trial Simulations

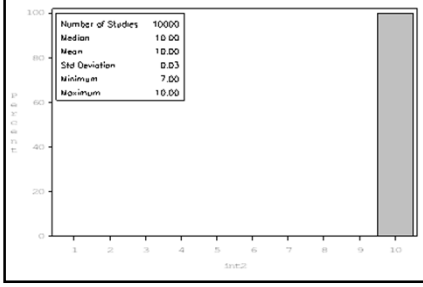
a. Comparisons 1 and 2



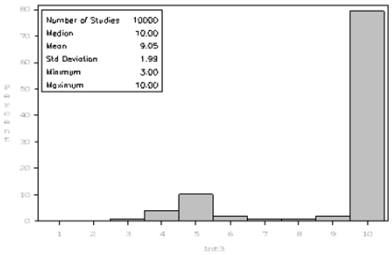

b. Comparison 3




c. Comparisons 2




d. Comparison 1

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# (SARA: Steroids for Allergic Reaction and Anaphylaxis)

Double blind randomised controlled trial of systemic corticosteroids for systemic allergic reaction or anaphylaxis

## SARA Sample Size

The trial will actually be analysed as a group sequential trial with 5 scheduled analyses at N=360, 720, 1080, 1440 and 1800. The maximum sample size to provide 90% power using this approach is 1800 in total, but the expected sample size will be 1024 if the assumed difference of 92% versus 96% is true or 800 if both arms have a 92% success rate.



## SARA Simulations

To investigate the properties of the design simulations were undertaken Assuming the effect on placebo is 92% simulations were used investigate at which analysis (1st, 2nd, 3rd, 4th or 5th) 50% of trials would be anticipated to stop

It is anticipated that trials would stop 50% or more of the time after the 2nd, 2nd, 2nd, 3rd, 3rd and 3rd interim analysis for effects of 99%, 98%, 97%, 96%, 95% and 94% respectively.

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## SARA Costings

- The total research costs will be £838,714 if the trial is terminated at 27 months (N=360), £1,136,893 for 32 months (N=720) £1,340,174 for 37 months (N=1080), £1,556,588 for 42 months (N=1440) and £1,685,663 for the maximum 46 months (N=1800)



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## Nerve Block Trial

- An adaptive, factorial, double blind randomised placebo controlled trial of bilateral superficial plexus nerve block (BSCPB) and local wound infiltration (LWI) for pain relief following thyroid and parathyroid surgery.
- Adaptive component allowed for a pre-planned change in strategy dependent on results of interim analyses, enabling a flexible and efficient trial design that addresses important clinical questions.

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# The PENNYWISE Trial

- Prolonged ENoxapariN in primarY percutaneous coronary intervention compared WIth Standard-of-care Bivalirudin thErapy - the PENNYWISE study
- An adaptive non-inferiority trial with interim analyses after 50 and 75% of patients recruited



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# Obstacles to Adaptive Designs

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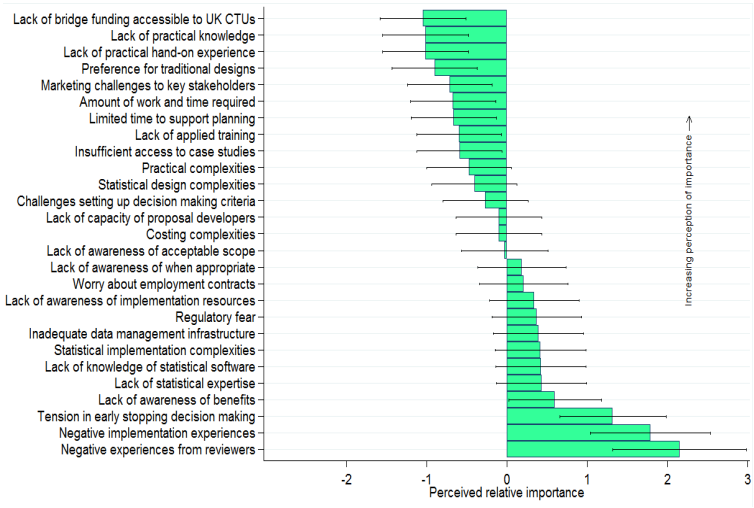
# CTRU Obstacles to Adaptive Designs



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# What are the low hanging fruit?

- Group Sequential trials to assess efficacy and futility
- Sample Size re-estimation

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# The Utility of Futility

- In the UK 55% of all publicly funded trials do not reach their target sample size
  - Studies with 80% power are less likely to recruit to target
- For publicly funded superiority trials a futility assessment would increase successful recruitment from 45% to 64%



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# Summary

- Proficient
- Efficient
- Sufficient
- Deficient


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QUESTIONS
?