ADAPTIVE HEALTH INTELLIGENCE

EVIDENCE IN ACTION

A novel decision-making framework for Bayesian adaptive trial designs

Michael Dymock

13th December 2023

TELETHON KIDS INSTITUTE
Discover. Prevent. Cure.

WESFARMERS CENTRE OF VACCINES & INFECTIOUS DISEASES

THE UNIVERSITY OF SYDNEY

THE UNIVERSITY OF WESTERN AUSTRALIA

Overview

- Adaptive clinical trial design
- Clinical trial decision-making
- The PICOBOO trial
  - Design
  - Model
  - Decision-making

Why design clinical trials?

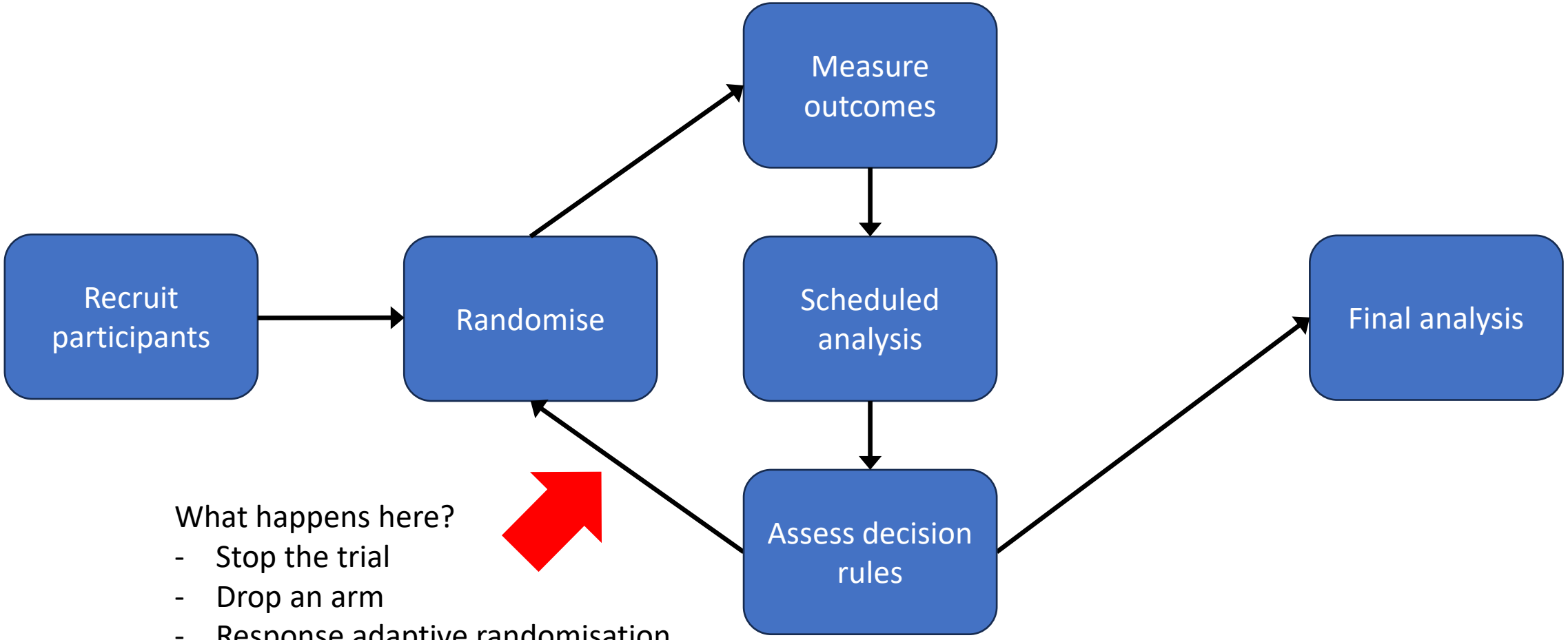
- Better science
- Efficient use of resources
- Answer the appropriate research question
- Ethical arguments

ADAPTIVE HEALTH INTELLIGENCE
EVIDENCE IN ACTION

Adaptive trial designs

- The trial design **adapts** in response to the accrued data
  - Number of trial arms, randomisation probabilities, sample size, etc. **may** change as the trial progresses
- "Hard" to design the trial
  - Requires simulations, many levers to pull
- "Hard" to implement the trial
  - More complicated for participants, analysts, scientists
- Opportunity gains?
  - Information gathered during the trial can be used to increase **design efficiency**

Adaptive trial designs



What happens here?

- Stop the trial
- Drop an arm
- Response adaptive randomisation

ADAPTIVE HEALTH INTELLIGENCE
EVIDENCE IN ACTION

Is this cherry picking?

- For an adaptive design we **prespecify** the decision rules
  - Although decisions are made conditional on the data, the rules for decision-making were agreed beforehand
- Impact of decision rules is explored prior to trial implementation (simulations)
- We have “freedom” with decision rules but typically use “superiority” and “futility” rules

ADAPTIVE HEALTH INTELLIGENCE
EVIDENCE IN ACTION

Decision rules galore

- In theory, these decision rules can be anything that we can compute
- Let $P(\theta|X)$ be the posterior distribution of a treatment effect θ
  - E.g., declare the treatment superior if: $P(\theta > 0|X) > 0.95$
- We could use a different threshold at each analysis
  - $P(\theta > 0) > 0.995$ at early analyses
  - $P(\theta > 0) > 0.94$ at the final analysis
- We could directly compare to a “clinically important difference"
  - $P(\theta > 0.5) > 0.9$
- We could define a decision rule based on another quantity entirely

The PICOBOO trial

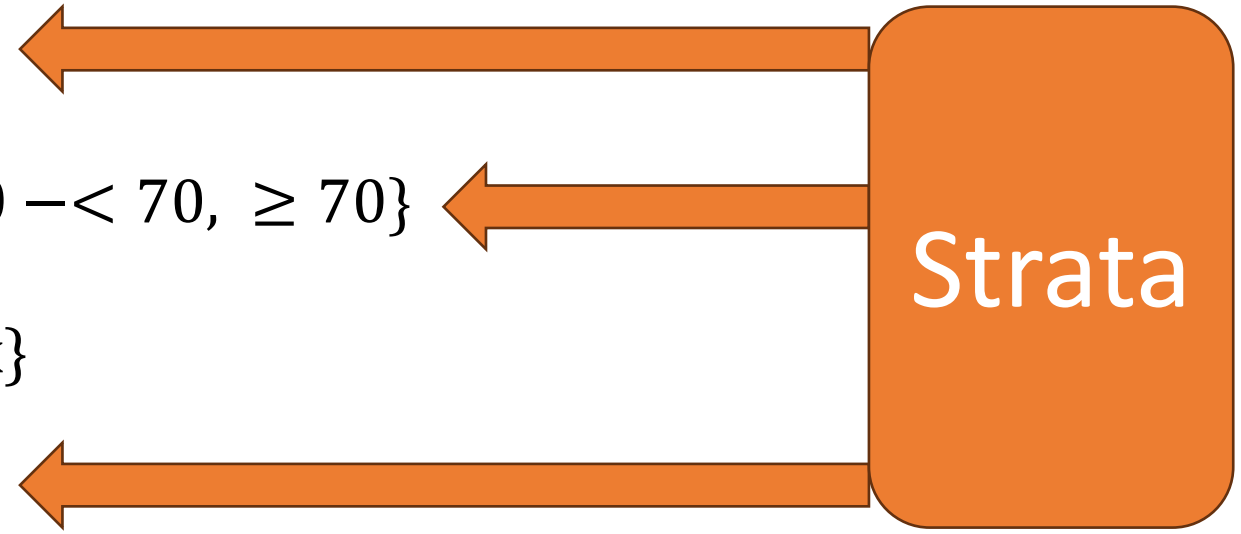
- Randomises participants to receive one or more COVID-19 booster vaccinations
- Strata: Primary schedule, age group and booster dose number
- Interventions: Pfizer, Moderna, Novavax, …
- Primary estimand: log10 ancestral SARS-CoV2 anti-spike IgG at 28 days
- Decision rules: **Not** based on superiority, futility or intervention comparisons

Our decision rule is based on the precision of the primary estimand!

ADAPTIVE HEALTH INTELLIGENCE
EVIDENCE IN ACTION

Notation (simplified)

- Participant: $i \in \boldsymbol{I} = \{1,2,\ldots,N\}$
- Primary Schedule: $j \in \boldsymbol{J} = \{\mathrm{AZ}, \mathrm{Pf}, \mathrm{Mod}\}$
- Age Group: $l \in \boldsymbol{L} = \{18 -< 50, 50 -< 70, \geq 70\}$
- Intervention: $k \in \boldsymbol{K} = \{\mathrm{Pf}, \mathrm{Mod}, \mathrm{Nvx}\}$
- Booster Number: $m \in \boldsymbol{M} = \{1,2,3\}$
- Outcome: $y_{ijklm} \in \mathbb{R}$



Model

$$Y_{ijklm} \sim \mathrm{N}\left(\mu_{jklm} + \cdots, \sigma_l^2\right)$$

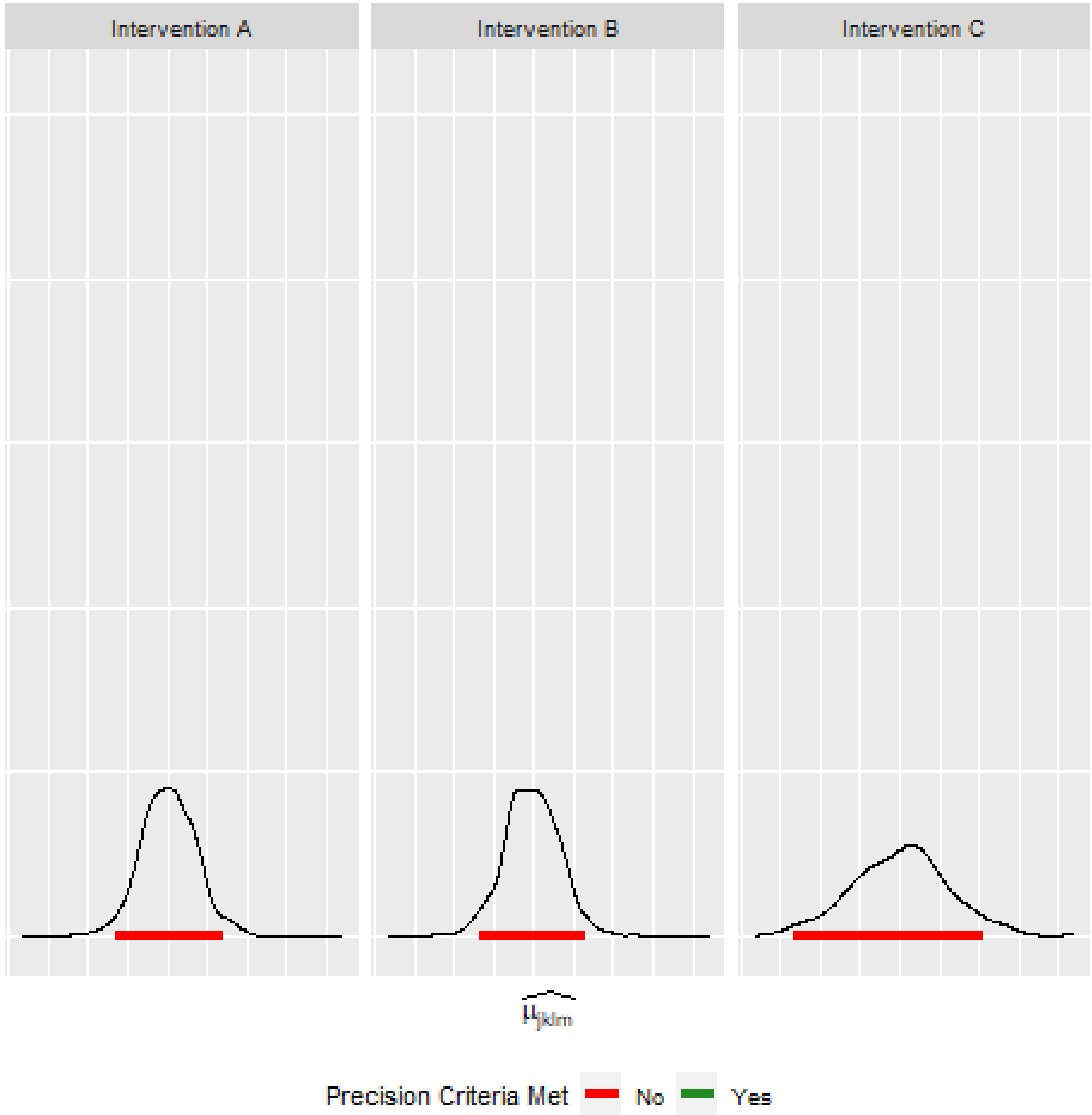
μ_{jklm} is mean response for intervention k within stratum $j \times l \times m$ when covariates are at their reference levels

~~Decision~~ Precision Rules?

- The statistical quantity of interest is μ_{jklm}
- We estimate μ_{jklm} via a posterior distribution with a 95% highest density credible interval
- The **width** of the interval crudely represents our **uncertainty**
- Once the interval width is **sufficiently narrow**, we claim that we have gathered **sufficient information,** and the precision criteria has been met
- Once the precision criteria is met for **each intervention within a stratum,** we stop recruitment into that stratum

What does that mean?

- As we gain information (collect data) our precision increases
- Once we have sufficient precision for each intervention, we cease recruitment within that stratum



Why would we do this?

- Vaccine immunogenicity outcomes **do not necessarily** correlate with protection
- It is difficult to say one intervention is **“better”** than another because it induced a higher **mean response** on one particular outcome measure
- Immunological assays are **expensive and time consuming** so we cannot rely on them for within-trial decision-making
- Instead, let’s **efficiently** collect quality data and **avoid wasting** our resources
- Our recruitment is guided into strata that maximise our **value of information**

Some final thoughts

- Adaptive designs allow for the accrued data to inform the design
- If it is uncertain how to define a **superiority condition** (decision rule) then what if we collected information until we were satisfied
- Conceptualise the trial as an **information gathering expedition**
- Stops us from over sampling (wasting resources) on data collection
- Is it time to rethink how we define decision rules?
- Is it time to rethink how we design clinical trials?

Acknowledgements

- PICOBOO Clinical Trial Team
  - Investigators, site staff, participants,…
- Coauthors:
  - Charlie McLeod
  - Tom Snelling
  - Peter Richmond
  - Julie Marsh