Adaptive and Platform Trials

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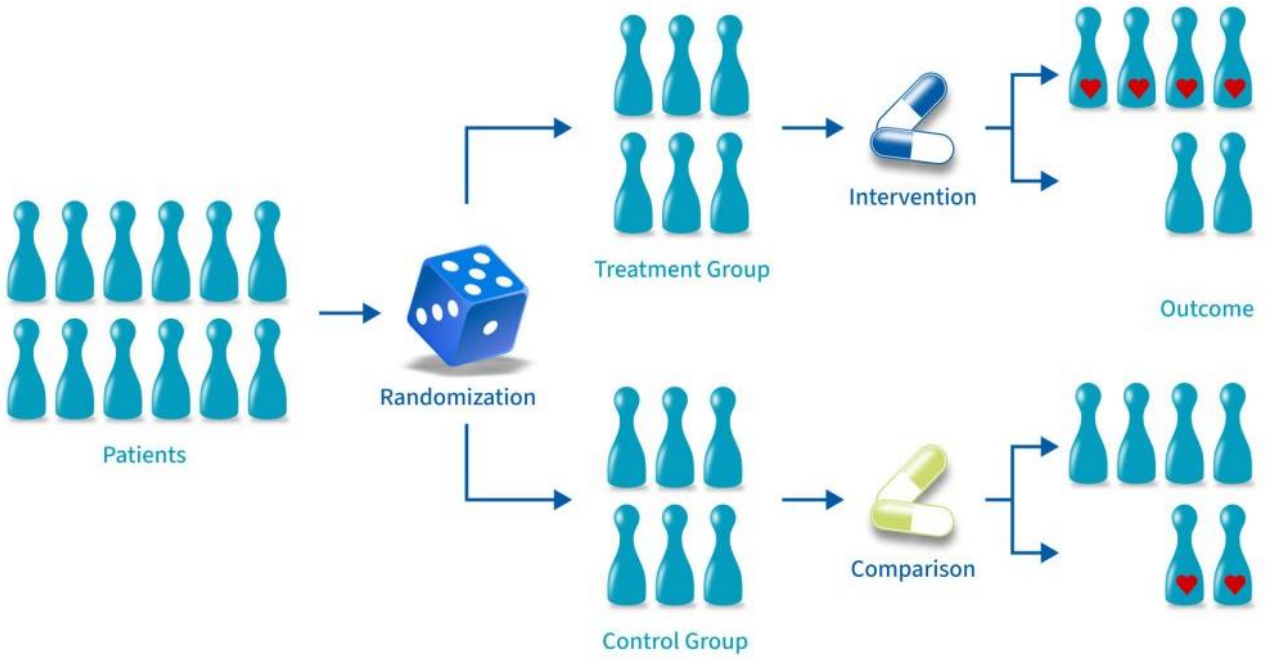
Acknowledgement of country

I would like to begin by acknowledging the traditional owners of this land, the Wurundjeri people, and pay my respects to their Elders past, present and emerging.

Overview

- Adaptive trials
- Platform trials
- Requirements for platform trials
- Pros and cons of platform trials
- Examples
- Bayesian statistics
- When to use a platform trial
- Common criticisms (and potential solutions)
- Increasing the use of platform trials
- Summary



Conventional, parallel arm, clinical trials are great but….

slow and expensive, and typically focus on a single research question

This limits the number of trials

And limits the evidence that is available to guide decision-making

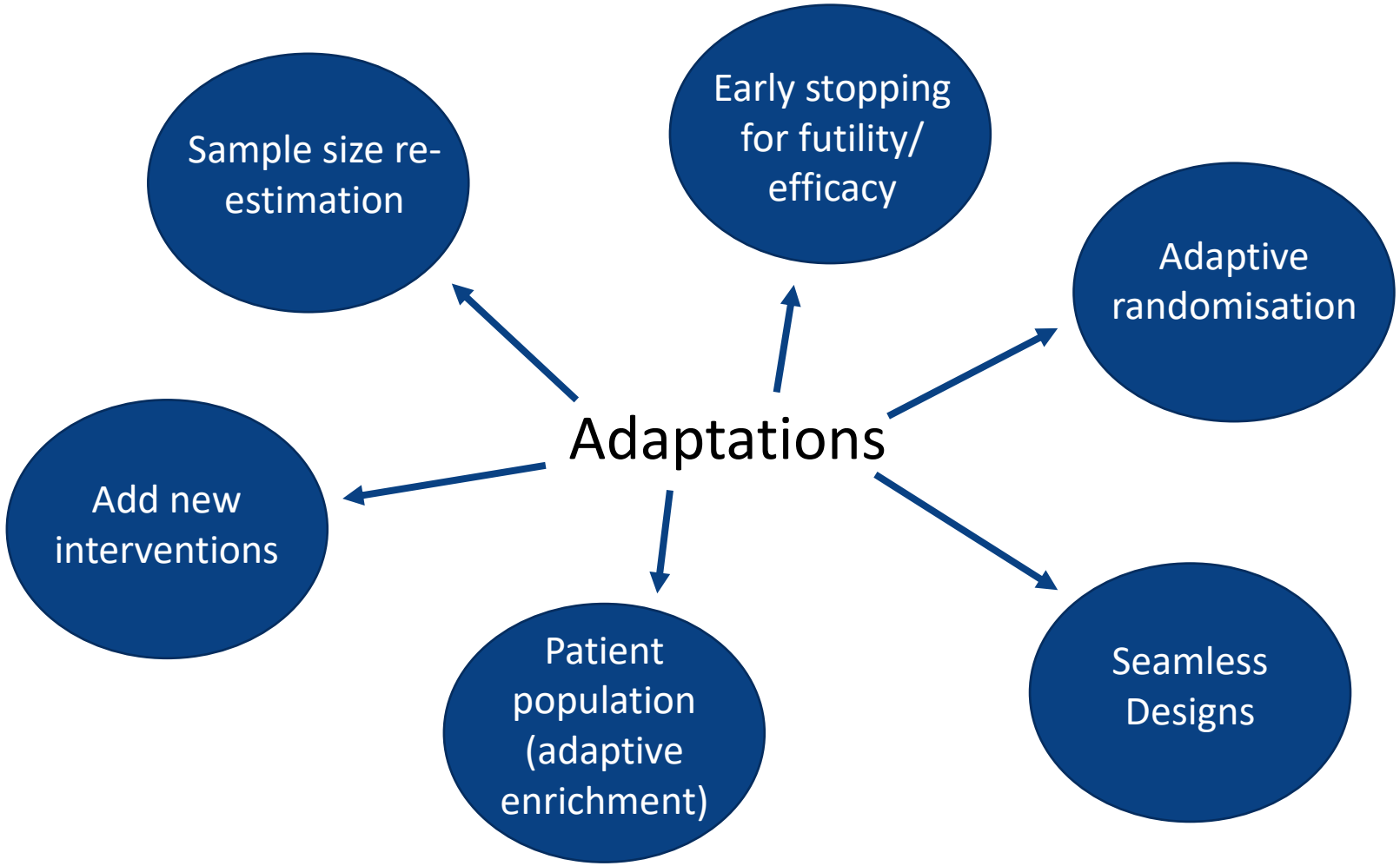
Adaptive trials

"…an adaptive design is defined as a clinical trial design that allows for **prospectively planned modifications** to one or more aspects of the design based on **accumulating data** from subjects in the trial." (Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry, Food and Drug Administration (FDA), 29 Nov 2019)

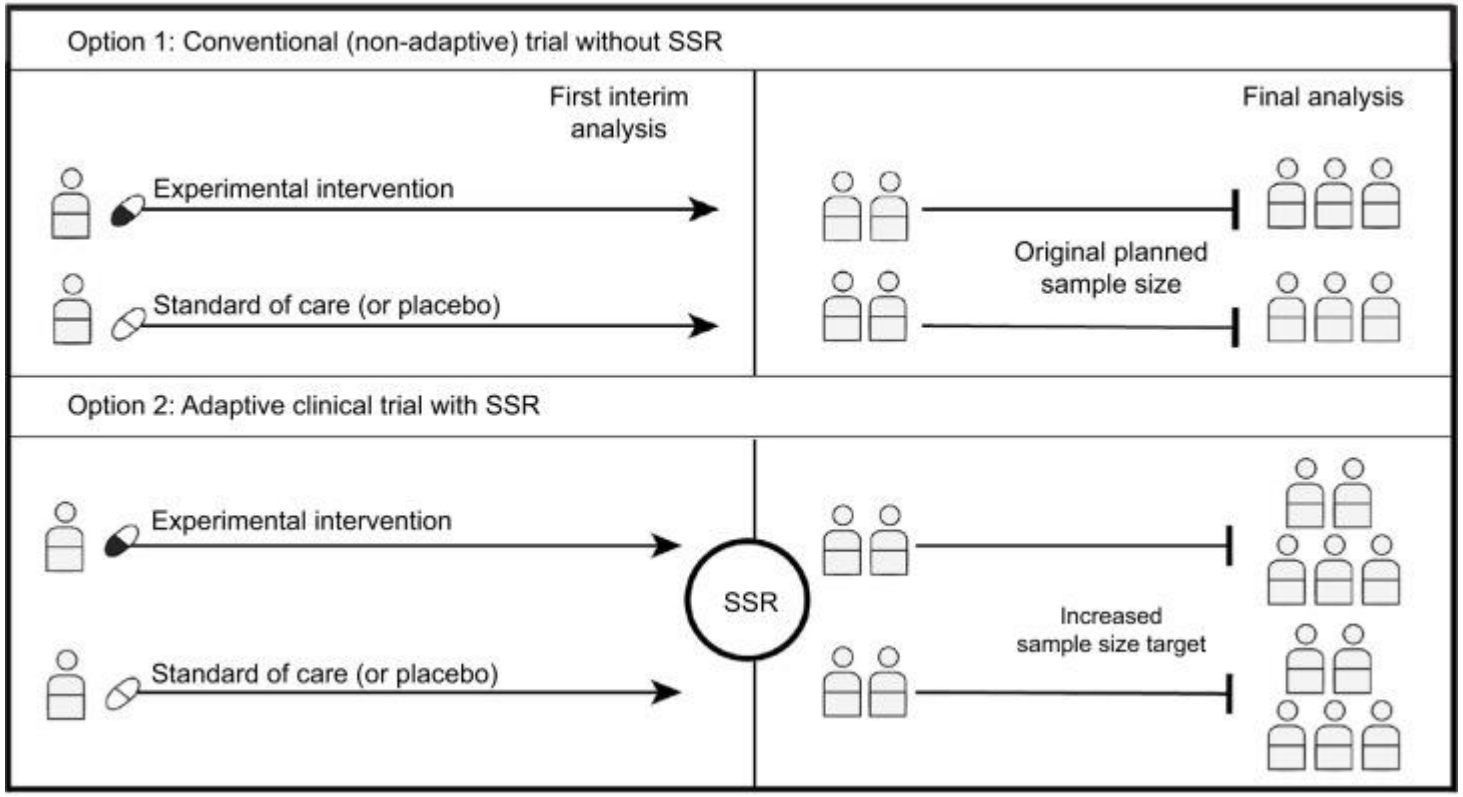
Have grown out of a need to develop more efficient, pragmatic trial designs that answer more complex research questions

Key principle: Adaptations should be clear prior to the start of the trial

Adaptive trials

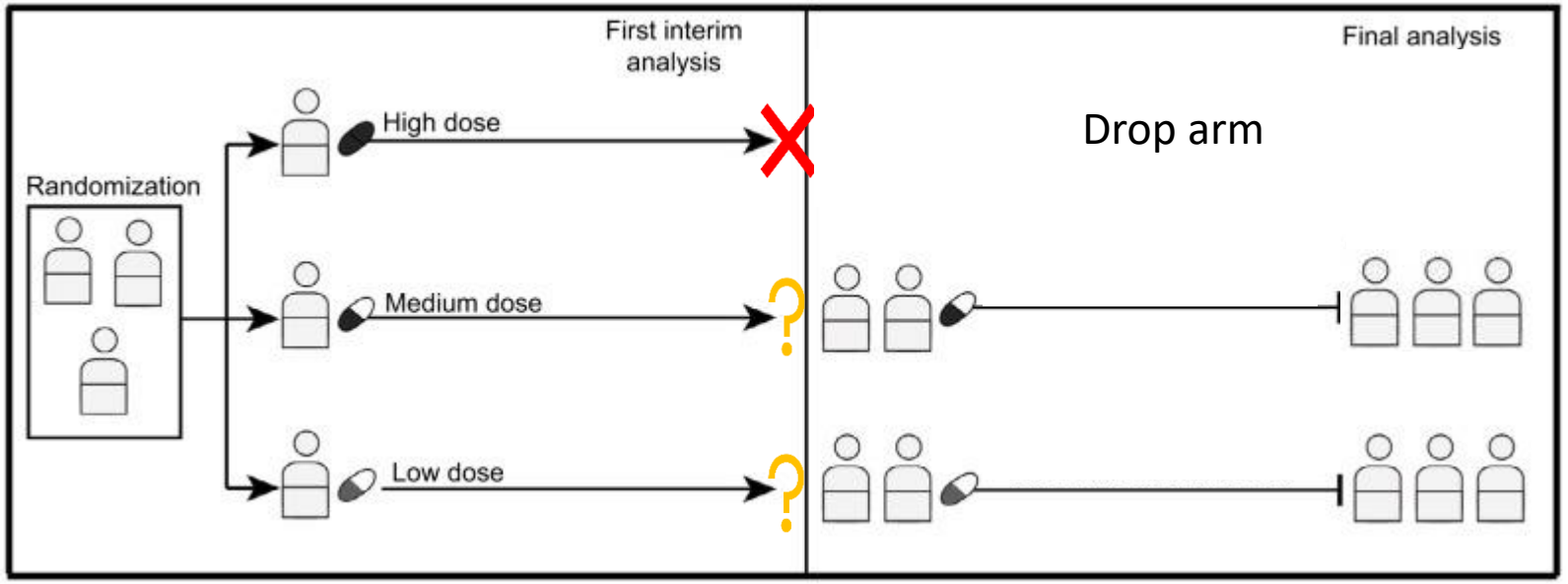


Sample size re-estimation



From: Park et al. Clinical Epidemiology 2018:10 343–351

Early stopping for futility/efficacy (arm dropping)



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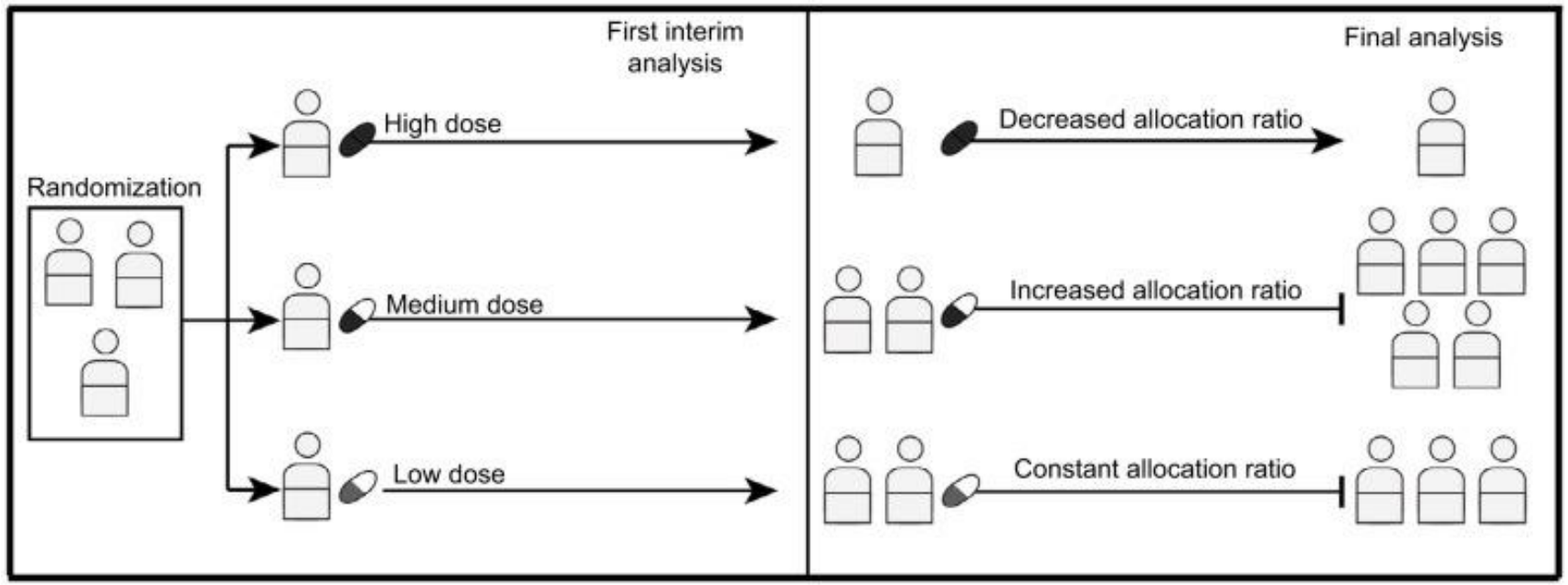
Response adaptive randomisation



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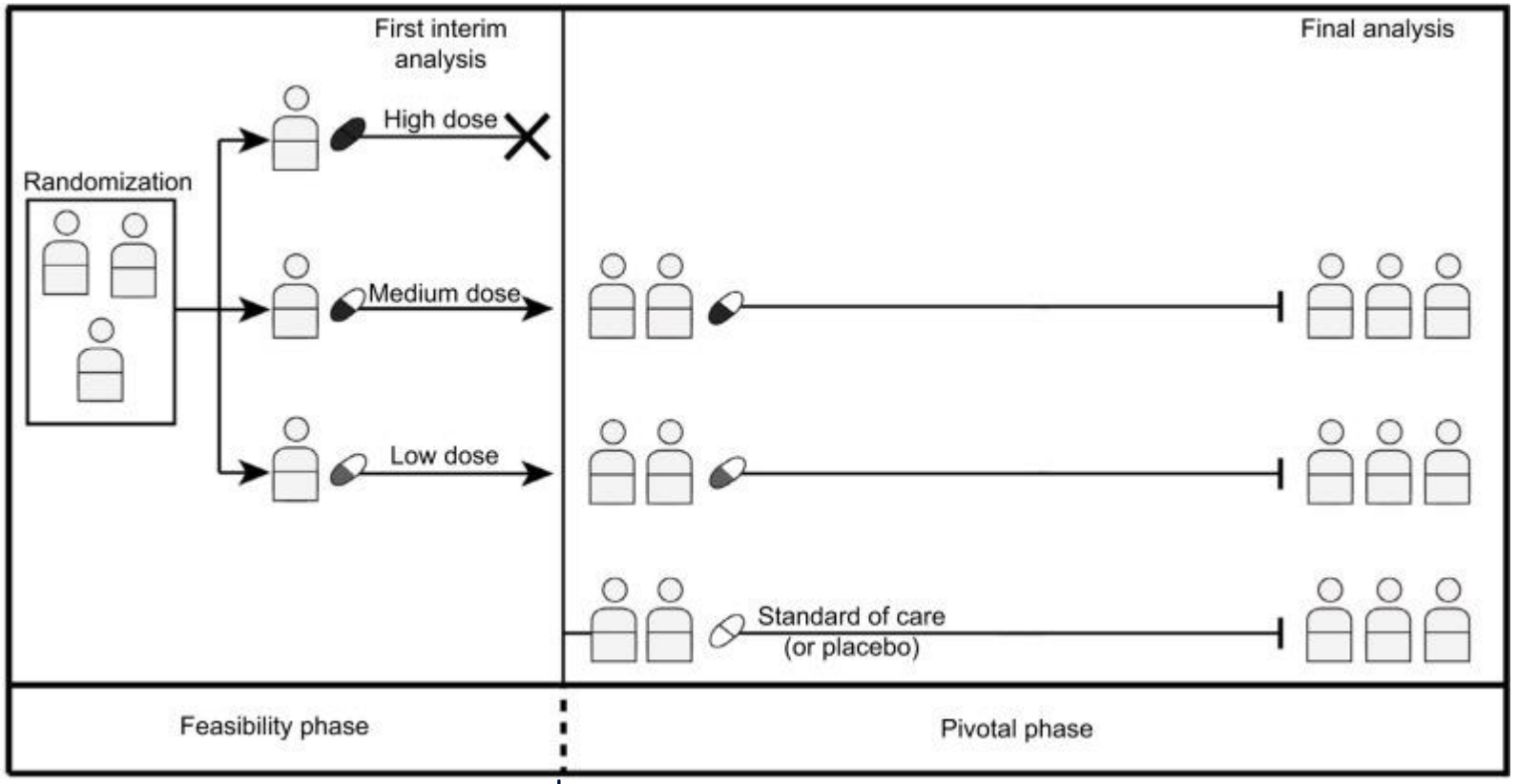
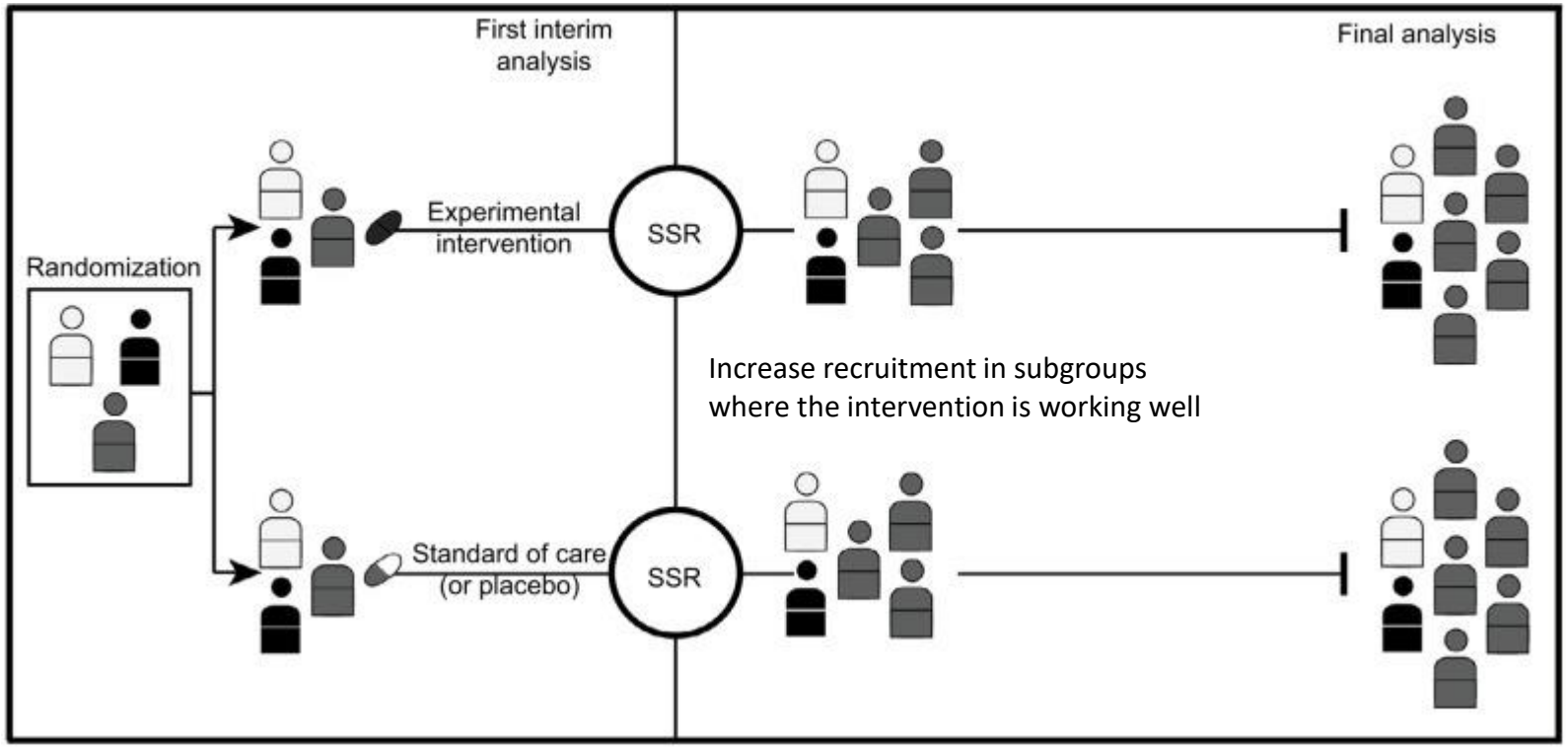
Seamless designs – e.g. phase II/III



Select the "best" doses based on safety and efficacy data

From: Park et al. Clinical Epidemiology 2018:10 343–351

Adaptive enrichment



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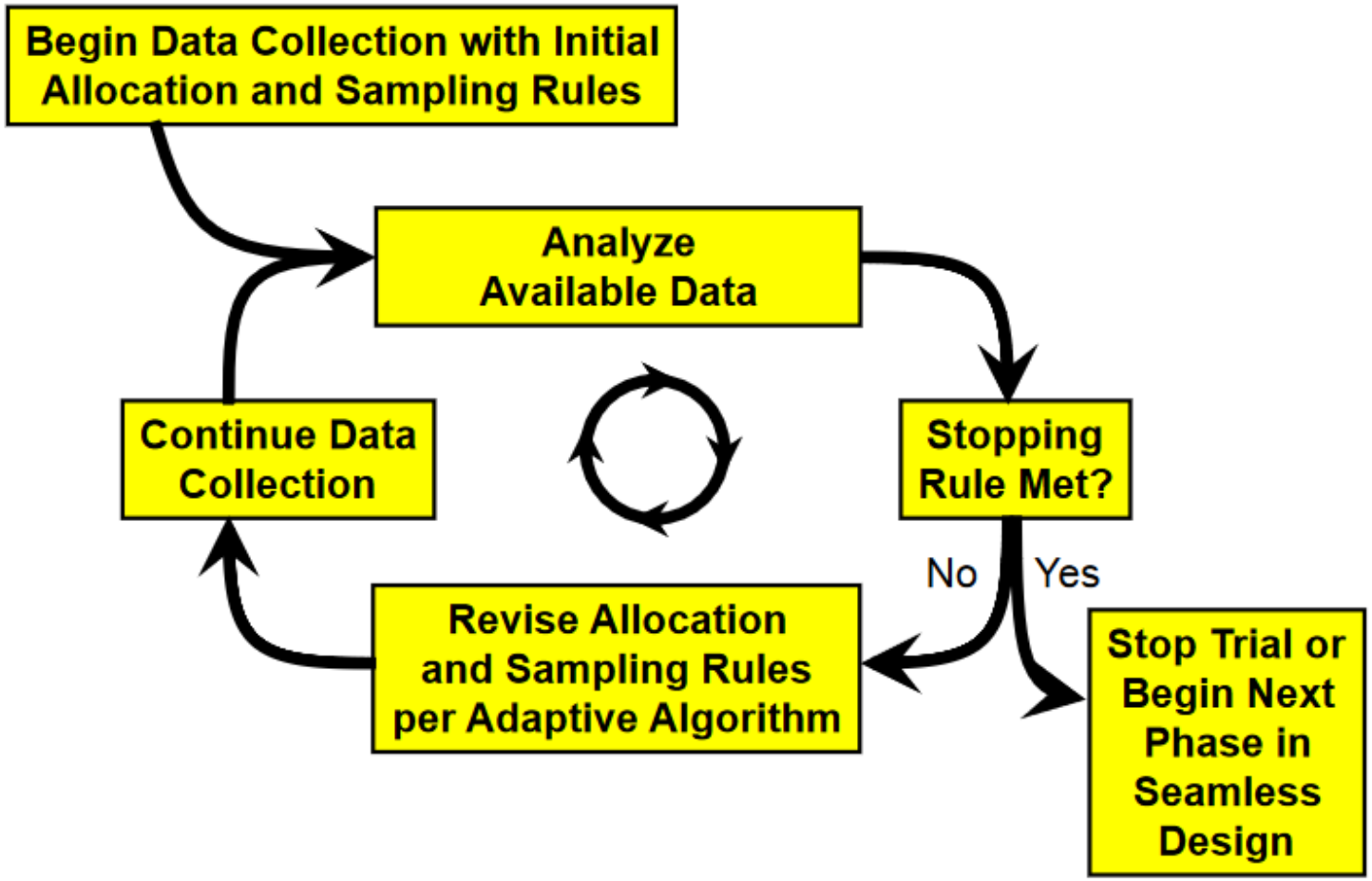
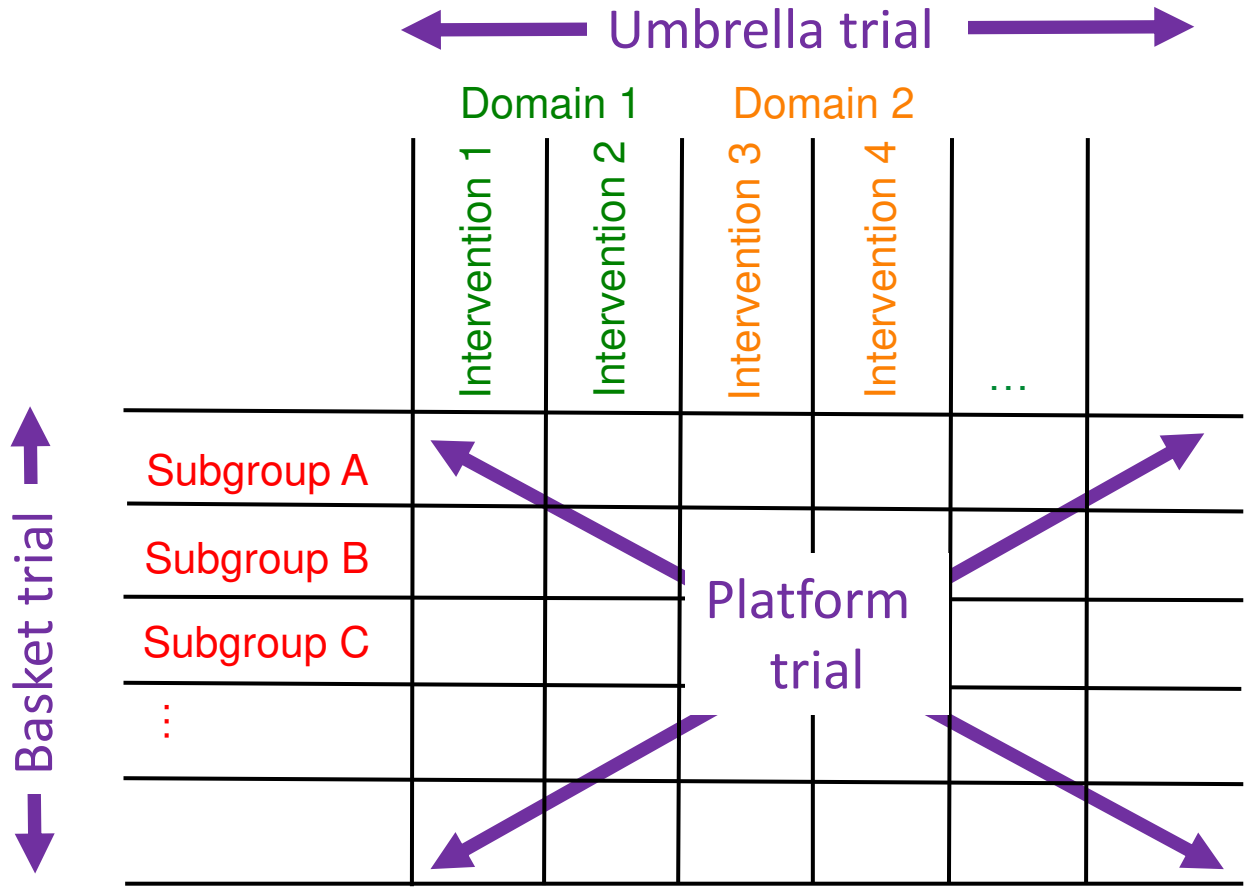
Adaptive trials



Platform trials

Examine the efficacy of multiple interventions across multiple domains simultaneously within different subgroups of participants under a single “master” protocol, with the ability to add interventions and to share information across subgroups

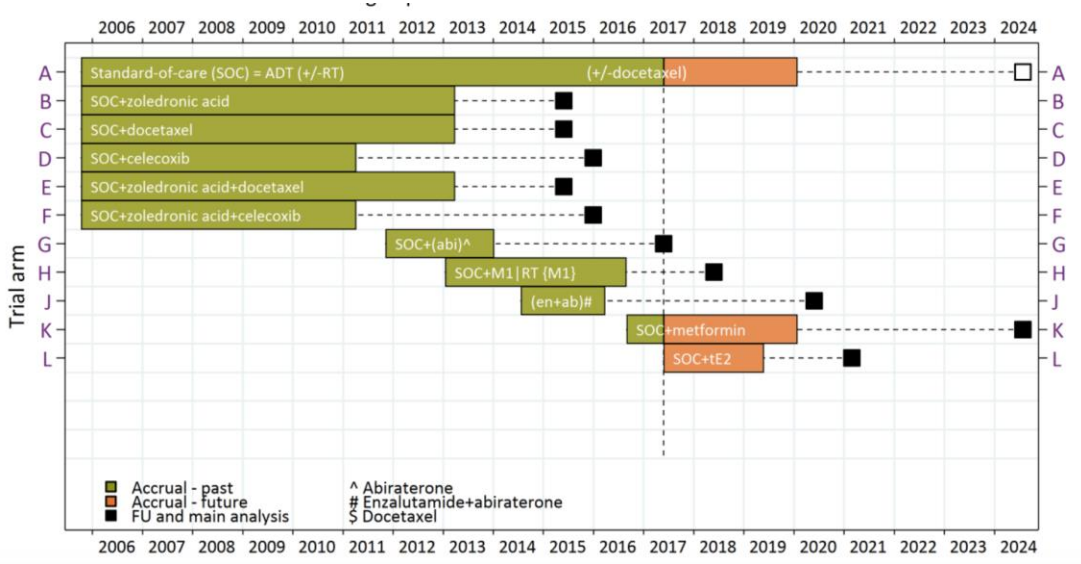


* Domain = competing interventions that share a common clinical mode of action

Platform trials

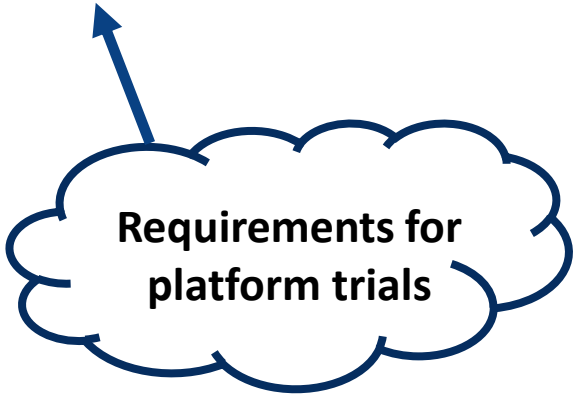
- Governed by a single master protocol
- Treatments can be added or removed
- Any number of subgroups
- No maximum sample size
- Involves frequent interim analyses
- Has predefined decision rules for adaptation
- Treatment assignment controlled by accruing data

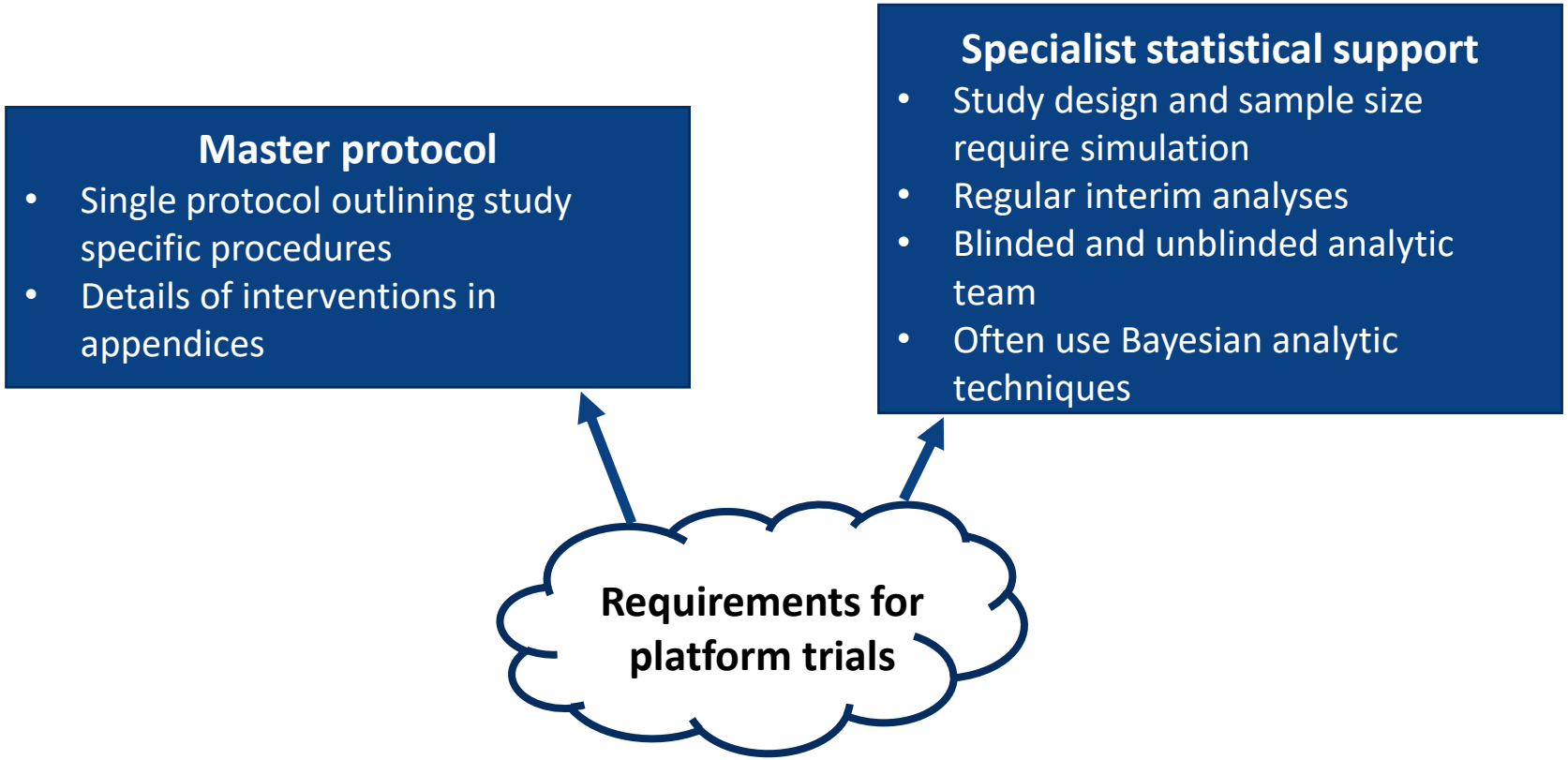
Example: The STAMPEDE trial (prostate cancer)

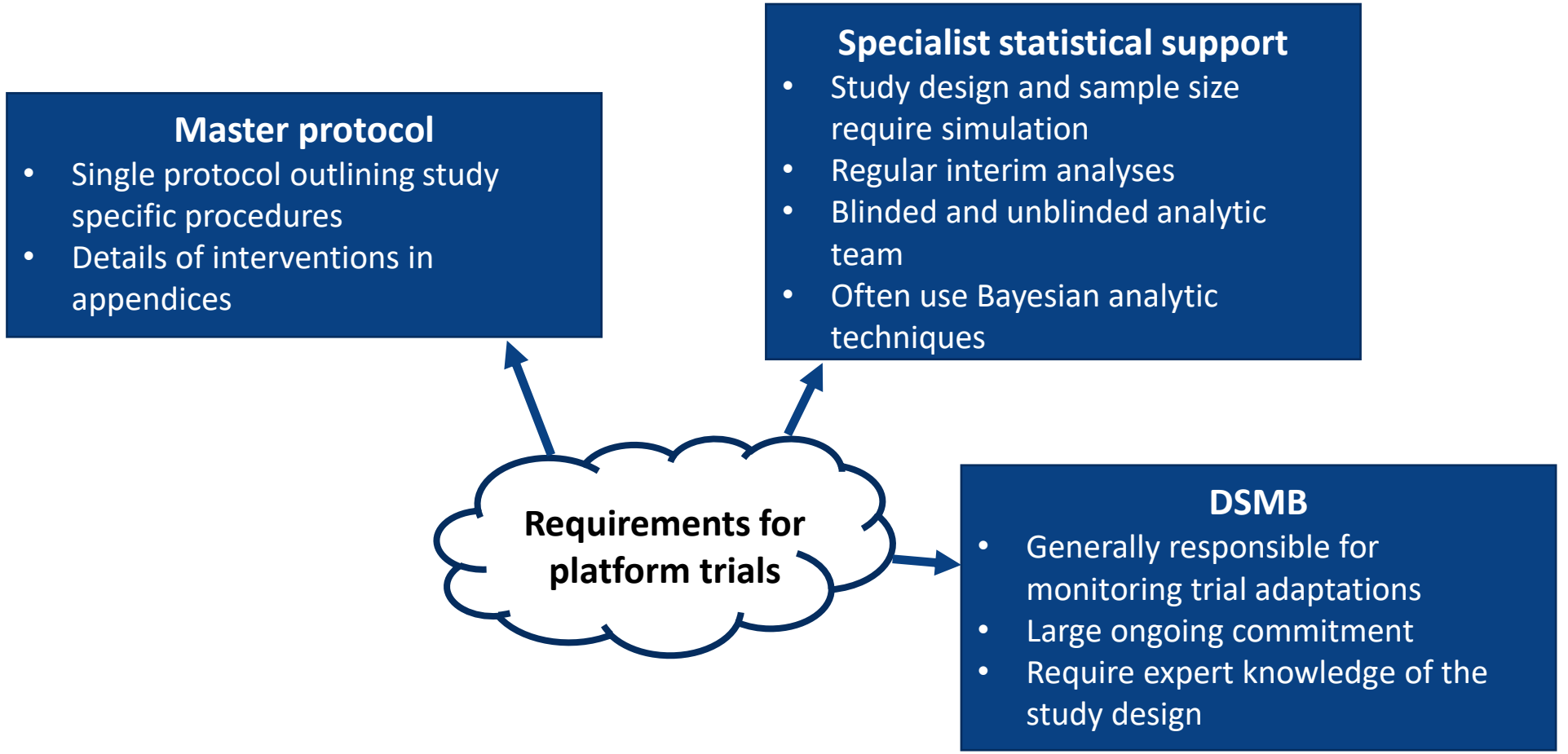


Master protocol

- Single protocol outlining study specific procedures
- Details of interventions in appendices




Master protocol
• Single protocol outlining study specific procedures
• Details of interventions in appendices
Specialist statistical support
• Study design and sample size require simulation
• Regular interim analyses
• Blinded and unblinded analytic team
• Often use Bayesian analytic techniques
Requirements for platform trials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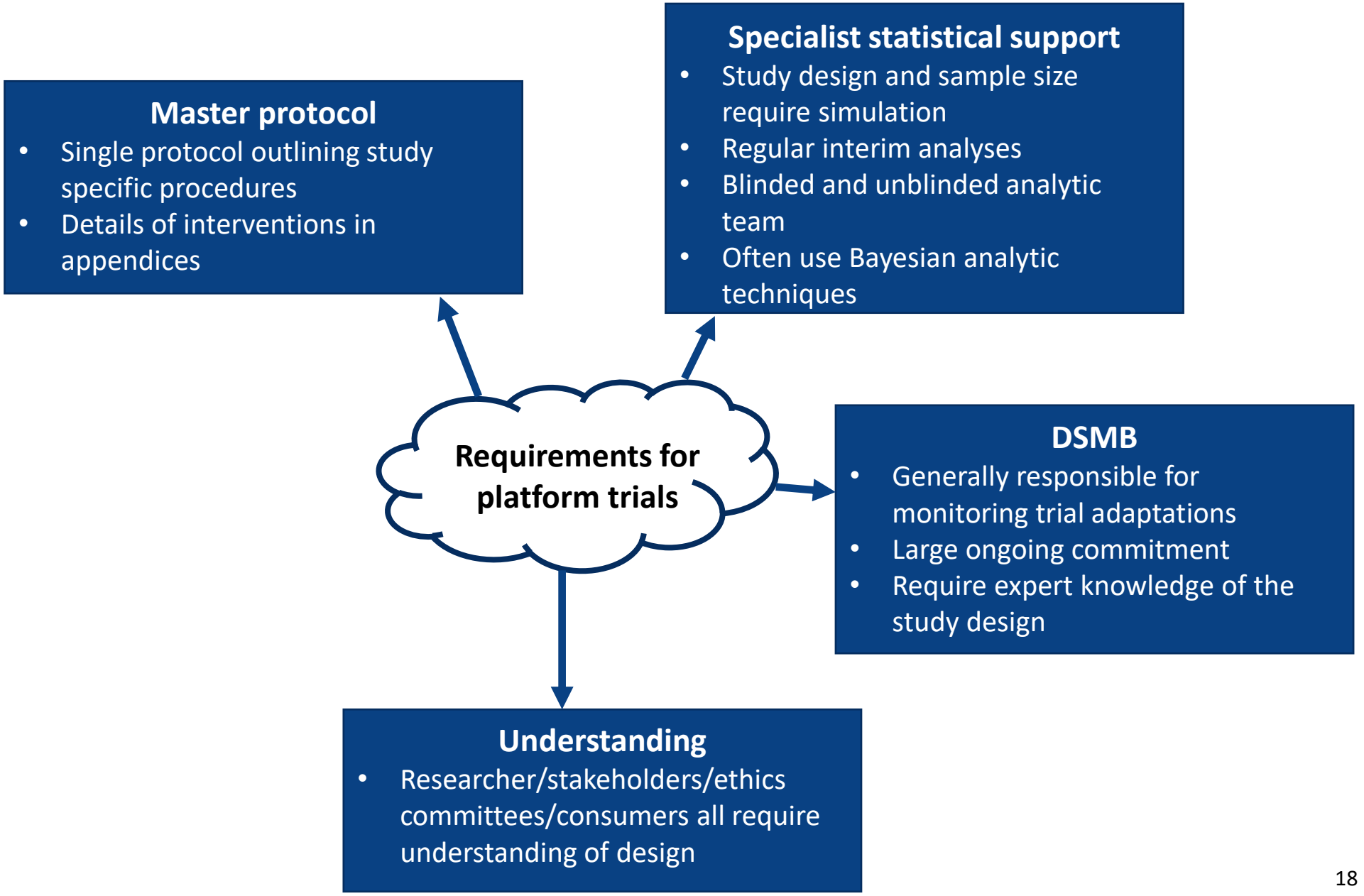
Requirements for platform trials
DSMB
• Generally responsible for monitoring trial adaptations
• Large ongoing commitment
• Require expert knowledge of the study design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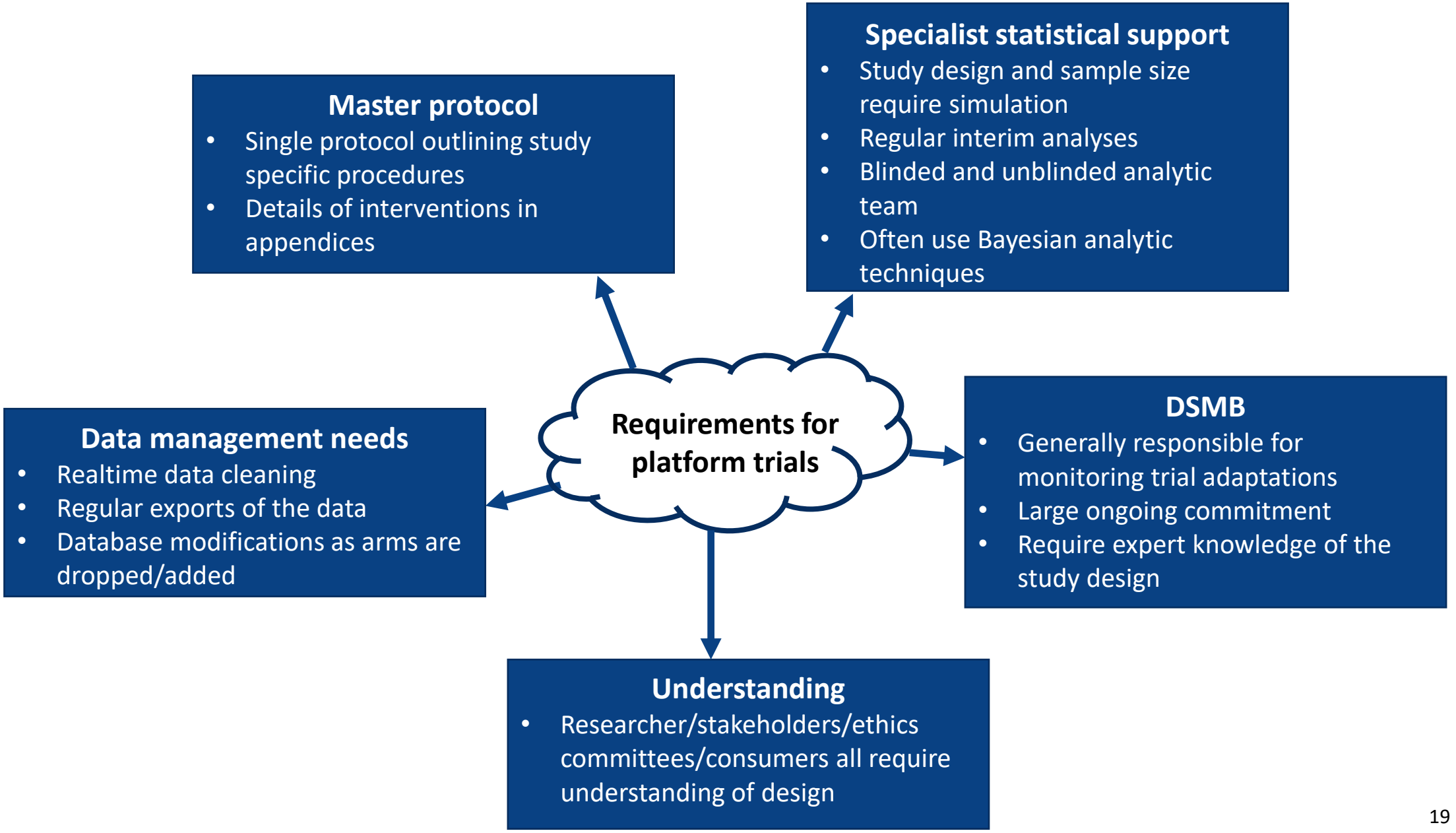
Understanding
• Researcher/stakeholders/ethics committees/consumers all require understanding of design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Requirements for platform trials
Data management needs
• Realtime data cleaning
• Regular exports of the data
• Database modifications as arms are dropped/added
DSMB
• Generally responsible for monitoring trial adaptations
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Pros and Cons of platform trials

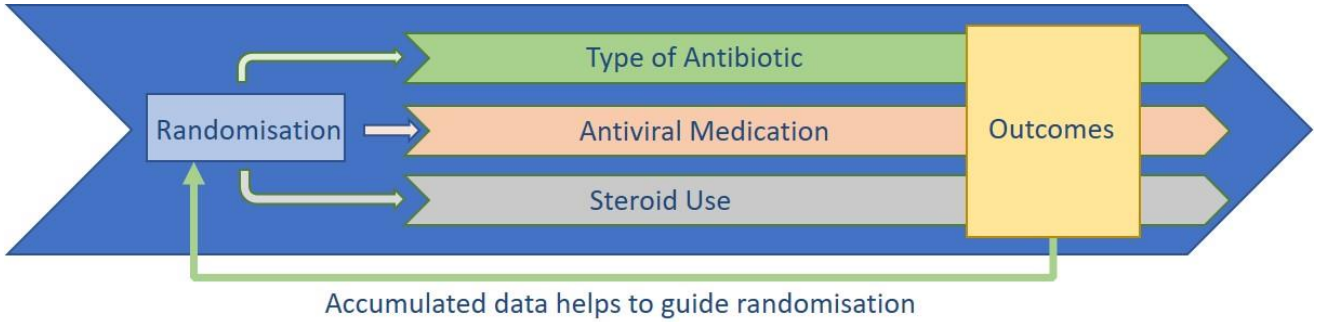
- ✓ Can answer multiple research questions simultaneously
- ✓ Greater statistical efficiency than conventional designs
- ✓ Ethical advantage – may allow fewer patients to be exposed to potentially inferior treatments
- ✓ Enables improved understanding of drug effects e.g. can determine efficacy in subgroups
- ✓ Greater Acceptability to stakeholders (due to added flexibility)

- ✗ All documents take much longer to write than for a conventional trial
- ✗ Heavily reliant on specialist expertise
- ✗ Takes a long time to set up
- ✗ Uncertainty of sample size creates uncertainty of resourcing required to complete trial domains.
- ✗ Logistical challenges (regular interim analyses, ongoing data cleaning,…)
- ✗ Can mean using non-concurrent controls for some treatment comparisons

Example of a platform trial: REMAP-CAP

A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia

- Eligible participants randomised to receive one intervention in each “domain” (set of mutually exclusive treatment options within a single mode of therapy)



- 17 domains (2 under construction)
- Can stop interventions for superiority/futility within a domain
- Can add and remove domain (5 domains concluded and randomisation closed)
- 2 states/sub-groups (critically-ill, not critically ill)
- 3 strata (pandemic infection, influenza, shock)

REMAP-CAP

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

The ATTACC, ACTIV-4a, and REMAP-CAP Investigators*

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ESTABLISHED IN 1812 AUGUST 26, 2021 VOL. 385 NO. 9

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JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Convalescent Plasma on Organ Support–Free Days in Critically Ill Patients With COVID-19
A Randomized Clinical Trial

Writing (

Intensive Care Med
https://doi.org/10.1007/s00134-021-06448-5

ORIGINAL

Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

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Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

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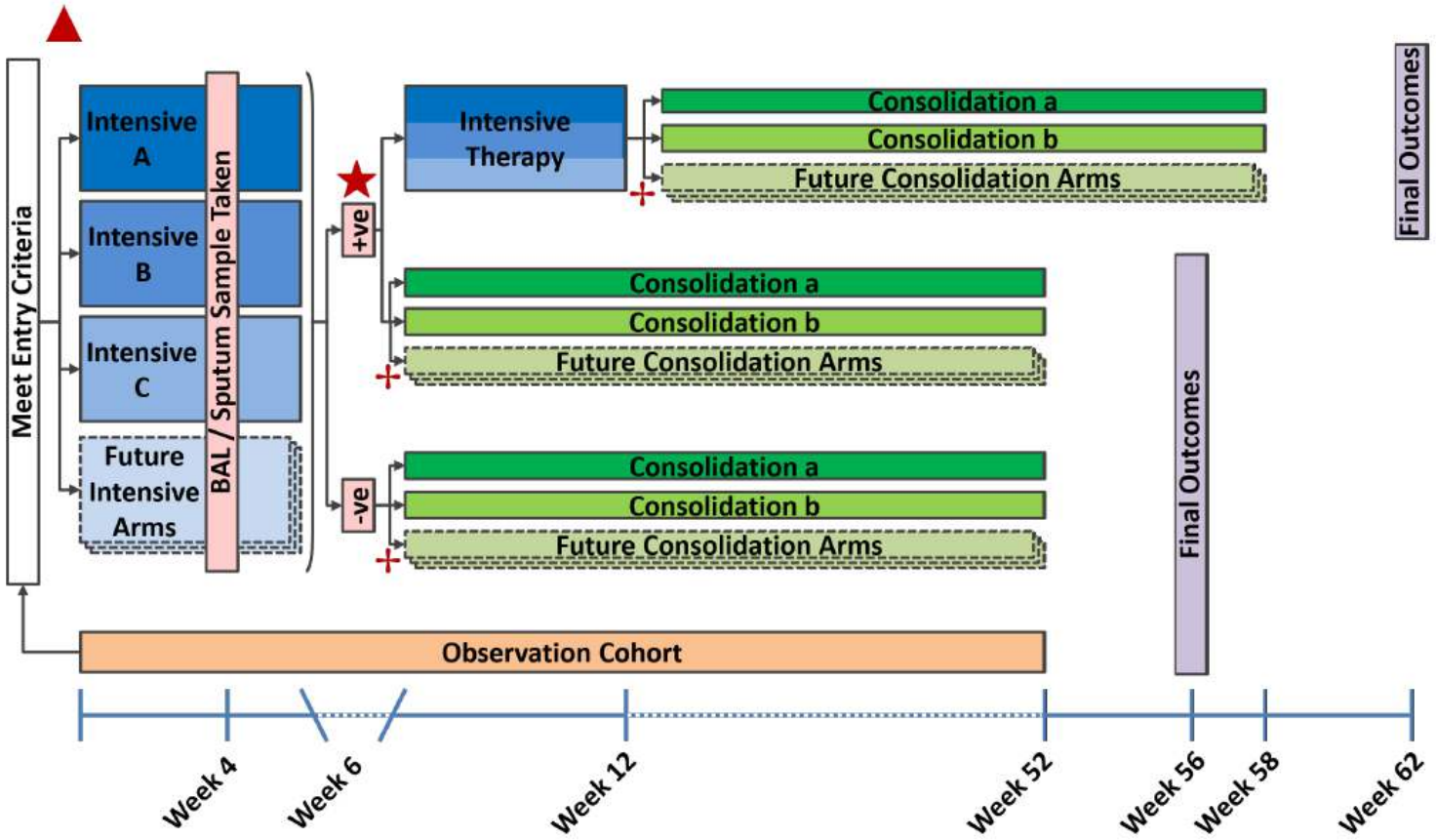
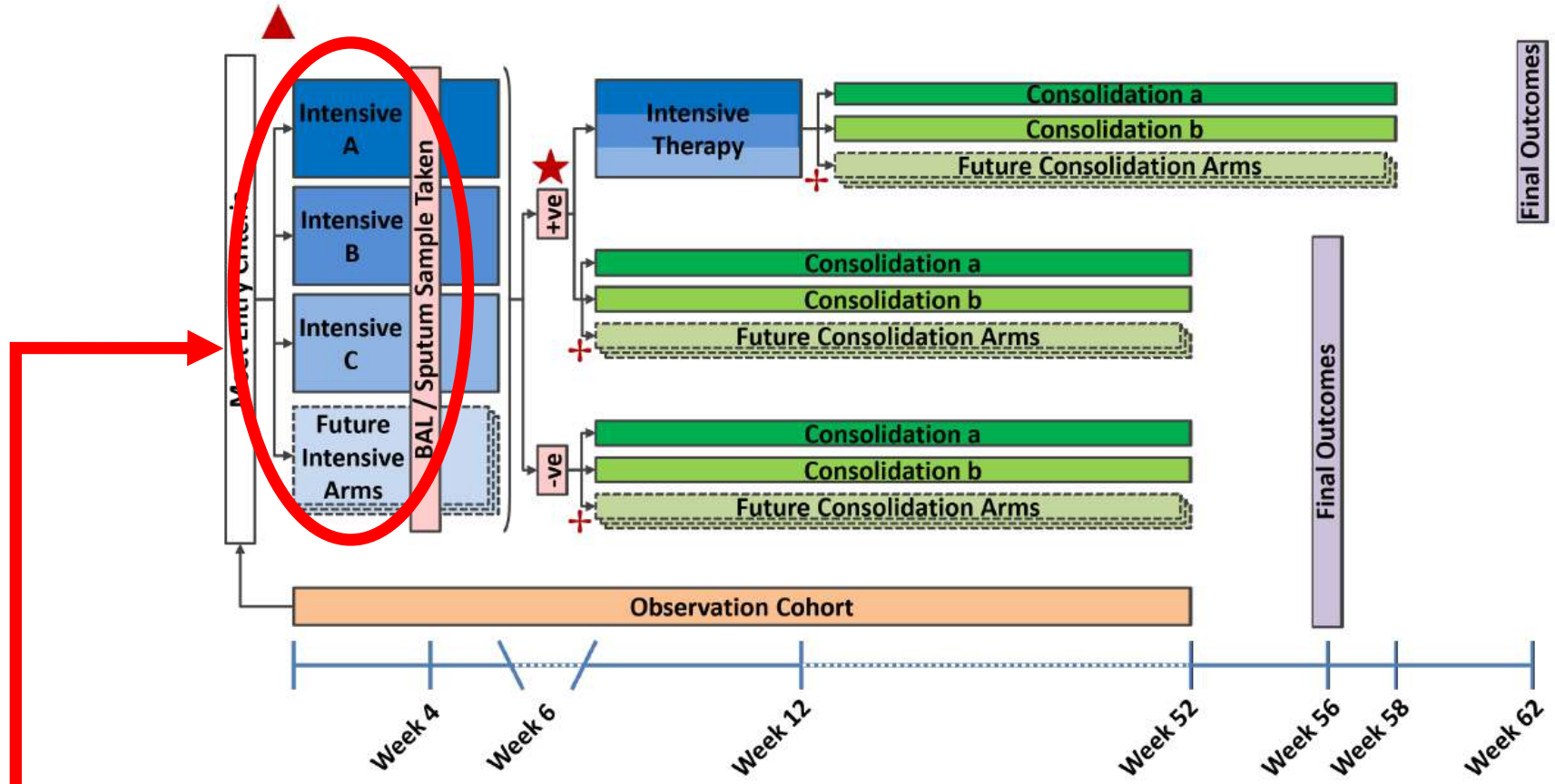
REMAP-CAP Writing Committee for the REMAP-CAP Investigators

Example of a platform trial: The FORMaT study



Finding the Optimal Regimen for Mycobacterium Abscessus (MABS) Treatment

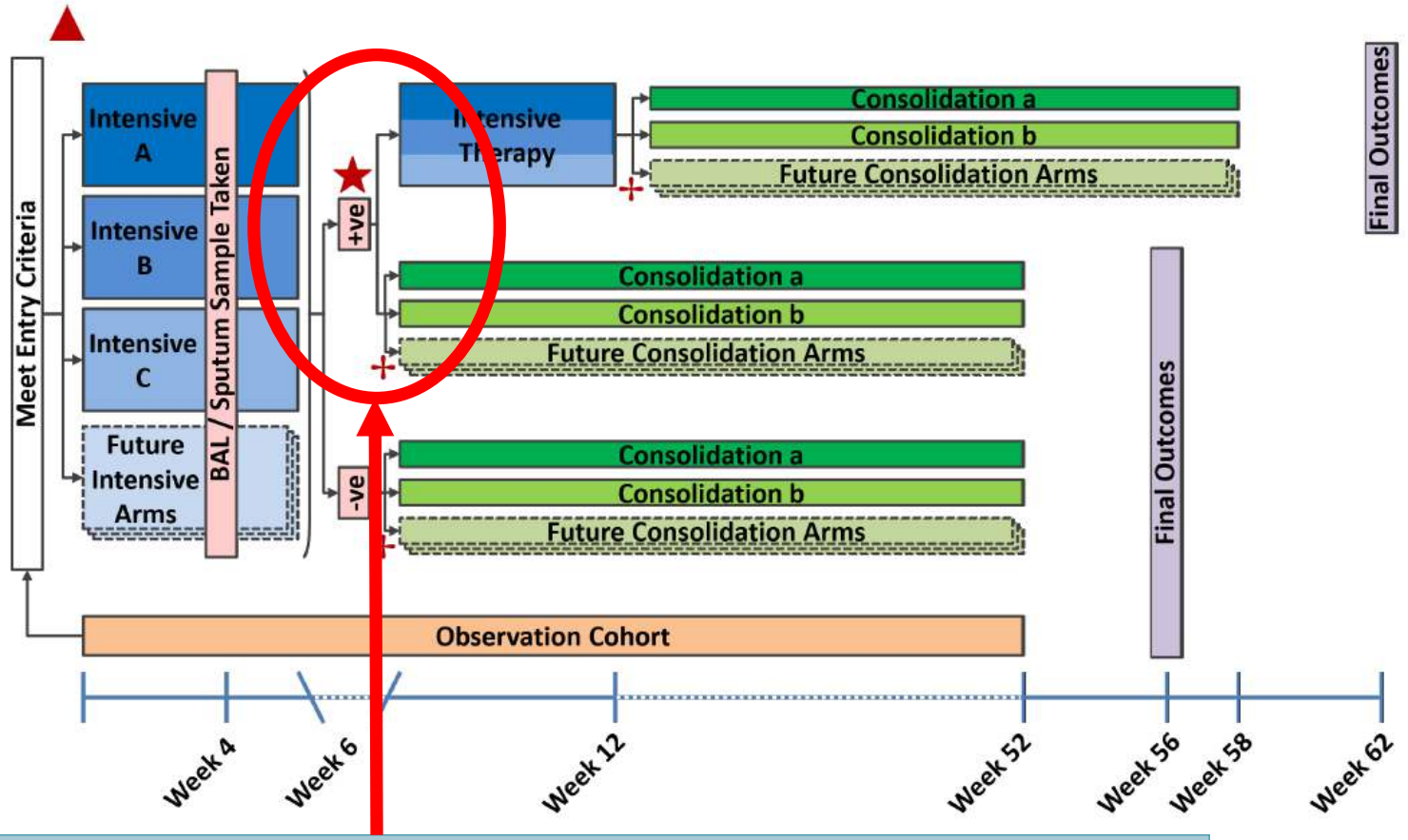
Example of a platform trial: The FORMaT study



Randomisation 1

Initially randomise between 3 different treatment combinations for the intensive phase (6 weeks)

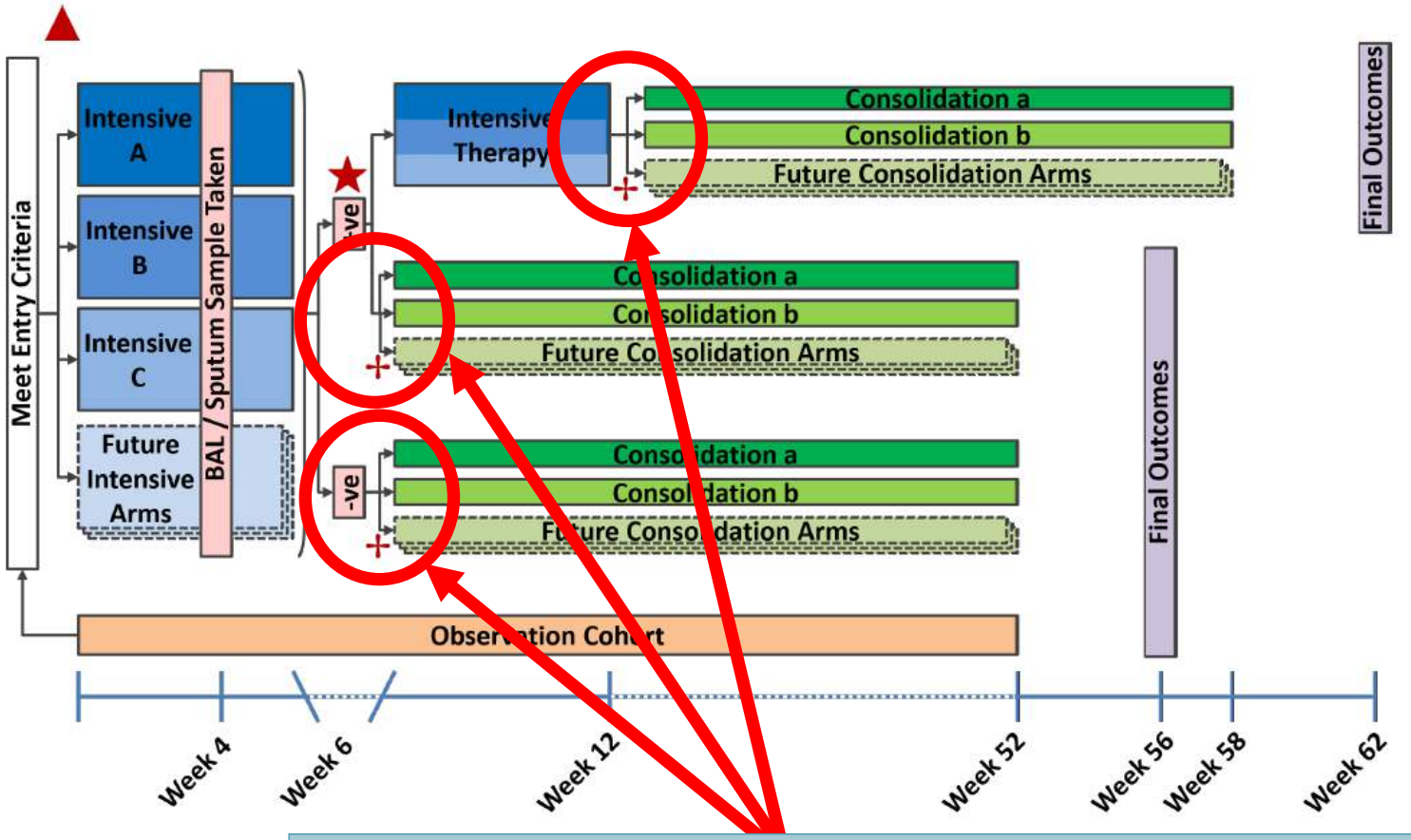
Example of a platform trial: The FORMaT study



Randomisation 2

In those who are MABS positive at week 6, randomise between continue intensive therapy or commence consolidation therapy.

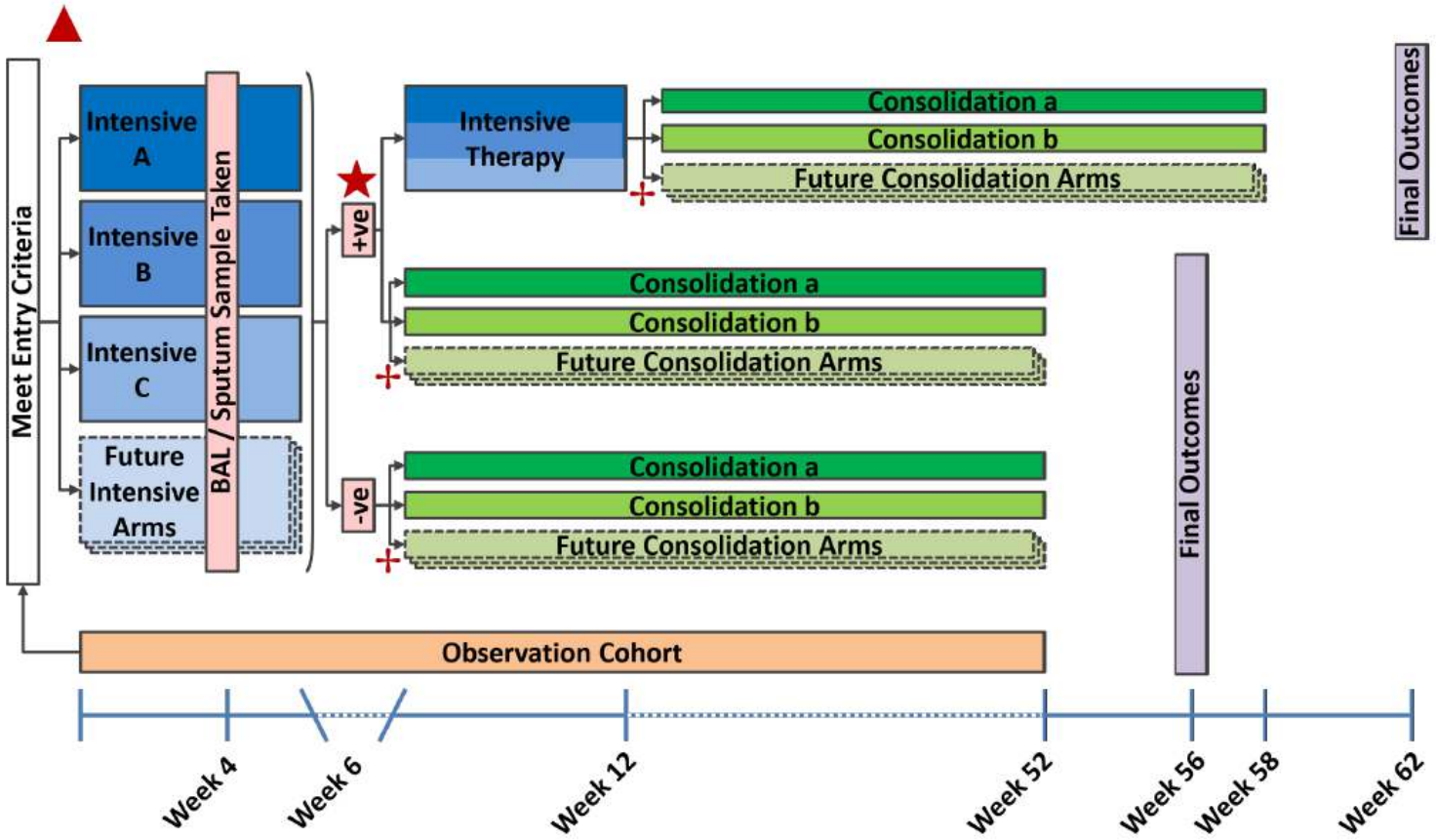
Example of a platform trial: The FORMaT study



Randomisation 3

Randomise between 2 different drug combinations for the consolidation phase

Example of a platform trial: The FORMaT study



This is also an example of a **sequential multiple assignment randomised trial** (SMART)
-> Can assess the effects of dynamic treatment regimens

Example of a platform trial: The FORMaT study

Designed to answers multiple questions simultaneously

- Best intensive therapy (R1)?
- Short or long intensive (R2)?
- Best consolidation (R3)?
- Best overall regimen?

Sequential Multiple Assignment Randomised Controlled Trial (SMART)

Response adaptive randomization

- More participants randomised to more promising interventions

Early stopping for efficacy

Ability to add in new interventions

Initially aim to recruit 300 participants but a pre-specified plan to expand (no finite sample size)

Bayesian statistics

Adaptations naturally fit with the Bayesian framework…

Bayesian statistics

Bayesian framework

- What is the probability that we are seeing a tank?

Bayesian statistics

Bayesian framework

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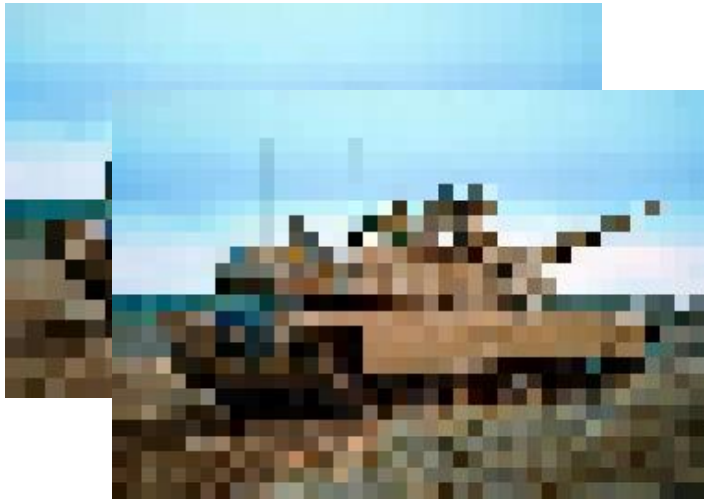

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- What is the probability that we are seeing a tank?

Frequentist framework

- Is it a tank?

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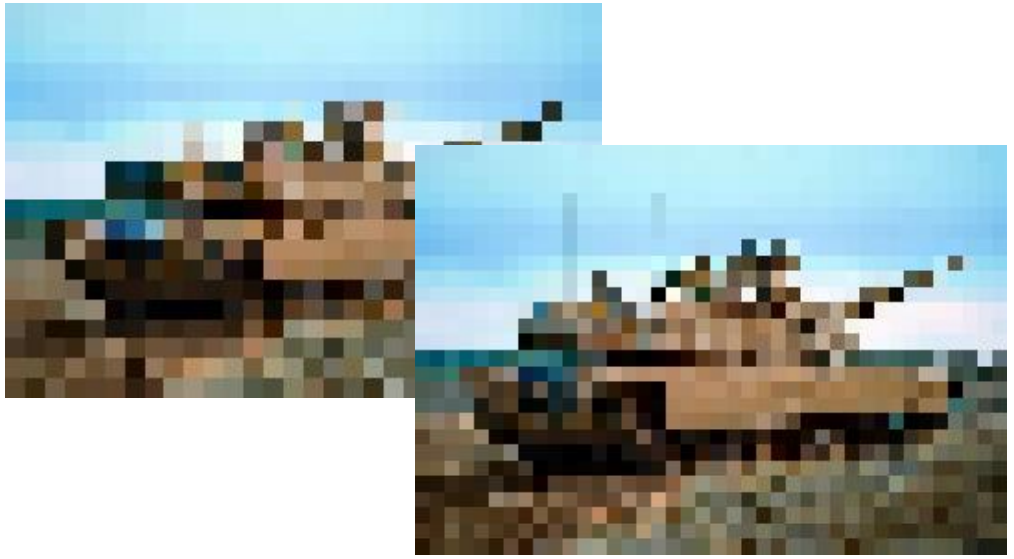

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Frequentist framework

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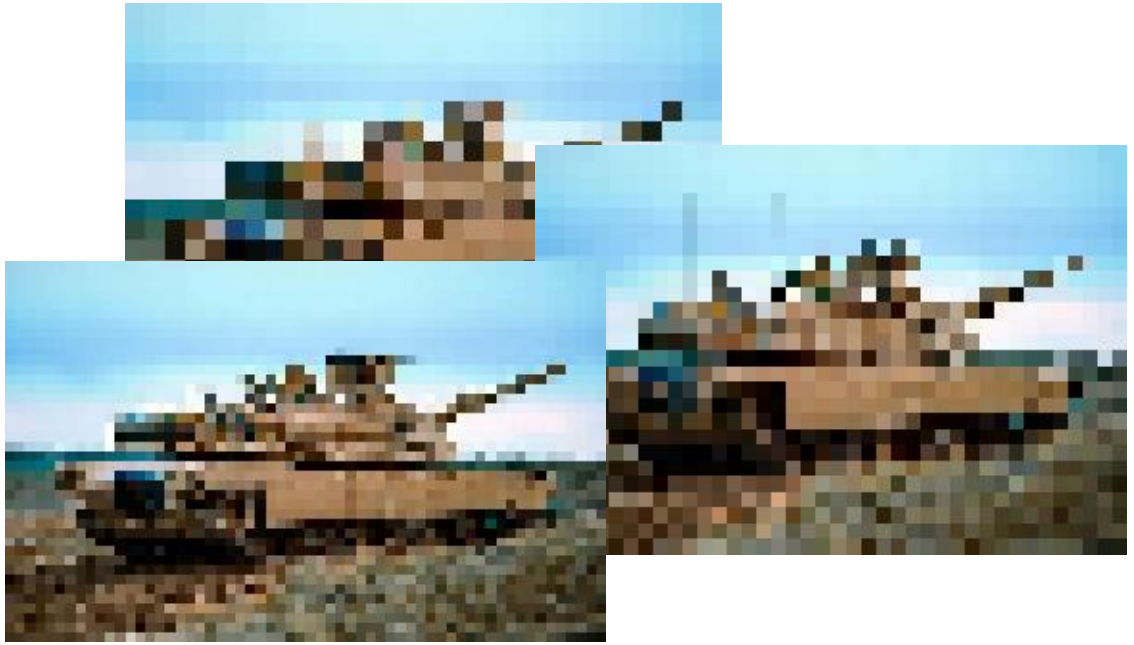

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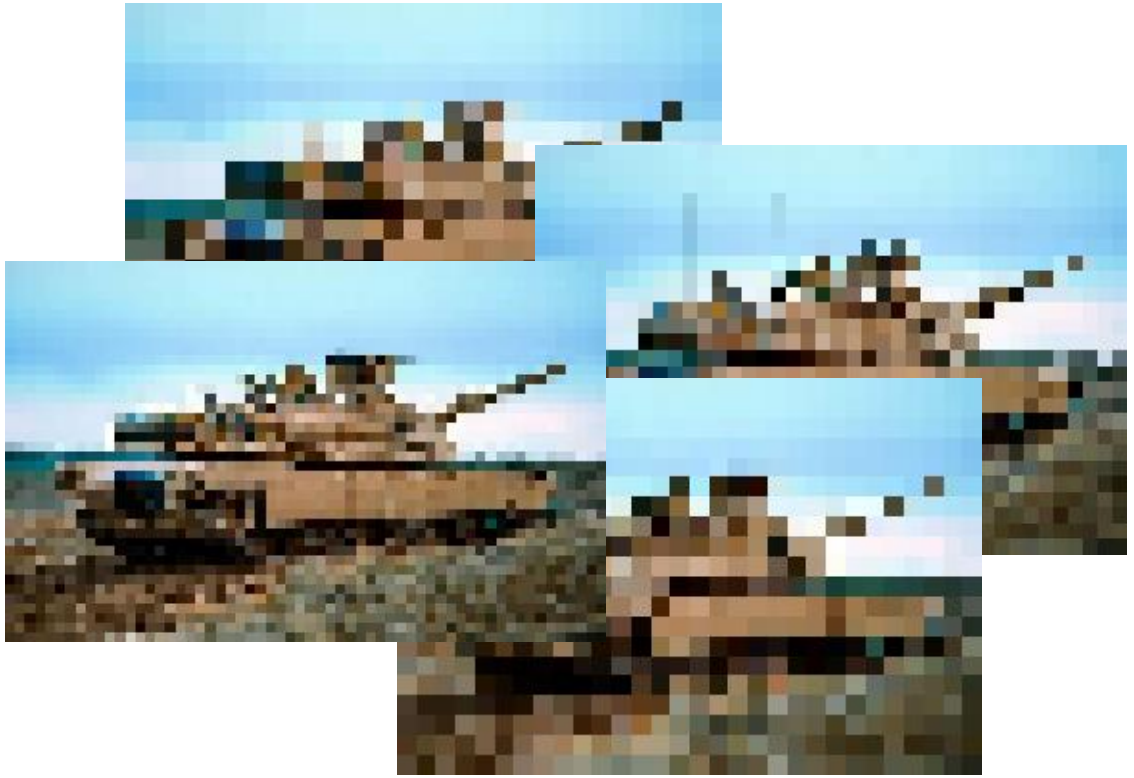

Bayesian statistics

Bayesian framework	Frequentist framework
Combines prior information with current data	Considers the data in light of the null hypothesis (no treatment effect)
Probability that there is a difference	Probability of the data if the null hypothesis were true
More flexible	Less flexible
Naturally handles multiple looks at the data	Need to penalize for multiple looks at the data
Less familiar	More familiar/routinely used
Requires specialised software	Software widely available

Bayesian statistics

- Can conduct many interim analyses
- No adjustment for multiple looks at the data
- Don’t need to consider Type I (finding no effect when there is an effect) and Type II (finding an effect when there is no effect) error
- Adaptations guided by the predictive probability of the experimental arms being superior to the control arm

  For example, arm dropping:

  - If the predictive probability of superiority is high (e.g. > 0.95) → stop for success
  - If the predictive probability of superiority low (e.g. < 0.5)→ stop for futility

→ Often used in platform trials

When to use a platform trial

- ✓ Short term outcome relative to the time frame of the trial
- ✓ Multiple therapies available
- ✓ Likely to be new therapies becoming available
- ✓ Potential heterogeneity of treatment response across subgroups
- ✓ When the team has access to expertise (e.g. statistical) to design and implement these trial designs

Common criticisms (and potential solutions)

1. Temporal changes & non-concurrent controls can produce biased effect estimates: model time effects in the primary analysis
2. Response Adaptive Randomisation is inefficient & produces bias effect estimates: delay time until start of RAR, fix control arm allocation
3. Increased potential for selection & operational bias: defined roles for blinded and unblinded study personnel (trial governance & integrity)
4. More resources needed to initiate trial: but may be resource saving overall
5. Slow collection/availability of high-quality data: technology
6. Need to custom-build response adaptive randomisation module
7. Shortage of researchers with training/skills to implement adaptive trials
8. Greater statistical burden & shortage of statisticians with appropriate skills
9. Knowledge gap in hospital governance, HREC and DSMC

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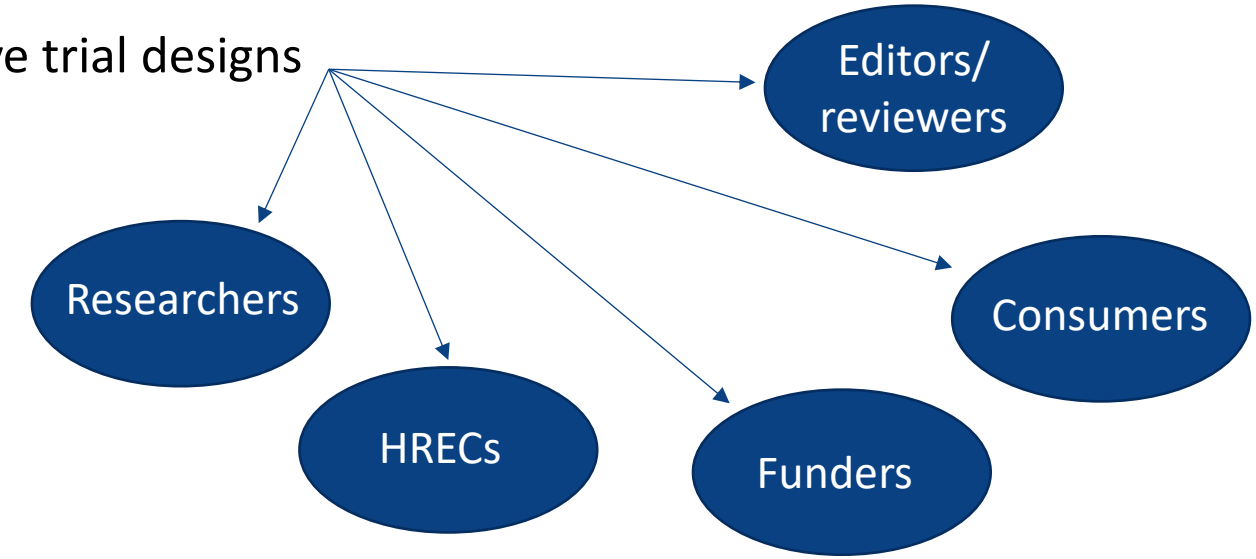
Need for increased training and capacity building

Increasing the use of platform trials

Increase knowledge of these innovative trial designs

- Training workshops
- Guidance documents
- Repository of references



Greater understanding of when such designs are and are not useful

Increased biostatistical capacity and specialist expertise to support adaptive platform trials

Summary

Adaptive and platform trials can be extremely useful because of their flexibility and efficiency

However, they need to be used with caution

- Is the outcome short enough to be useful to guide adaptations?
- Require an extremely long lead-time
- Requires ongoing specialist expertise

There is an ongoing need to increase knowledge and understanding of these innovative trial designs nationally if they are to be used in future research

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Questions?

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