Rethinking Clinical Trial Design

Should We Consider the Value of Information?

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A confession

This is a statistics talk…

AND a philosophy of science talk!

It may be (a little) provocative…

so, if any content concerns you….

good! Let’s discuss afterwards!

Some questions to ponder

Clinical trials produce useful evidence

- Do they always?
- How often do results inform policy and practice?

Hypothesis testing is central to clinical trial design

- Why?
- Should it *always* be?

The traditional approach

- Define primary outcome, statistical model and parameter/s of interest
- Construct hypothesis test
- Estimate a required sample size based on power, type one error rate, etc.
- Choose a trial design that meets feasibility, ethical and **statistical** criteria
- Conduct the trial
- Hope you meet a decision rule and publish the results
- Hope that the results **translate** into policy and practice

What are (some) limitations?

- Decision-makers consider multiple clinical and health economic outcomes
- But the design was driven only by the primary outcome (for statistical reasons)
- Results from secondary analyses may be highly uncertain
- Perhaps we could have collected more data to resolve this uncertainty
- Perhaps we collected too much data and could have decided earlier

What if we did it differently?

- What if we **knew** what the decision-maker needed and designed a trial to answer this question **directly**?
- Suppose we had a function to represent their decision-making process
- Could we collect **just** enough information to **sufficiently** inform the decision?
- Could we **“bridge”** the gap (abyss) between clinical research and translation?
- No longer concerned with statistical errors because we have no interest in making declarations about the value of the effect parameter

Can we do it?

How? Value of information (VOI) methods

- Suppose you have decision function $U(d, \boldsymbol{\Theta})$ for decision d and parameters $\boldsymbol{\Theta}$
- We might ask:
  - Given our current uncertainty, what decision is better in expectation?
  - What is the expected **value** of eliminating parameter uncertainty?
  - What is the expected **value** of reducing parameter uncertainty?
  - Given the expected value accrued, is it worthwhile conducting my trial?

The ~~traditional~~ value-based approach

- We can estimate if data collection is **valuable** (and therefore justifiable)
- Choose a design that optimises this trade-off
- But:
  - The methods can be computationally challenging
  - Recently developed approximation methods work well
  - Still rarely implemented in practice (usually supporting information)
  - Computational concerns? Conceptually unorthodox? Dogma?

Extensions to adaptive designs

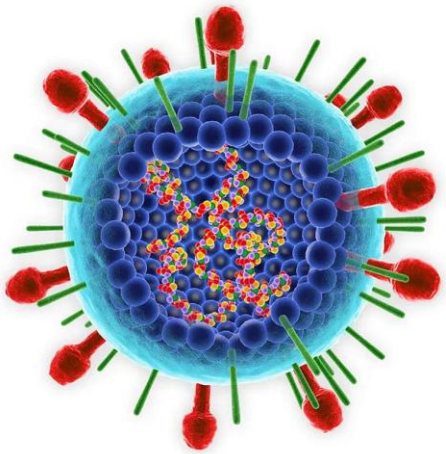
- Could we use a value-based decision rule to drive trial adaptations?
- Why? All designs rely on pre-trial assumptions that may be wrong
- How? Revise VOI calculation at interims and stop if no longer sufficiently valuable
- Analytical solutions exist but no trial has ever been designed this way
- Why?
  - Validity of assumptions of the current solutions in real-world settings?
  - Computational concerns? Conceptually unorthodox? Dogma?

Value-driven adaptive design

- Uses VOI as a decision rule at interims
- Repeatedly reduce parameter uncertainty and revise VOI calculation
- Applicable to trials where assumptions required by other methods do not hold
- Flexible to any statistical model, decision model and research cost function
- Extended calculation to account for value accrued external to the trial
- Methods to estimate VOI of continuing to the next analysis, or one after, etc.
  - But no free lunch! Computationally intensive to look further ahead!
- Generic methods implemented in R package (**michaeldymock25/ValueAdapt**)

RSV Case Study

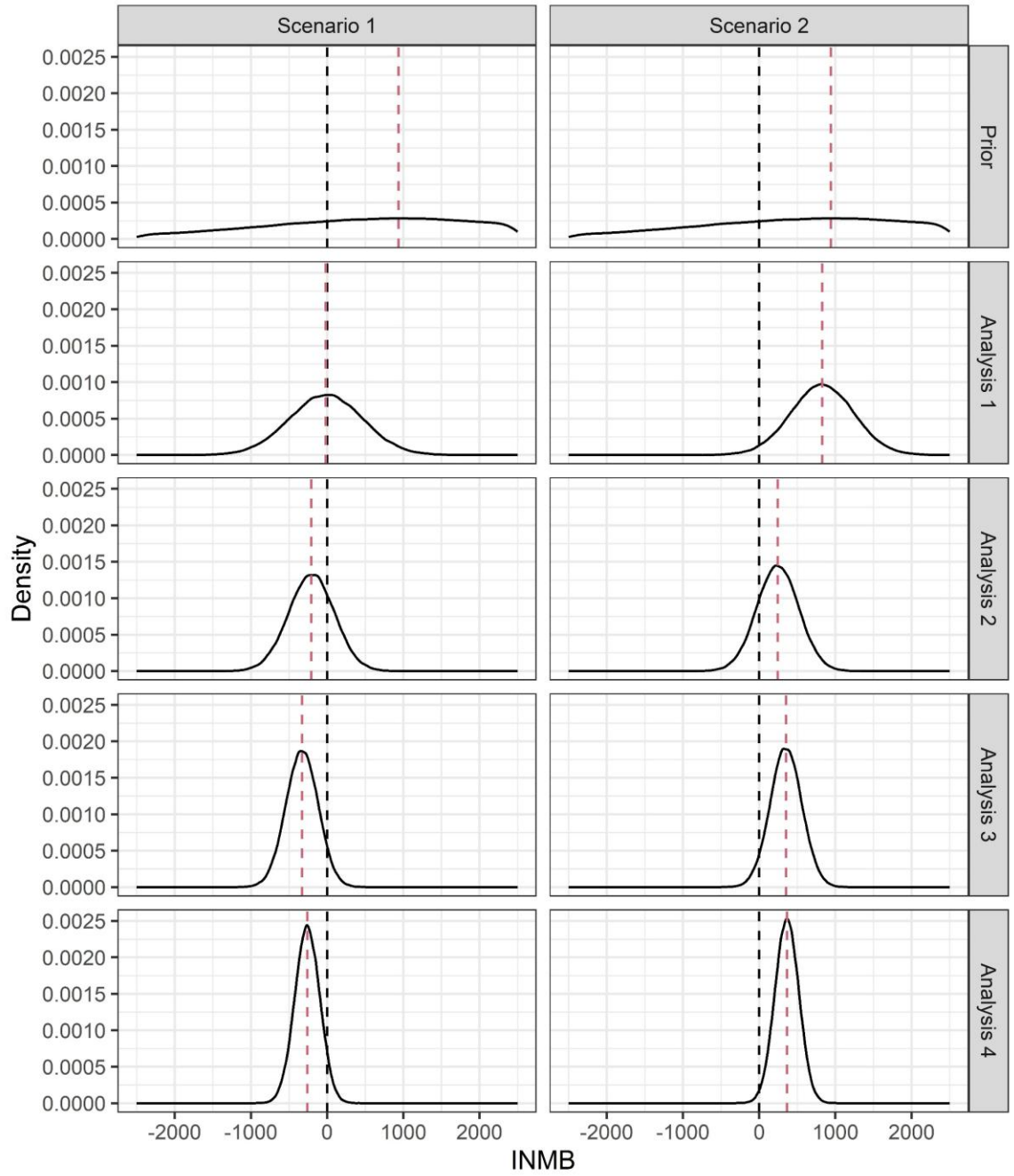
- Respiratory syncytial virus (RSV) infection accounts for approximately 3.6 million hospitalisations each year
- In Australia it is unknown whether maternal vaccination (MV) or infant immunoprophylaxis (II) will be more cost-effective
- Interested in the trade-off between the cost and effectiveness of the strategies



Scenarios for illustration

1) The incremental effectiveness of II compared to MV is **large** (i.e., II is preferred)
2) The incremental effectiveness of II compared to MV is **small** (i.e., MV is preferred)

- For both scenarios we estimate the initial VOI to be $121 million
- This exceeds the initial trial cost (e.g., $2 million) so we proceed
- Recruit 500 participants, compute the VOI, compare the cost (e.g., $1 million), repeat


Scenario 1
Scenario 2
Prior
Analysis 1
Analysis 2
Analysis 3
Analysis 4
Density
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
-2000
-1000
0
1000
2000
INMB

Summary

Clinical research should* be designed to inform decision-making

The value-driven adaptive design is fundamentally different to traditional designs (adaptive or not) in its philosophy

- Not based on a hypothesis test (i.e., no statistical error)

- Focused on the value of reducing a decision-maker's uncertainty

There are further complexities to consider (an adaptive design may not be appropriate, the decision model may be more complex, etc.)

Future direction is to design a hypothetical RSV trial using a transmission decision model

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- References:
  - Too many: available on request

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ADAPTIVE HEALTH INTELLIGENCE

EVIDENCE IN ACTION

The decision function

Absolute difference in strategy costs

5%-time discount over 15 years

Willingness to pay to avoid one MA-RSV

$$\mathrm{INMB}(p_{\mathrm{II}}, p_{\mathrm{MV}}) = \frac{1}{1{,}000{,}000} \times \sum_{t=0}^{14} 1.05^{-t} \times 300{,}000 \times (5200(p_{\mathrm{II}} - p_{\mathrm{MV}}) + 260)$$

Scale to $1 million units

Average annual number of Australian births

Absolute difference in MA-RSV probabilities between strategies

A final confession: abstract amendment

“We will investigate scenarios where a traditionally designed trial stops too early (i.e., collects insufficient data) and stops too late (i.e., wastes resources collecting unnecessary data) and show how a value-driven adaptive design would have outperformed its traditional counterpart.”

If you read my abstract and you were hoping to see this, I am sorry!

Upon reflection, this makes no sense!

The goal posts can be moved arbitrarily!