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Adaptive Designs Making Clinical Trials More Flexible and Efficient

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Overview

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Introduction

Adaptive Designs Working Group

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Adaptive Designs

Scope

The Adaptive Designs Working Group collaborates to increase uptake of methods, to improve knowledge and to link with key stakeholders such as regulators and industry in this important area for improving the speed and efficiency of trials.

Objectives

Besides undertaking research on methods for adaptive designs (list of current research interest), the Network plays a vital role in increasing the implementation of adaptive design methodology, with the main barriers to implementation already identified as a lack of software and a lack of expertise. The future plans for this group include continued annual meetings, strengthening the engagement with industry and the development of collaborative inter-Hub visits to develop novel adaptive designs.

The group is focusing its efforts on preparing tutorial papers for applied journals and mainstream medical journals; presentations and lectures to increase uptake of methods amongst stakeholders; and the development of computer software to help researchers to undertake trials with adaptive designs. To support these activities the working group has a dedicated Outreach officer.

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Motivation

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Attrition rates for new developments (Arrowsmith 2011a, 2011b)

- phase II: $>$80%
- phase III & submission: $\sim$50%

Reasons for failure (Arrowsmith & Miller 2013)

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Phase II (2011–2012)

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Phase II (2011–2012)

Phase III & submission (2011–2012)

Problems and solutions

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Likely causes for failure:

- taking forward futile treatments
- studying the wrong patient population
- poor precision (optimal dose, maximum tolerated dose, safety)

Can we do better?

- avoid going straight into large and expensive phase III
- take more care during phases I and II
- consider adaptive and Bayesian designs

Idea

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Modify an ongoing trial

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Modify an ongoing trial

by design or ad hoc

based on reviewing accrued data at interim

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Modify an ongoing trial

by design or ad hoc

based on reviewing accrued data at interim

to enhance flexibility

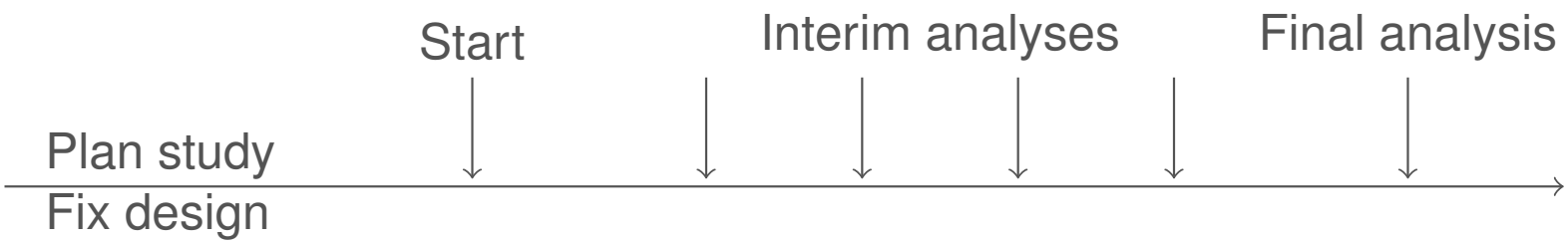
without undermining the study's integrity and validity.

(Chow et al. 2005)

Fixed sample design

- **total** sample size known in advance
- no adjustment possible

Adaptive design



- larger **maximum** sample size
- lower **expected** sample size

At each interim:

- decide whether or not to stop
- change sample size
- drop or add a dose
- change the endpoint
- change the question

Pros and cons

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+ highly flexible
+ very efficient
+ reflects medical practice
+ shorter trial and/or more accurate estimates
+ ethical

– highly flexible
– inefficient
– time-consuming to design
– post-trial estimation difficult
– simple estimates may be biased
– interim analyses may require unblinding

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A Bayesian Group Sequential Design: UK-REBOA

REBOA

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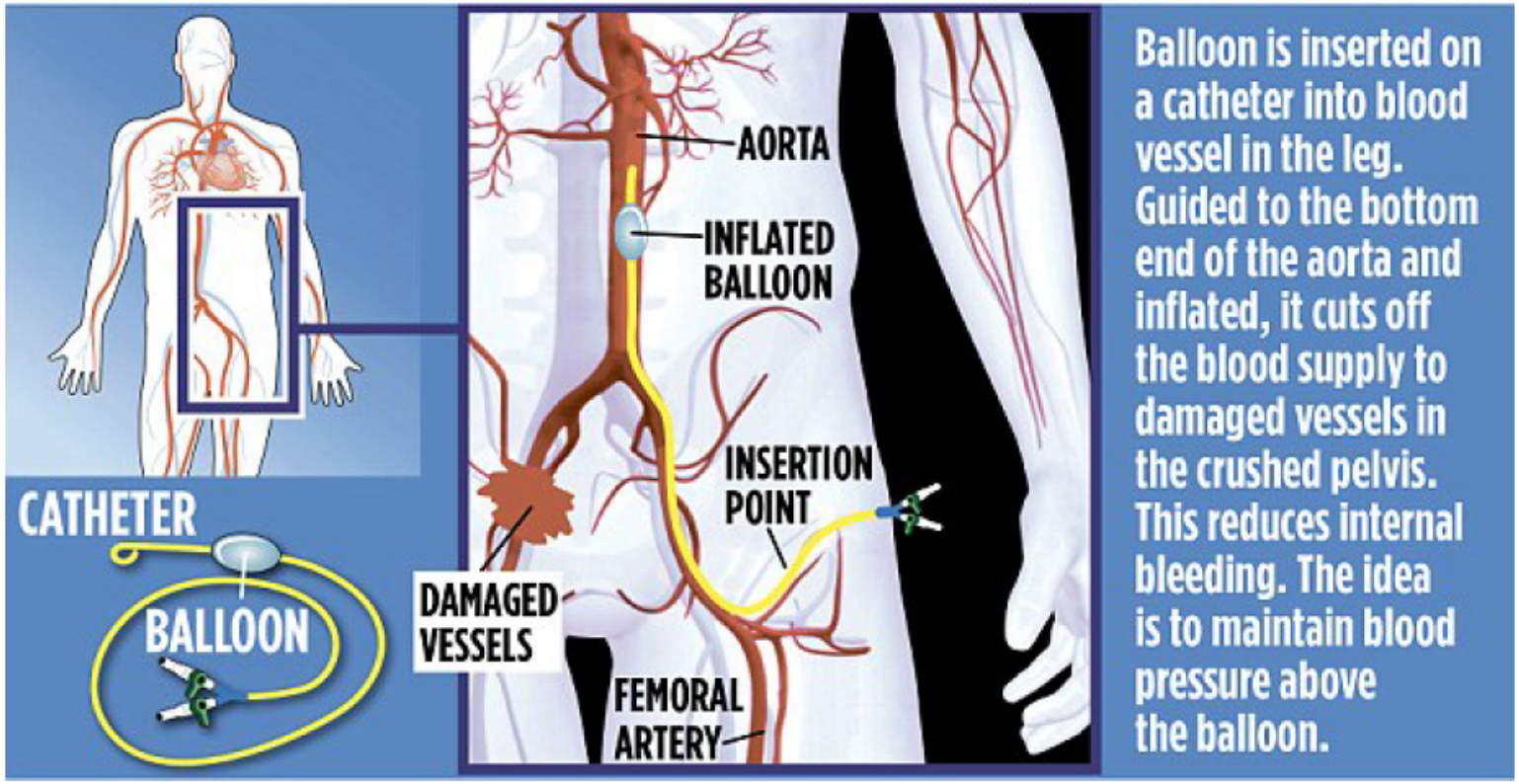
Resuscitative Endovascular Balloon Occlusion of the Aorta



From: Daily Mail (13 June 2015)

Little and Conflicting Evidence

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Only a few observational studies and case series but no RCTs

- Propensity-matched retrospective cohort study (Japan) Norii et al. (2015)
  $\rightarrow$ REBOA is probably harmful
- Prospective observational study (USA) Brenner et al. (2013)
  $\rightarrow$ REBOA is probably beneficial
- Prospective observational study (USA) DuBose et al. (2016)
  $\rightarrow$ REBOA has no effect

The UK-REBOA Trial

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Randomised two-arm design (REBOA + standard vs. standard)

Primary endpoint: 90-day survival

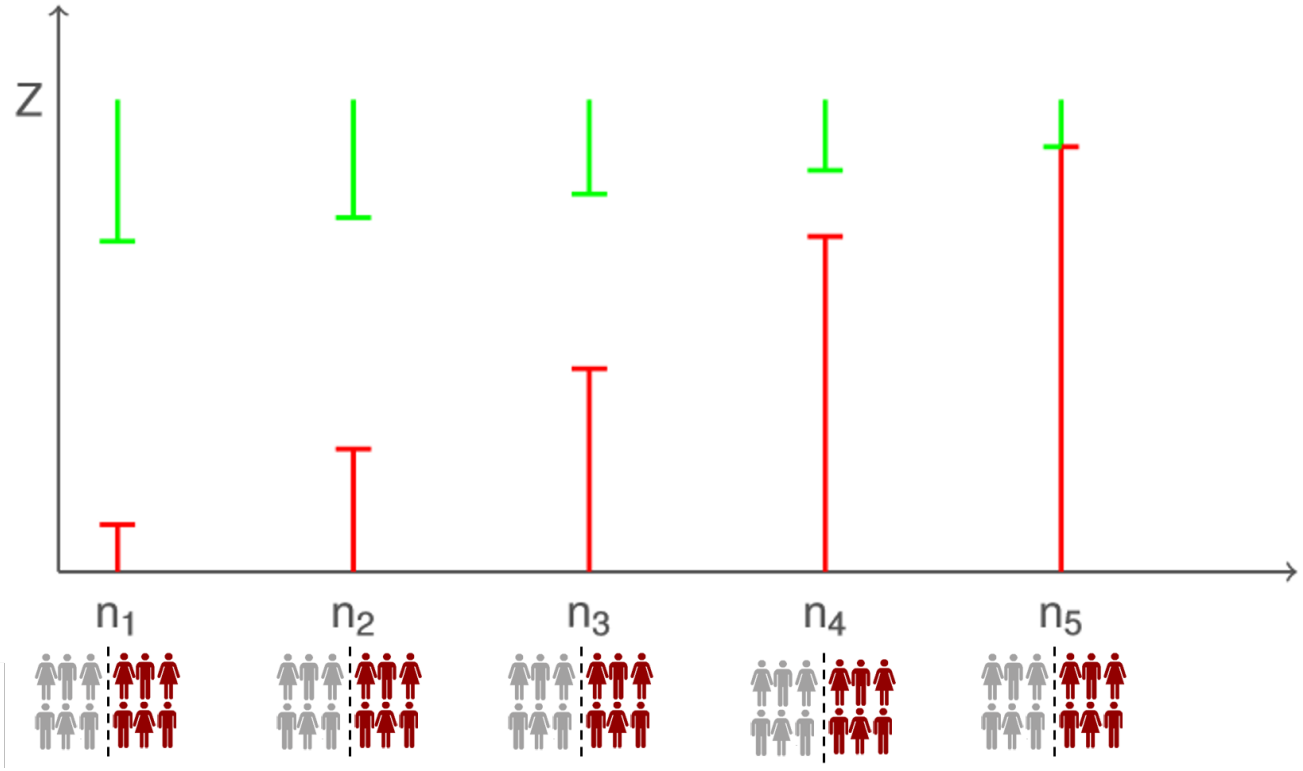
- 66.5% with standard care
- Even slight improvement is interesting

< 80 eligible patients per year $\Leftrightarrow$ conventional trial needs 400

Requirements:

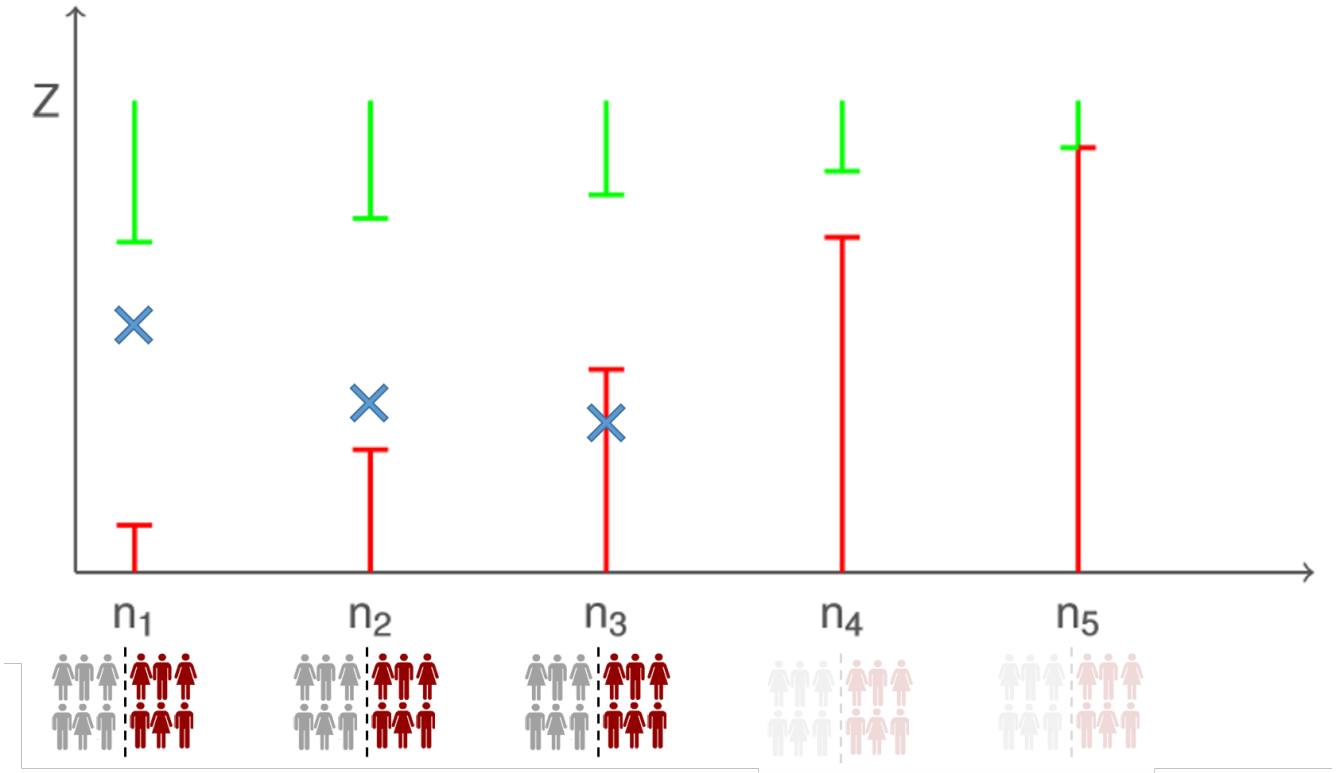
- Early stopping for futility
- Bayesian analysis

Group Sequential Trials



(Whitehead 1997)

Group Sequential Trials



(Whitehead 1997)

Bayesian Group Sequential Design

Gsponer et al. (2014)

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Randomised two-arm three-stage design:

- max. 120 patients from 10 major trauma centres
- early stopping for futility after ~ 40 and ~ 80 patients

$\delta = log(OR)$ of 90-day survival

Bayesian futility criterion for stages 1,2,3:

$$\mathbb{P}(\delta < 0 | \text{ data}) \geq 0.9$$

Bayesian success criterion for stage 3:

$$\mathbb{P}(\delta > 0 | \text{ data}) \geq 0.95$$

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A Multi-Arm Multi-Stage Design: TAILoR

TAILoR

Pushpakom et al. (2015)

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- Phase II study to evaluate treatment for side effect of HIV tri-regimen treatment (TAILoR)
- Superiority trial
- Several possible doses
- Continuous endpoint

MAMS designs

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Planned trial

MAMS designs

First interim

MAMS designs

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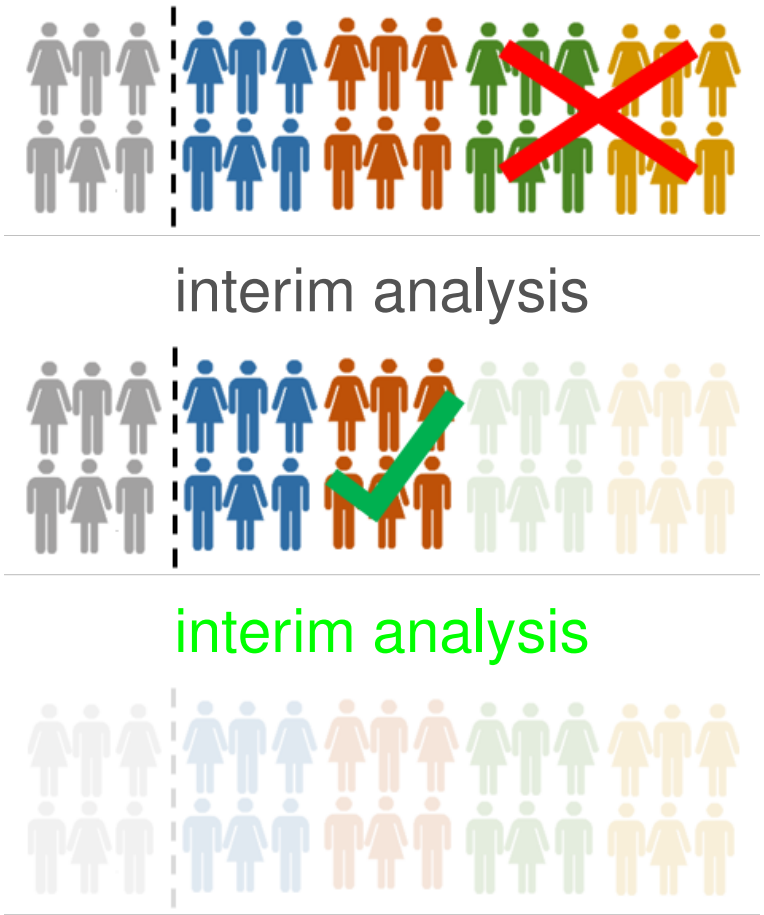
Second interim



Design

Magirr et al. (2012)

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- 3 active arms compared to control
- Equal randomization between actives and control
- one interim analysis
  - Stop for superiortiy
  - Stop if no active arm appears promising
  - Drop any active arms that are not sufficiently promising
- In the trial we underestimated drop-out and could adjust at interim

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Sample Size Re-Estimation: DEVELOP-UK

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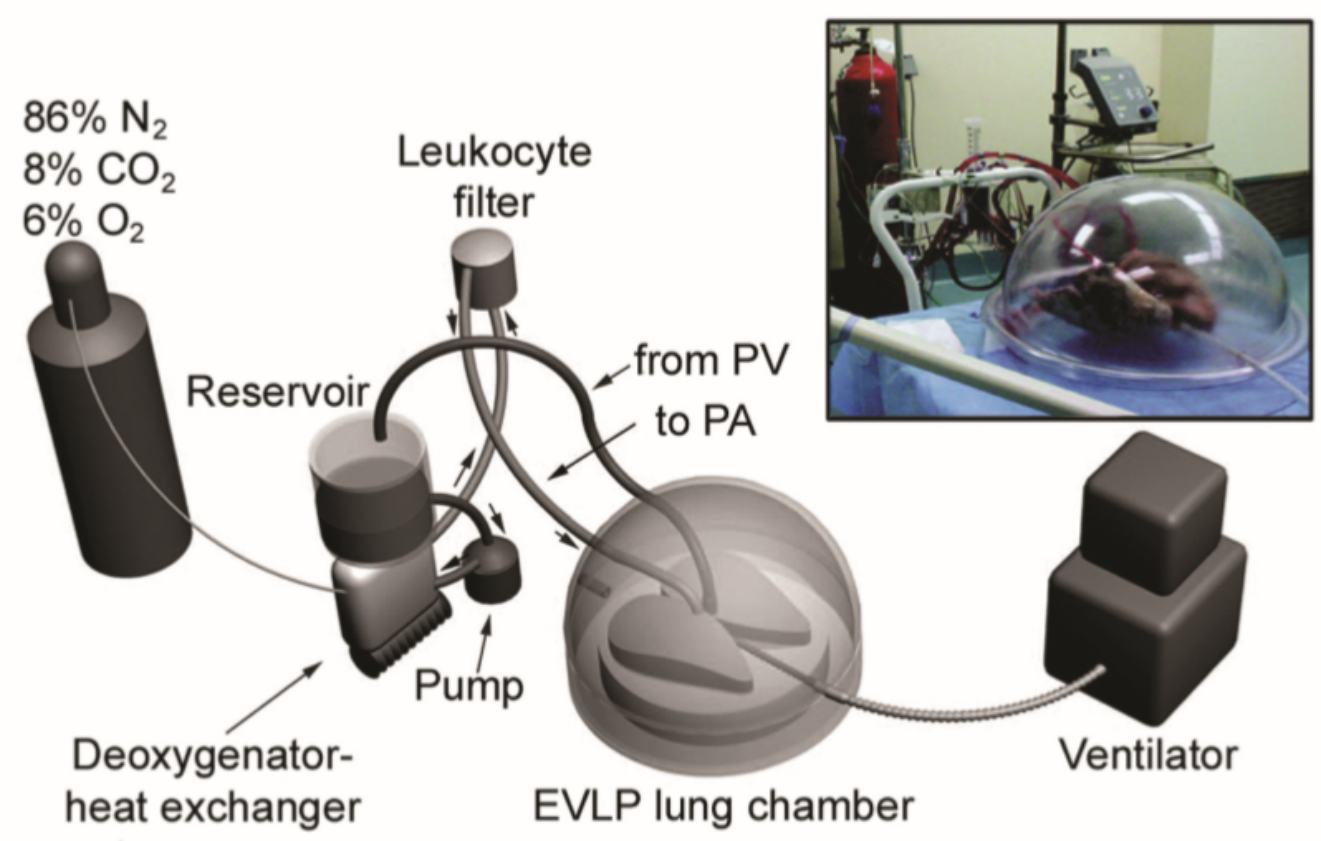
Ex-Vivo Lung Perfusion



From: Cypel *et al.* (2009)

DEVELOP-UK trial

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- transplantation of reconditioned vs. standard donor lungs
- ex vivo lung perfusion (EVLP)
- phase III, multi-centre, unblinded, non-randomised, non-inferiority observational study
- primary endpoint: 12 months survival
- uncertainty in design parameters (only 50 transplants worldwide)

www.develop-uk.net

DEVELOP-UK trial: Design (1)

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- survival estimates: 94.2% (1 month), 91.2% (3 months), 78.7% (1 year)
- aim: at most double hazard rate of death using reconditioned lungs
- doubling: 88.7% (1 month), 83.2% (3 months), 61.9% (1 year)
- 80% power, one-sided 5% level
- improvement of standard care could compromise the desired power

DEVELOP-UK trial: Design (2)

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- 408 patients randomised to EVLP and standard
- 3:1 in favour of standard to ensure all available lungs are used
- interim analyses after 1/3 and 2/3 of total sample size
  - first: early stopping
  - second: early stopping, sample size re-assessment
- significance levels: 0.005 (first), 0.014 (second), 0.045 (final)

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Other adaptive methods

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Phase I

- 3+3 design
- Continual Reassessment Method (CRM)
- Escalation with Overdose Control (EWOC)

Phase II

- Response Adaptive Randomisation (RAR)
- Covariate Adjusted Response Adaptive (CARA)
- Mulit-Arm Multi-Stage (MAMS)
- MCP-Mod

Phase III

- Biomarker Adaptive
- Population Enrichment
- Group Sequential
- Sample Size Re-esitmation

Literature

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