The new generation of clinical trials: is Australia ready?

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Outline

What are adaptive trials?

REMAP-CAP

Statistical challenges

Other challenges

Is Australia ready?

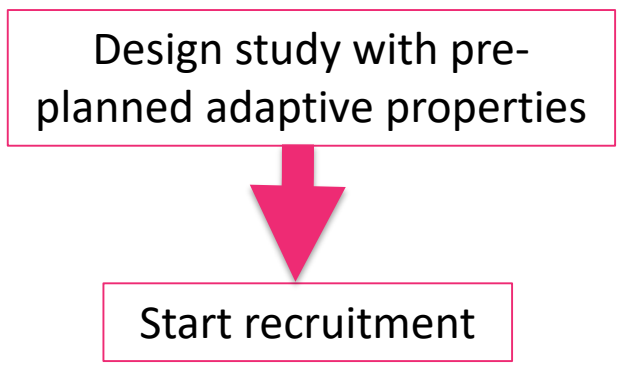
What are adaptive trials?

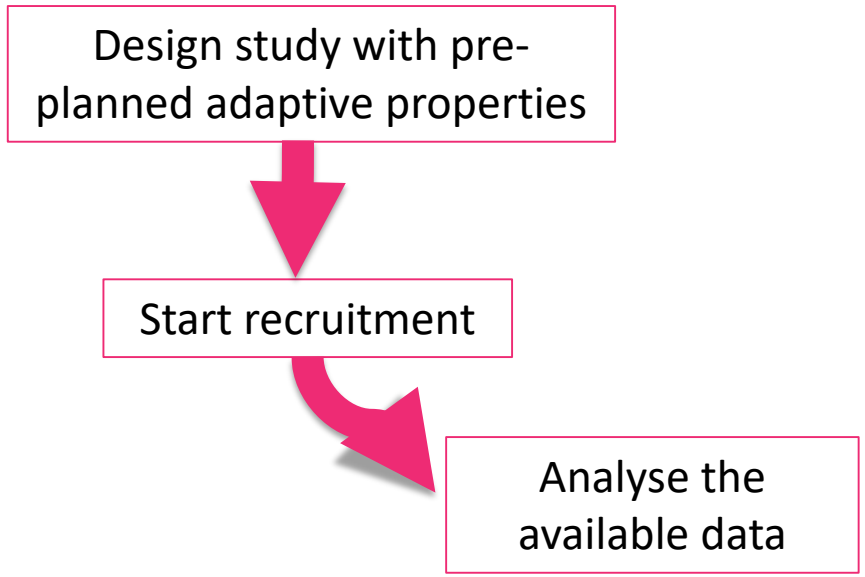
"…design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial."

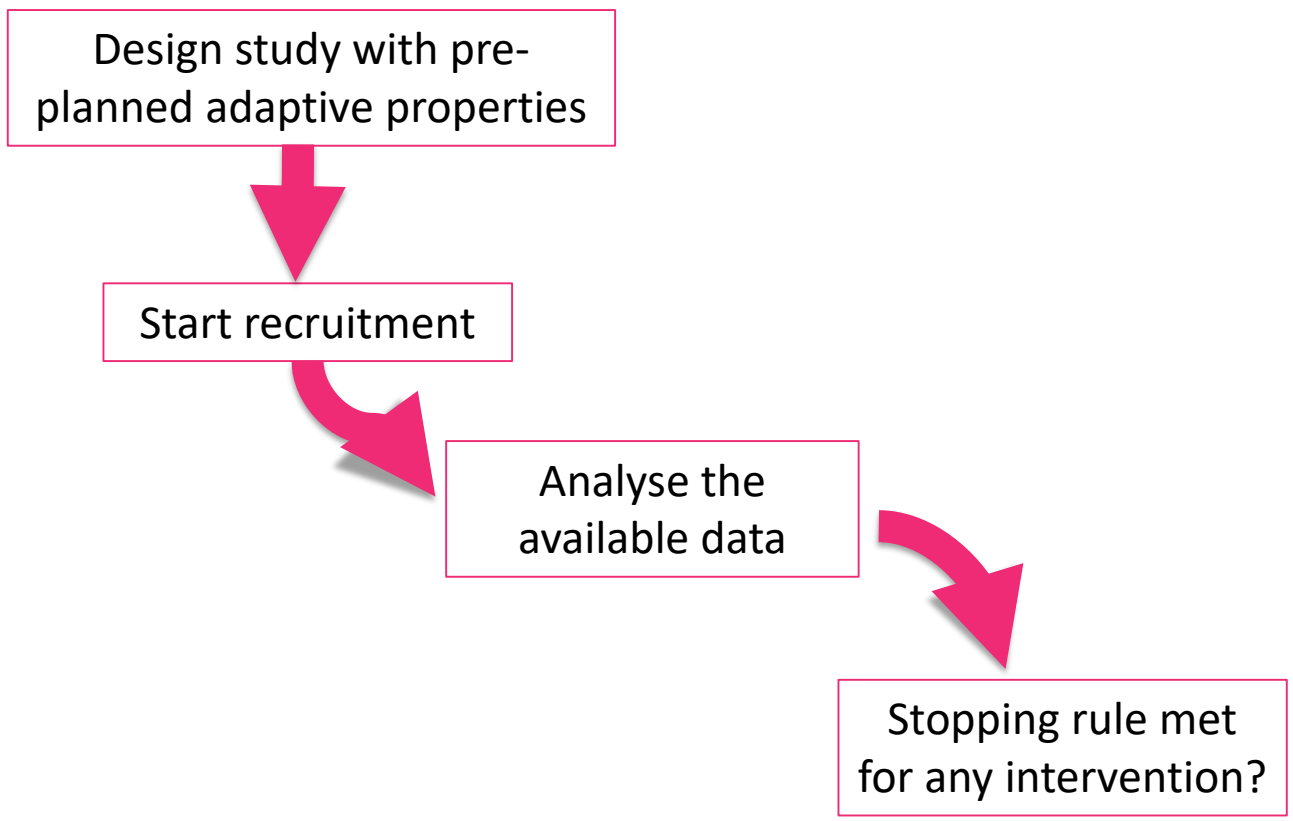
FDA, 2018

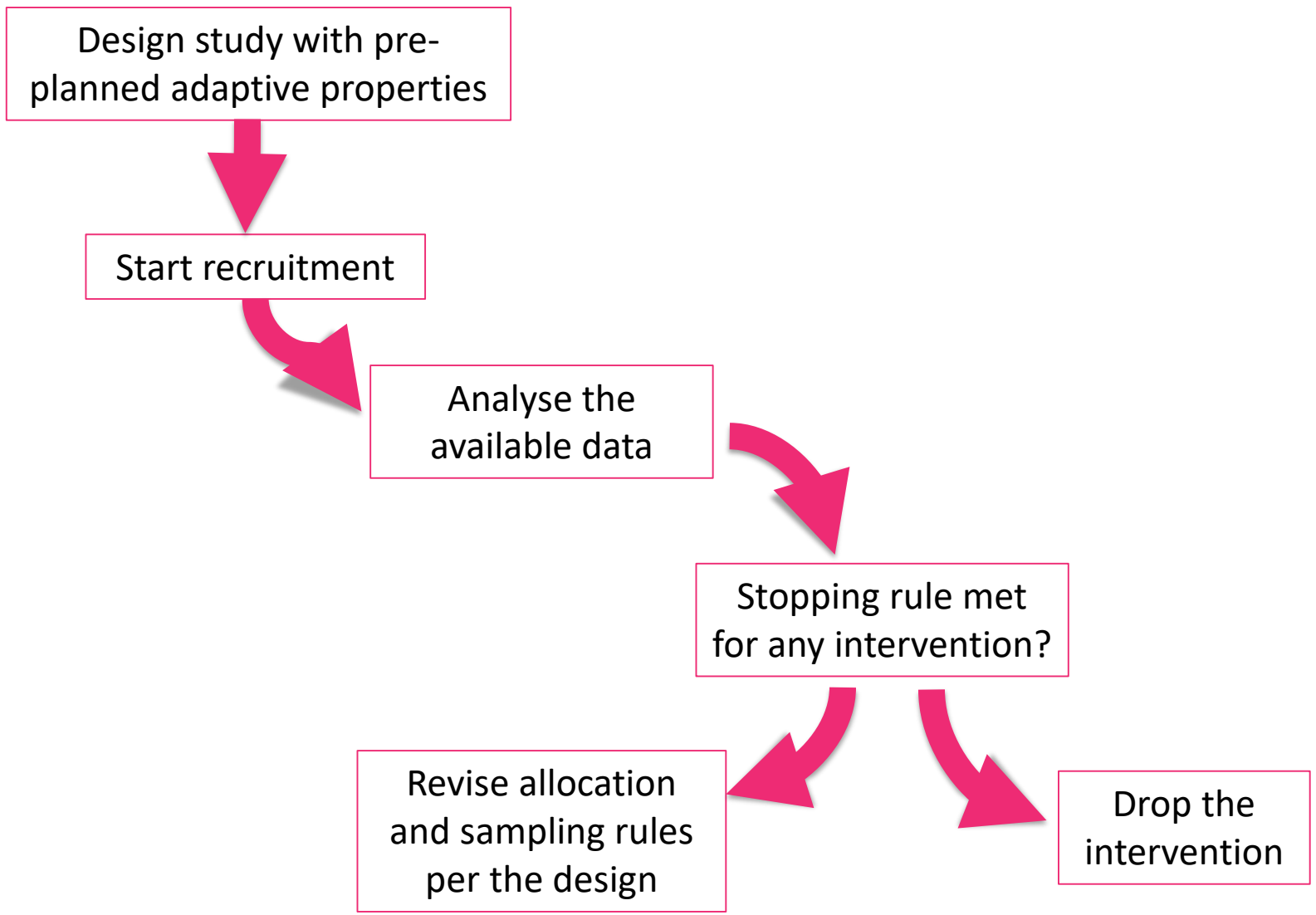
Involves pre-planned modification of an aspect of the trial depending on the accumulating data, such as dosage, sample size, interventions, patient selection criteria…

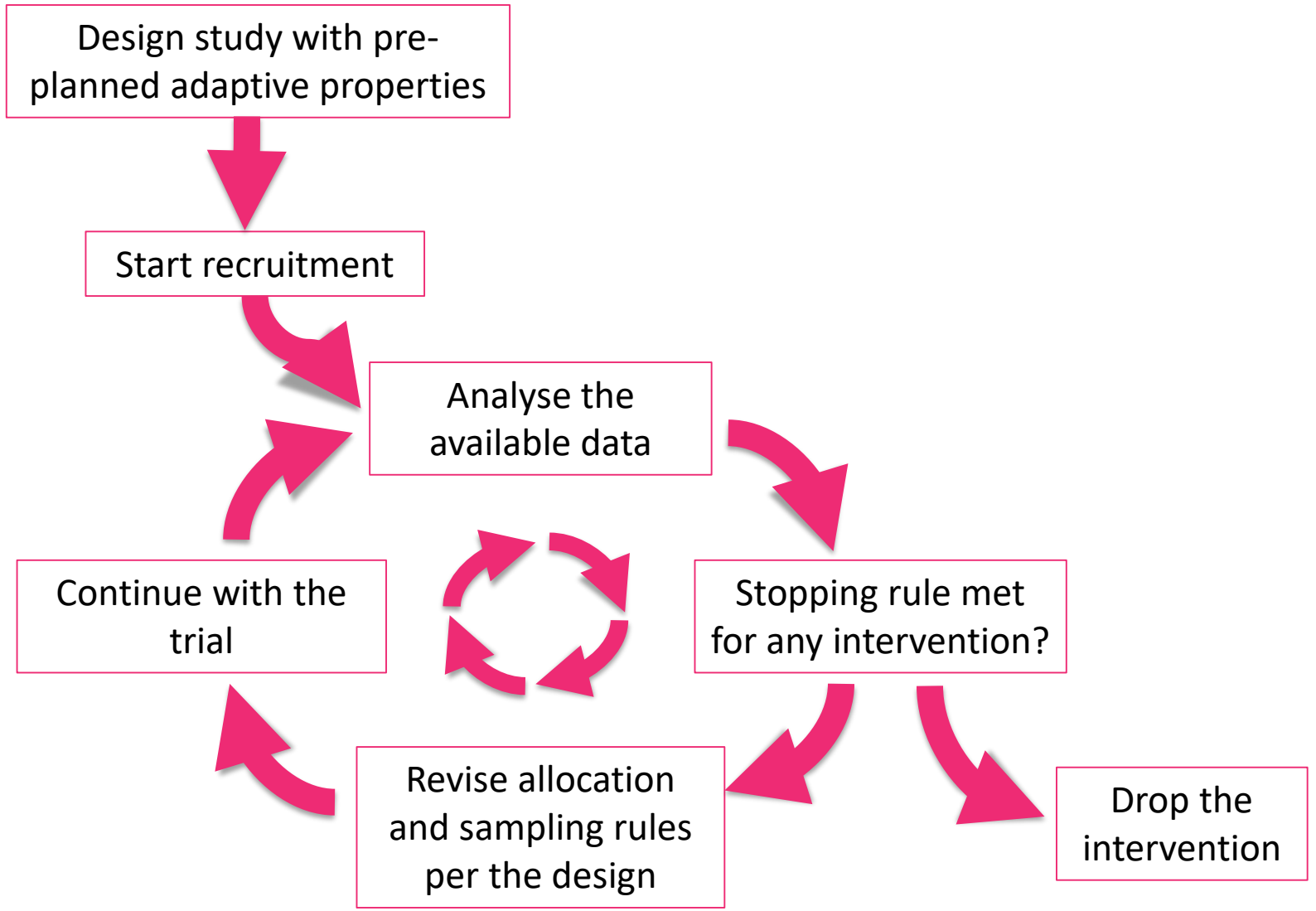
Design study with pre-planned adaptive properties

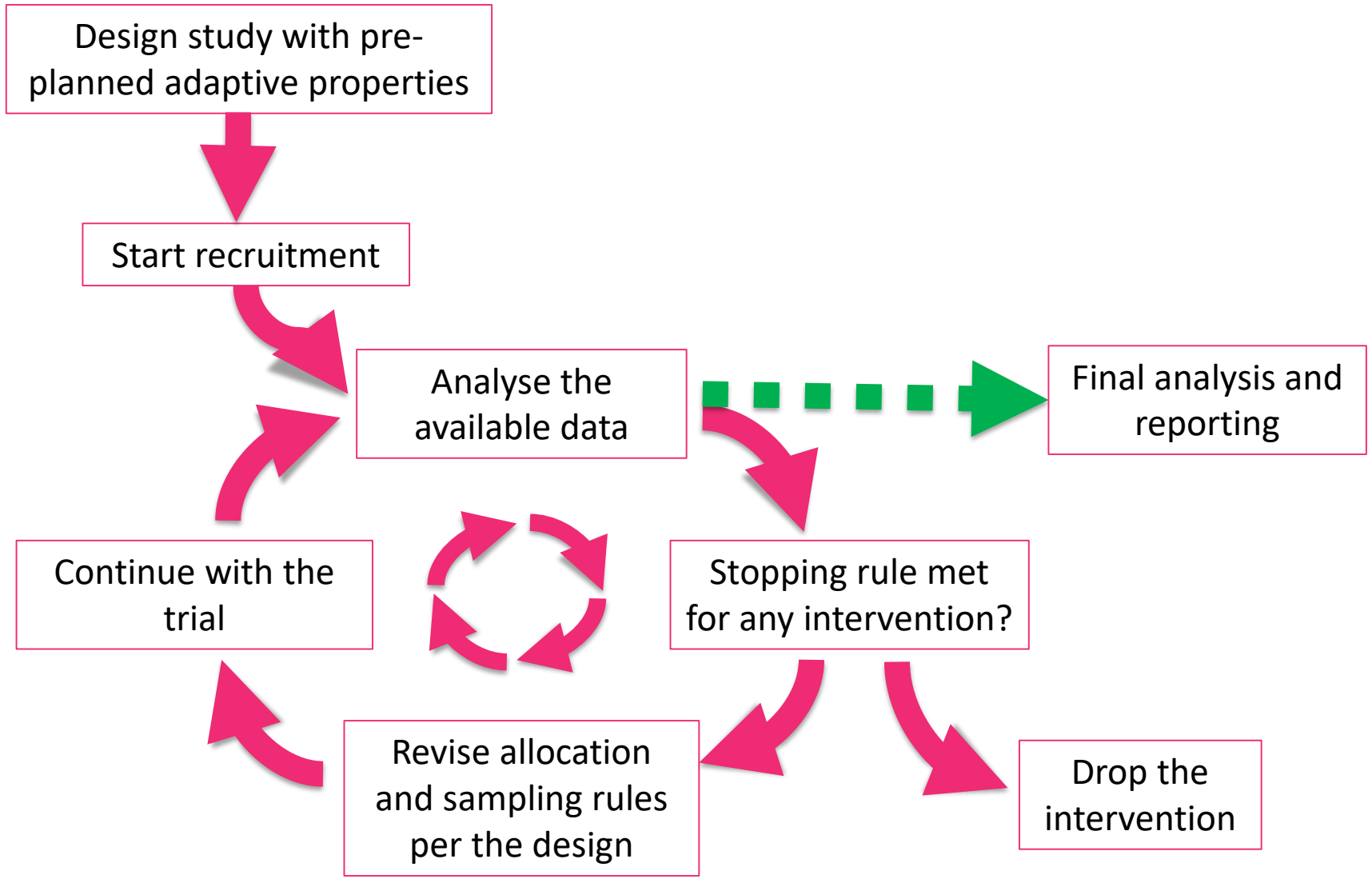

Design study with pre-planned adaptive properties
Start recruitment


Design study with pre-planned adaptive properties
Start recruitment
Analyse the available data


Design study with pre-planned adaptive properties
Start recruitment
Analyse the available data
Stopping rule met for any intervention?


Design study with pre-planned adaptive properties
Start recruitment
Analyse the available data
Stopping rule met for any intervention?
Revise allocation and sampling rules per the design
Drop the intervention

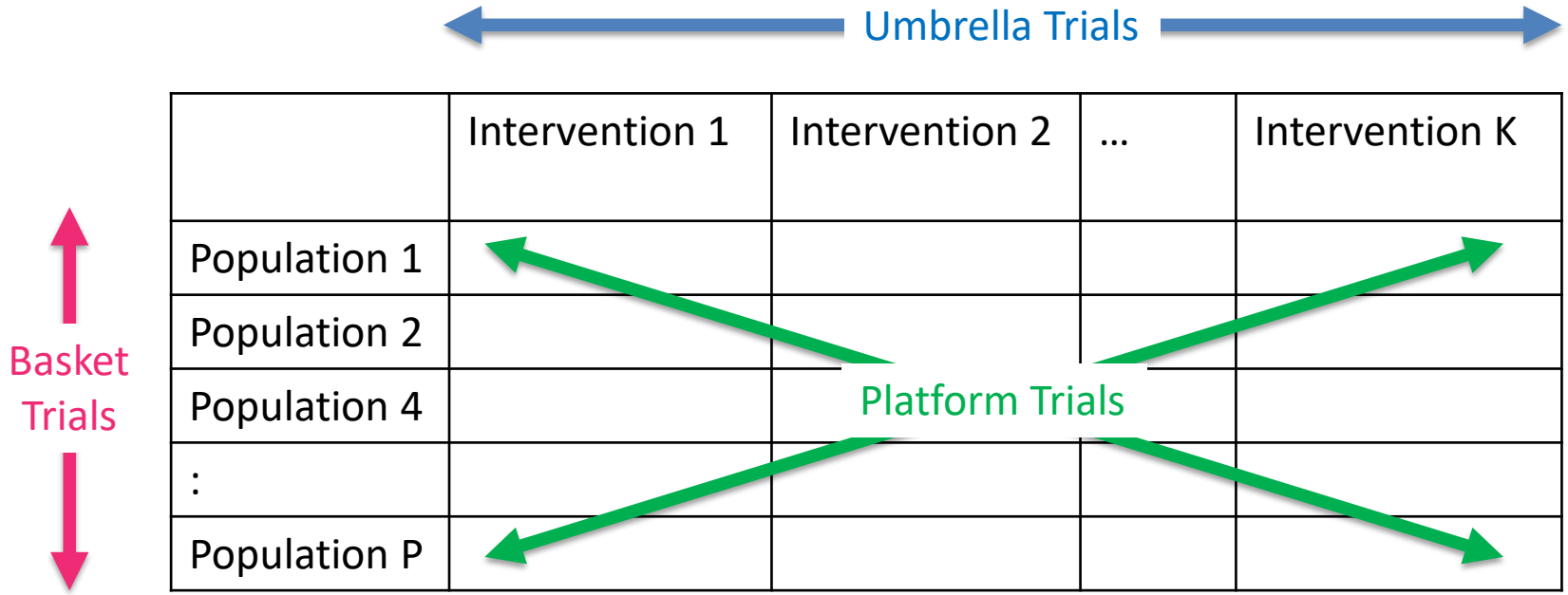

Design study with pre-planned adaptive properties
Start recruitment
Analyse the available data
Stopping rule met for any intervention?
Drop the intervention
Revise allocation and sampling rules per the design
Continue with the trial


Design study with pre-planned adaptive properties
Start recruitment
Analyse the available data
Final analysis and reporting
Continue with the trial
Stopping rule met for any intervention?
Revise allocation and sampling rules per the design
Drop the intervention

Advantages of adaptive designs

- Allow the trial to adjust to information that was not available when the trial began
- Can be very flexible (e.g., in terms of sample size, number of study arms…)
- Can be more efficient (in terms of time and cost)
- Can have greater statistical power
- Can provide ethical advantages (e.g. stop an intervention if it is unlikely to demonstrate effectiveness)
- Can address broader research questions (e.g. effectiveness in a given population)

Platform trials: a special type of adaptive trial



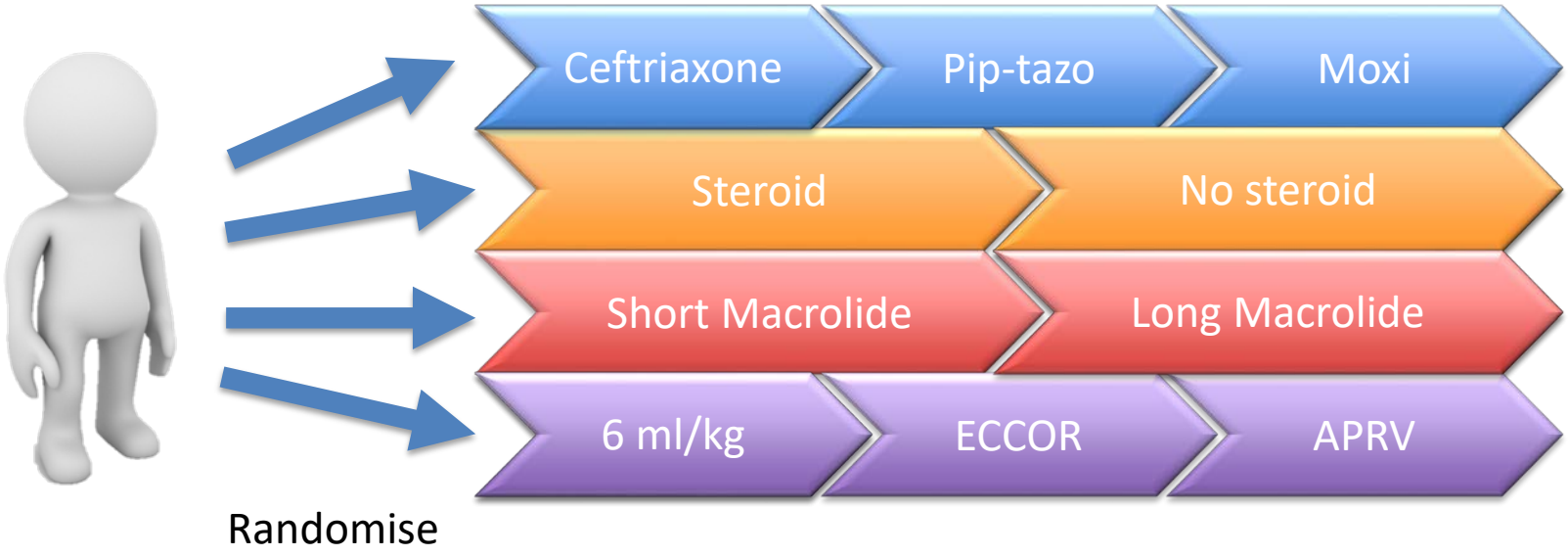
REMAP-CAP

- The Randomised Embedded Multifactorial Adaptive Platform Trial for Community Acquired Pneumonia
- Simultaneous evaluating optimal antibiotic, whether to give steroids, duration of macrolide, and oxygen saturation target on 90-day mortality
- 6,800 patients
- PIs: Prof Steve Webb (Monash University), Dr Colin McArthur (Medical Research Institute of New Zealand), Marc Bonten (UMC Utrecht) and Lennie Derde (UMC Utrecht)

REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

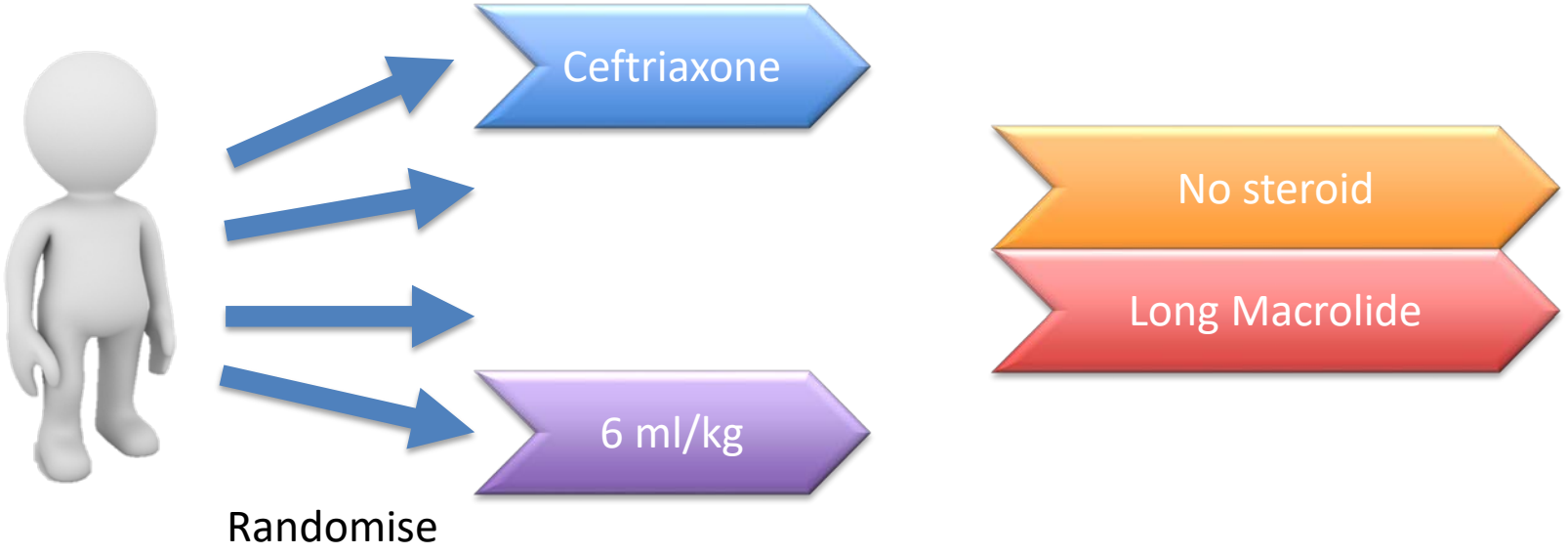
REMAP-CAP: Design

Multifactorial interventions across 4 domains whose effectiveness may vary by strata (shock or no shock, and maybe others)



REMAP-CAP: Design

Multifactorial interventions across 4 domains whose effectiveness may vary by strata (shock or no shock, and maybe others)



Statistical Challenges

- Sample size calculation
  - Generally cannot be conducted using standard methodology
  - Requires simulation of a range of potential scenarios to determine trial design, including decision thresholds and estimation of Type I and II errors
- Response adaptive randomisation
  - Give greater randomisation priority to the more promising treatment combinations
- Interim analyses
  - Ongoing monitoring requires often Bayesian analyses
- Trial monitoring
- Final analysis

REMAP-CAP: Trial design and sample size

Potential trial designs and required sample size are evaluated by simulation across a range of plausible assumptions:

- Number of domains
- Number of interventions per domain
- Different treatment effects of intervention within a domain
- Differential treatment effects depending on the treatment allocation in the other domains (treatment-treatment interactions)
- Number of strata
- Differential treatment effects in the different strata (treatment-strata interactions)
- Statistical thresholds used for interventions to be defined as superior/inferior or equivalence

- New simulations as new domains/interventions/strata are added

Other Challenges

- Management challenges
  - Time required for planning (including simulations)
  - Obtaining funding
  - Getting through ethics
  - Finding (informed) DSMB members
- Logistical challenges
  - Consenting participants
  - Data availability in real time
  - Developing the randomisation system
- Clinical challenges
  - Understanding the design

JAMA 2006;296:1955-1957

Is Australia ready?

- Need to increase experience and knowledge of such designs within Australia
  - In particular, require development of biostatistical expertise

> "To be a world-class Cancer Centre we needed a world-class Biostatistics Unit"
>
> Kim-Anh Do, Chair of Biostatistics, MD Anderson Cancer Centre

- Need to increase awareness of adaptive trial design (investigators, funding bodies, ethics committees, regulatory bodies, consumers,…)

References

Chow SC, Chang M, Pong A. Statistical consideration of adaptive methods in clinical development. J Biopharm Stat. 2005;15:575–91.

Mahajan R and Gupta K. Adaptive design clinical trials: Methodology, challenges and prospect. Indian J Pharmacol. 2010 Aug; 42(4): 201–207.

Berry SM, Connor JT and Lewis RJ. The Platform Trial: An Efficient Strategy for Evaluating Multiple Treatments. JAMA. 2015;313(16):1619-1620. doi:10.1001/jama.2015.2316

FDA. Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry, 2018. https://www.fda.gov/downloads/drugs/guidances/ucm201790.pdf

Kuehn BM. Industry, FDA Warm to “Adaptive” Trials. *JAMA.* 2006;296(16):1955–1957.