Rethinking clinical research:

How can we design vaccine trials to efficiently inform policy?

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Acknowledgements

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Outline

- Vaccine clinical practice recommendations in Australia
  - What is the process? What is the quality of evidence?

- Clinical research from first principles
  - Why do we do it? How do we do it?

- The value-driven adaptive design
  - An alternative?

Vaccine clinical practice recommendations in Australia

What is the process?

What is the quality of evidence?

Vaccine clinical practice recommendations in Australia

- Applications are made to the Therapeutic Goods Administration (TGA)
- The Australian Technical Advisory Group on Immunisation (ATAGI) make recommendations to the Department of Health and Aged Care
- Vaccine clinical practice recommendations approved by the National Health and Medical Research Council (NHMRC) are implemented in the Australian Immunisation Handbook

Australian Government
Department of Health and Aged Care

Australian **Immunisation** Handbook

Vaccine clinical practice recommendations in Australia

- ATAGI's decision-making process is transparently documented
- GRADE method implemented by National Center for Immunisation Research and Surveillance (NCIRS) to develop recommendations
- Set the policy question (PICO)
- Identify literature (mostly clinical trials)
- Determine outcome-specific and overall GRADE
- Make recommendation (or no recommendation)

Grading of Recommendations Assessment, Development and Evaluation (GRADE)

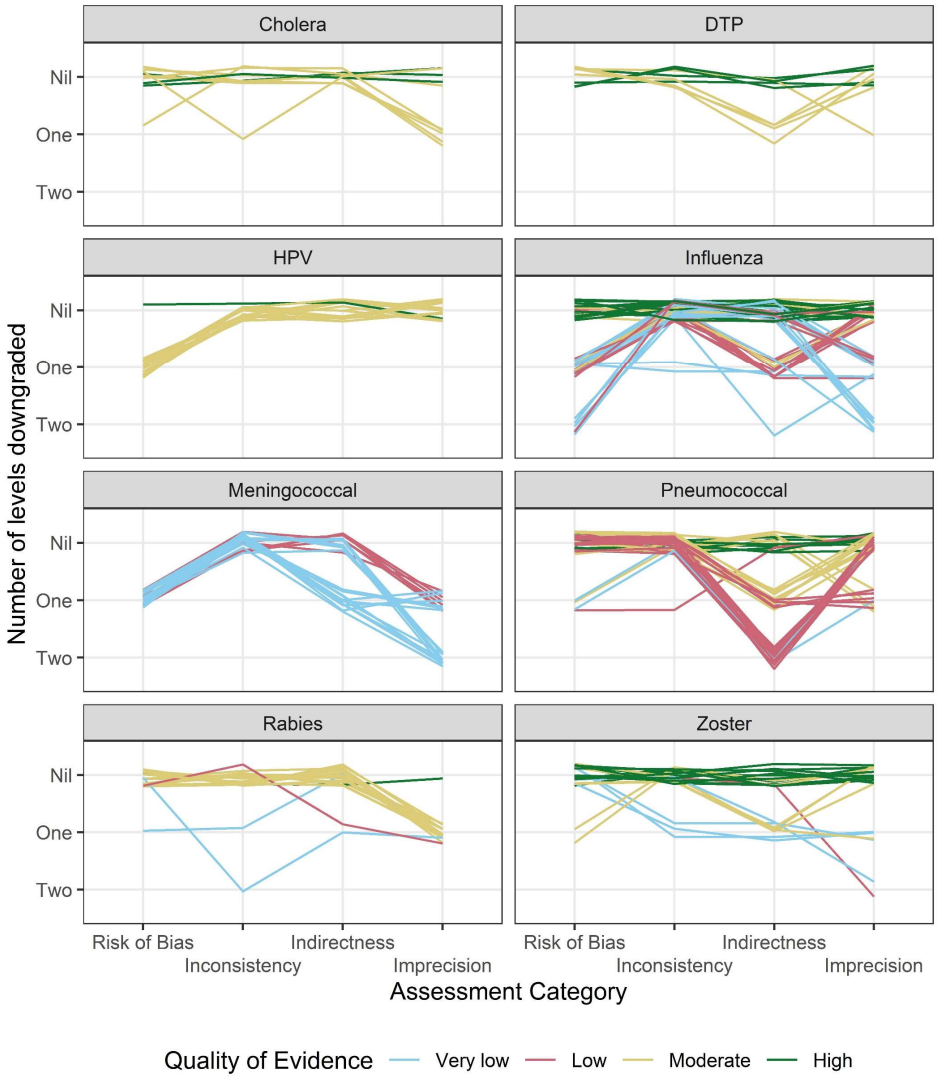
- Used internationally by the NHMRC, World Health Organization (WHO) and the Advisory Committee on Immunization Practices (ACIP)
- Each outcome assessed for *risk of bias*, *inconsistency*, *indirectness* and *imprecision*
- Evidence **certainty** classified as *very low*, *low*, *moderate* or *high*
- RCT data starts at *high* and observational data starts at *low*

Vaccine clinical practice recommendations in Australia

- We summarised assessments for cholera, DTP, HPV, influenza, meningococcal, pneumococcal, rabies and zoster vaccines
- Overall, **56%** of policy questions received a GRADE of **low*** or **very low***
- Common reasons were:
  - Potential confounding (e.g., when only observational data was available)
  - Mismatch between the policy question and study-specific research question (e.g., interventions, schedules and populations)
  - Uncertainty in effect estimation (i.e., lack of precision)

- Outcomes for individual research questions tended to be downgraded for similar reasons

- E.g., pneumococcal and indirectness



How can we improve the quality of the evidence?

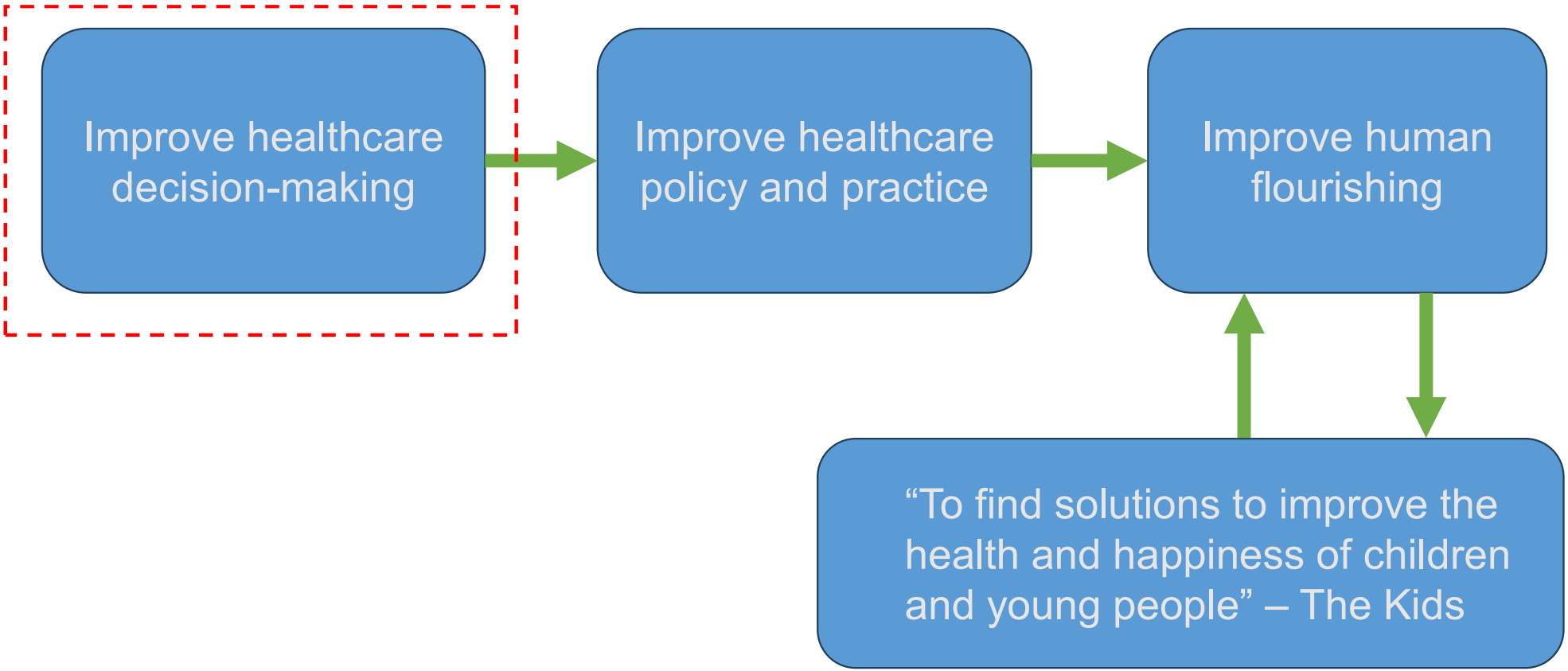
- **Align** trial design with policy question (e.g., interventions and schedules)
- Increase **inclusivity** with respect to targeted subpopulations (e.g., age groups, immunocompromised groups, ethnicity)
- Involve policy-makers in setting research questions **before** the evidence is generated rather than afterwards
- Generate evidence that **informs** the policy-maker's decision efficiently

Clinical research from first principles

Why do we do it?

How do we do it?

Why do clinical research?



Is there a problem?

- Results from clinical research only slowly and inconsistently inform policy and practice
- Many reasons for this (of which some are statistical)
- Clinical research is typically designed for drug/vaccine registration
- But it *should** **prioritise** informing the **decision-making** of consumers, clinicians and policy-makers (i.e., improve healthcare decision-making)

Hypothesis testing

- A scientific hypothesis is distilled into a statistical hypothesis test
  - Suppose we want to estimate a treatment effect
  - E.g., **A**: treatment has **no** effect vs **B**: treatment has a **positive** effect
- Scientists (humans) want to make a declaration: **A** is true, or **B** is true
  - This is a **truth claim** - it may be wrong

		Does the treatment have a positive effect?	
		Yes	No
Did I declare that the treatment has a positive effect?	Yes	Power	Type One Error
	No	Type Two Error	

Traditional designs

Everything focuses on this comparison:

Our decision rules (i.e., stop or continue recruitment)

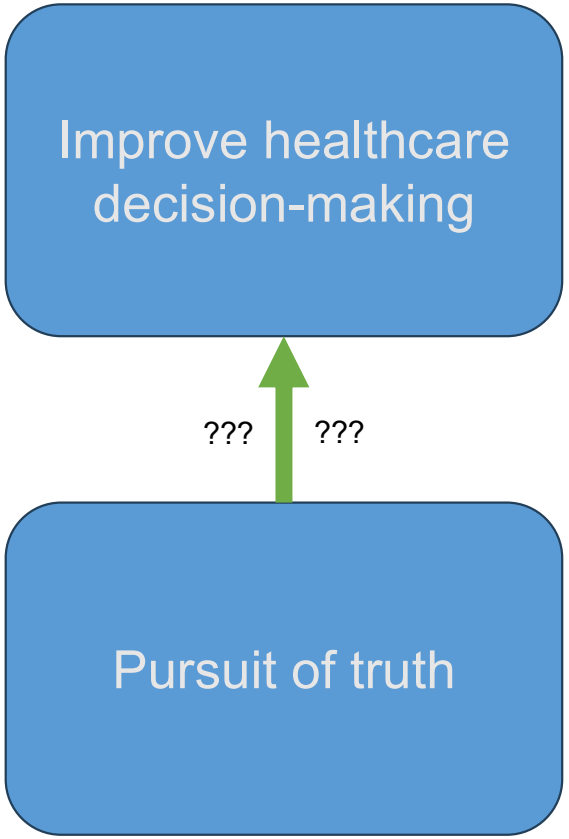
Our sample size (at least in theory)

Our determination of trial “success”

Our decision on how to publish

Does this suit clinical research?

- We aim to improve healthcare **decision-making**
- Usually, we specify a single effect measure for a single primary outcome and make a single declaration
- But! A decision-maker will consider multiple outcomes (e.g., efficacy, safety, cost) and cares about the effect sizes and their uncertainty!



The role of science in the pursuit of truth

- "Science" is a tool we can use to uncover truths about the universe
- It is good to do science to better understand phenomena
- It will lead to improved healthcare decision-making and human flourishing
- But! We have finite resources!
- We should pursue the **right** amount of truth to the **right** questions

The value-driven adaptive design

An alternative?

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 type one error and power 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?

Specifying the decision-making process

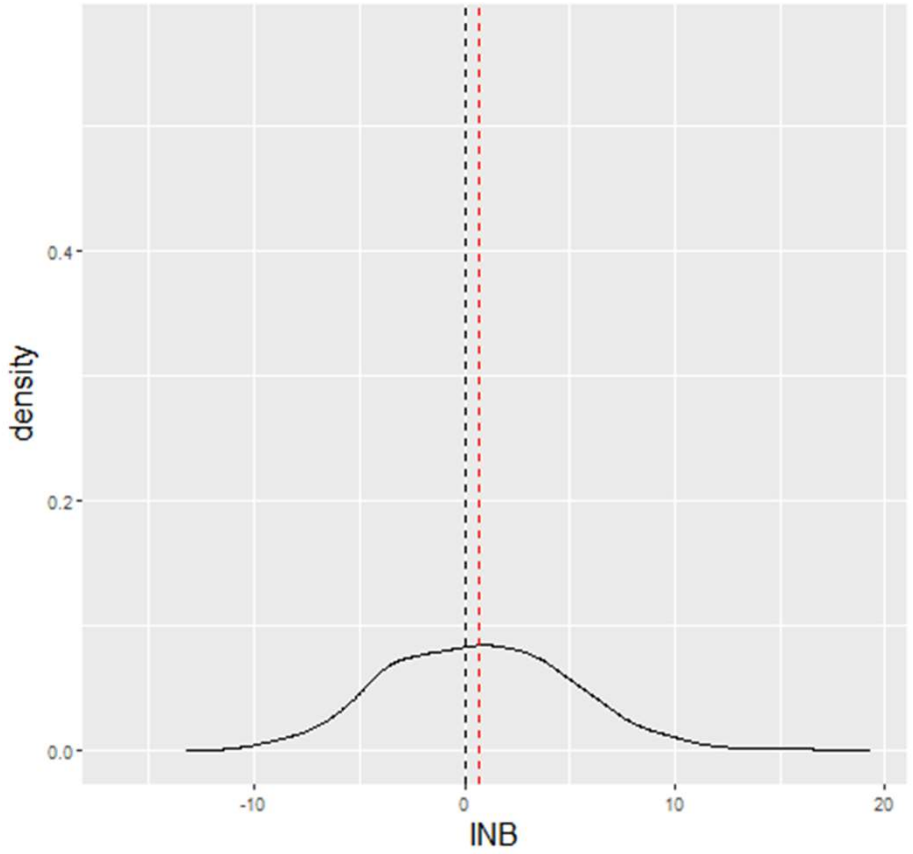
Notation	Definition	Examples
$d \in \{1,2,\ldots,D\}$	Decision option	Treatments, vaccine strategies

Choose the decision option that maximises the net benefit function:

E.g., if $\mathrm{INB} > 0$ we choose decision A instead of decision B – easy!

But what about the uncertainty?

- Our current understanding of $\boldsymbol{\Theta}$ is a distribution, not an exact value
- We can visualise the distribution of the INB
- If **forced** to decide now we could use the expected value $E_{\boldsymbol{\Theta}}[\mathrm{INB}(\boldsymbol{\Theta})]$
- Is it worthwhile reducing the uncertainty by collecting information?
- We can quantify this mathematically

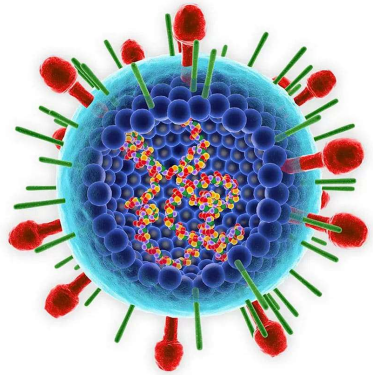


The value-driven adaptive design

- What if we collected data until the **cost of further recruitment** outweighed the **incremental benefit to our decision-making**?
- Recalculate the **value** at each interim analyses to make stop-go decisions
  - E.g., stop once the (prospective) value added is below zero
- Choose the best decision option and report out the results
- Caveat: requires a decision model to be prespecified

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



The (simplified) health economic model

Absolute difference in strategy costs

5% time discount over 15 years

Willingness to pay to avoid one MA-RSV

$$\mathrm{INB}(\boldsymbol{\Theta}) = \frac{1}{1{,}000{,}000} \times \sum_{t=1}^{15} 1.05^{1-t} \times 300{,}000 \times (\lambda(p_{\mathrm{II}} - p_{\mathrm{MV}}) + 260)$$

Scale to $1 million units

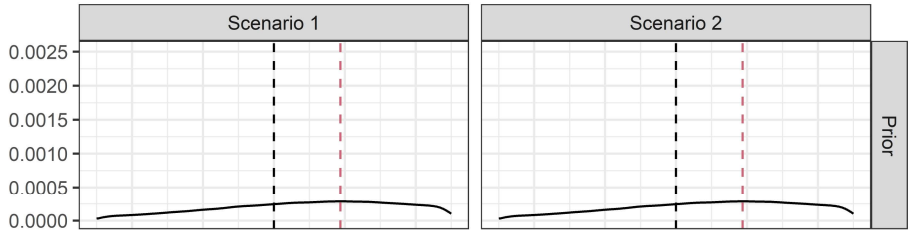
Average annual number of Australian births

Absolute difference in MA-RSV probabilities between strategies

A clinical trial

- We conduct a clinical trial to reduce the parameter and decision uncertainty
- Randomise up to 1,000 mother-infant dyads to each strategy
- Dyads have 12-month MA-RSV outcome
- Analyses after every 250 dyads per strategy
- Two scenarios:

1) The incremental effectiveness of II over effective MV is large ($p_{\mathrm{II}} = 0.10$ and $p_{\mathrm{MV}} = 0.18$)
2) The incremental effectiveness of II over effective MV is small ($p_{\mathrm{II}} = 0.10$ and $p_{\mathrm{MV}} = 0.12$)


Scenario 1
Scenario 2
Prior
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000

Expected net benefit of sampling

Analysis	Scenario 1	Scenario 2
Prior	$121 million	$121 million
Analysis 1	$101 million	-$76 million
Analysis 2	$6 million	
Analysis 3	<$0.1 million	

Summary

Clinical research should* be designed to inform decision-making

The value-driven adaptive design is philosophically different to a traditional design

- Not based on a hypothesis test (i.e., no type one error or power)

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

Current state and future directions

- Quality of evidence paper submitted in December
  - Preprint: https://www.medrxiv.org/content/10.1101/2025.03.05.25323463v1
- Value-driven adaptive design paper submitted last week
- Code implementation: https://github.com/michaeldymock25/ValueAdapt
- May be useful to explore a more complex/realistic decision model
- One day perhaps we could prospectively design a trial using these methods
- Watch this space