The value-driven adaptive design

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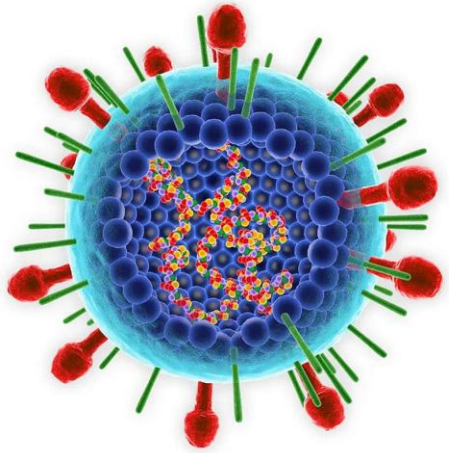
Outline

- RSV case study
- Traditional approach to trial design
- Value-based approach to trial design (including adaptive extension)
- Value-driven adaptive design (including implementation)
- Demonstration

RSV Case Study

- Respiratory syncytial virus (RSV) infection accounts for approximately 3.6 million hospitalisations and over 100,000 deaths each year, globally
- 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 of the strategies and the effectiveness in preventing medically attended RSV events (MA-RSV) in the first 12 months of life



Traditional approach

- Define primary outcome (e.g., MA-RSV), statistical model and parameter/s of interest
- Construct hypothesis test comparing interventions MV and II
- Estimate a required sample size based on power, type one error rate, etc.
- Choose a trial design that meets feasibility 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

Limitations to translation

- 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 asked decision-makers to specify a function that represents their decision-making process
- What if we designed a trial to collect **just** enough information to **sufficiently** inform the decision?
- No longer concerned with statistical errors because we have no interest in making declarations about the value of the effect parameter
- Could we **“bridge”** the gap (abyss) between clinical research and translation?

The (simplified) decision function

Absolute difference in strategy costs

5%-time discount over 15 years

Willingness to pay to avoid one MA-RSV

$$\mathrm{INMB}(p_{\mathrm{II}}, p_{\mathrm{MV}}) =$$

Average annual number of Australian births

Scale to $1 million units

Absolute difference in MA-RSV probabilities between strategies

Value of information (VOI)

- Suppose you have decision function $U(d, \boldsymbol{\Theta})$ for decision d and parameters $\boldsymbol{\Theta}$
- Given our current uncertainty, what decision is better in expectation?

$$\underset{d}{\operatorname{argmax}}\, E_{\boldsymbol{\Theta}}[U(d, \boldsymbol{\Theta})]$$

- What is the expected value of reducing parameter uncertainty (with data)?

$$\mathrm{EVSI} = E_{\boldsymbol{X}}\left[\max_{d} E_{\boldsymbol{\Theta}|\boldsymbol{X}}\left[\mathrm{U}(d, \boldsymbol{\Theta})\right]\right] - \max_{d} E_{\boldsymbol{\Theta}}[\mathrm{U}(d, \boldsymbol{\Theta})]$$

Value based approach

- We can estimate if data collection is **valuable** using EVSI
- If EVSI exceeds the cost of data collection, then the trial may be justified
- Choose a design that optimises this trade-off
- But the first EVSI term is computationally challenging
  - Requires simulation over potential datasets (e.g., 10,000)
  - Requires statistical model and decision model to be evaluated each time
- But there are recently developed approximation methods that work very well
- Still rarely implemented in practice (usually supporting information)

Extensions to adaptive designs

- Could we use a value-based decision rule to drive trial adaptations?
- Revise VOI calculation at interims and stop if no longer sufficiently valuable
- Flight et al. found that no one had implemented this before
  - VOI had been estimated at interims but never used to drive decisions
  - No trial has been prospectively designed using a value-based rule
- There are methods to compute iterative VOI
  - i.e., recruit one more participant, compute VOI, stop or continue, repeat
  - BUT the assumptions required are unreasonable

Value-driven adaptive design

- Our value-driven adaptive design using 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.

ValueAdapt R package

- Generic methods implemented in R package (michaeldymock25/ValueAdapt)
- User-specified:
  - Decision model, parameter uncertainty (e.g., prior distribution), external population state
  - Research cost function, approximation method (if any), sampling function
  - Statistical model (posterior), correction for future analyses, computational parameters

```
enb_sample <- function(D, U, Theta, t, prop, cost, method = "NP", K = 10000,
                       samp_args = list(), samp_fun = NULL, post_args = list(), post_fun = NULL,
                       stat_fun = NULL, model = NULL, INB_partial = NULL, Q = 50,
                       correct = NULL, num_cores = 1, num_threads = 1){
```

Back to the RSV case study

- Consider two scenarios (for illustration):

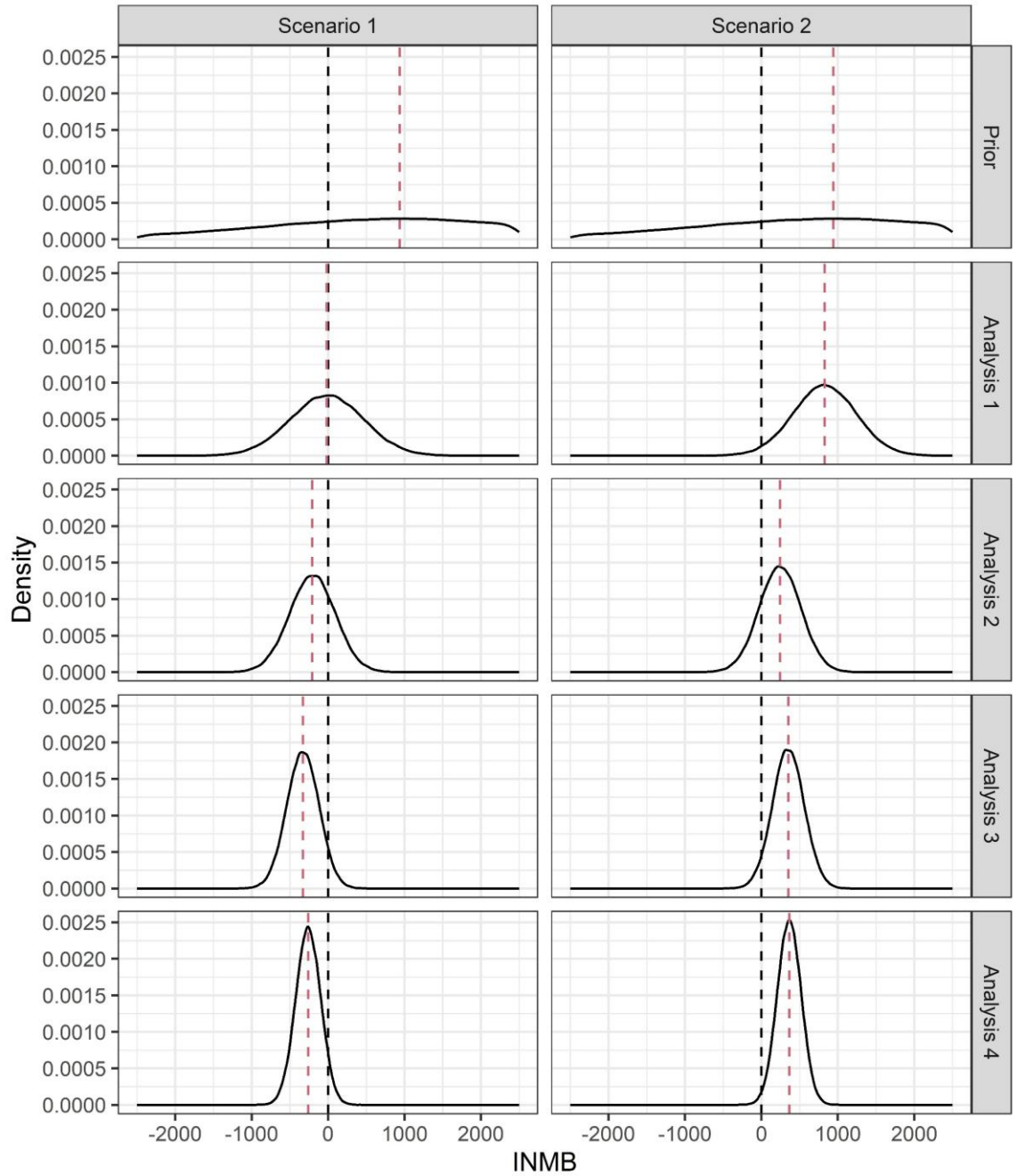
  1) The incremental effectiveness of II compared to MV is large ($p_{\text{II}} = 0.10$ and $p_{\text{MV}} = 0.18$)

  2) The incremental effectiveness of II compared to MV is small ($p_{\text{II}} = 0.10$ and $p_{\text{MV}} = 0.12$)

- For both scenarios we estimate the 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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