Government of **Western Australia**
Child and Adolescent Health Service

Introduction to Adaptive Trials Methodology

Professor Tom Snelling
Sydney School of Public Health, University of Sydney

15 May 2020

Research Skills Seminar Series | CAHS Research Education Program
Research support, development and governance

Healthy kids, healthy communities

Compassion | Excellence | Collaboration | Accountability | Equity | Respect

Neonatology | Community Health | Mental Health | Perth Children's Hospital

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OVERVIEW

1. The need for more efficient trials
2. What are adaptive trials?
3. What are platform trials?
4. Use of adaptive features in trial design
   - Response adaptive randomization
   - Bayesian borrowing
5. Suggestions for implementation

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1. The need for efficient trials

The need for efficient trials

Rapidly rising clinical trial costs worry researchers

This is part of a series of articles on clinical trials that will run in the CMAJ News section throughout 2009.

The cost of conducting a clinical trial for a drug is rising like mercury on a summer afternoon, a trend that researchers say is hampering the development of new medicines and is bad news for academia, pharmaceutical companies and consumers.

From the 1980s to the 1990s, the clinical trial costs of drug development increased 5 times faster than preclinical costs, according to the Tuft Center for the Study of Drug Development. In 2003, some health economists in the United States estimated the average cost of bringing a drug to market at US$802 million. Estimates of typical research and development costs today are in the US$1.3 billion-to-US$1.7 bil-

The boom in pharmaceutical development in recent decades has yielded so many new drugs that it has become increasingly difficult for drug companies to prove their products are better than those already on the market. To detect modest benefits, companies must run bigger and more expensive clinical trials.

Collier et al. CMAJ, 2009; 180:277–8

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The need for efficient trials

- ~90% UK public-funded trials are simple parallel group designs
- ~50% do not meet recruitment targets
- Overburdened healthcare system & low trial participation rates

Traditional trials

- Methods unable to address heterogeneity and complexity of modern diseases
- Hard to translate results to meaningful clinical information
- Too many unknowns

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The need for efficient trials

Explanatory trials
-Confirm hypothesis

Pragmatic trials
- Real world implementation

Efficacy	Effectiveness
• Narrow eligibility • Outcome optimised to detect an effect • Smaller sample sizes • Potential overestimate of benefit / underestimate of harm	• Broad patient groups • Clinically relevant outcome • Larger sample sizes • Minimally biased benefit / harm estimate

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The need for efficient trials

We need the ability to:

- Evaluate interventions in specific groups of patients
- Allocate more participants to better interventions
- Add new interventions when they become available
- Drop interventions that don't improve outcomes
- Increase/stop recruitment in patient subgroups
- Evaluate multiple treatments options in a more time-efficient way
- Learn which treatments are best where there is uncertainty

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The need for efficient trials

- Especially important for when there are many uncertainties
- Highlighted by current COVID-19 epidemic
- Our team is supporting a number of adaptive trials aiming to find the best treatments/prevention for COVID-19

https://www.sydney.edu.au/news-opinion/news/2020/05/11/digital-health-platform-to-provide-real-time-data-covid-focus.html

https://about.unimelb.edu.au/newsroom/news/2020/april/clinical-trial-into-two-potential-covid-19-treatments-commences

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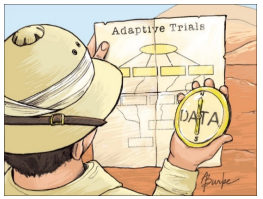
2. What are adaptive trials?

What are adaptive trials?

Traditional trials are *fixed*

- **Fixed** design
- **Fixed** treatments
- Higher chance of not answering questions

Adaptive trials are ***flexible***



- Can change the trial based on how people respond to treatment

Source images: Mark Zanzig; JAMA

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What are adaptive trials?

- An adaptive trial is 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 DRAFT GUIDANCE, Sep 2018
https://www.fda.gov/downloads/drugs/guidances/ucm201790.pdf

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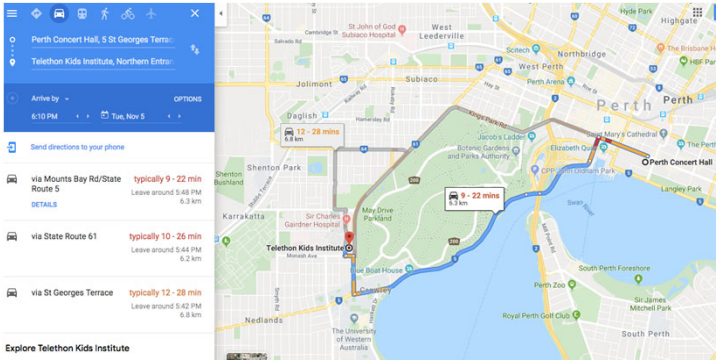
What are adaptive trials?



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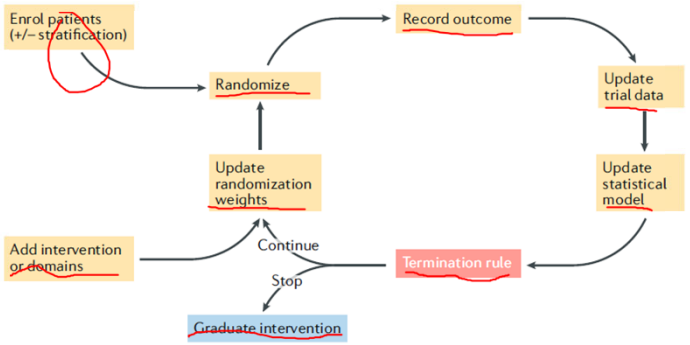
What are adaptive trials?



Roger J. Lewis (2012)

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What are adaptive trials?

Adaptive features can include:

- Flexible stopping rules to optimise sample size
  - Perform repeat analyses as data accumulates
  - Estimate probability of success/failure given the current data
  - Compare this probability to a threshold (e.g. > 95% probability, declare treatment superior)

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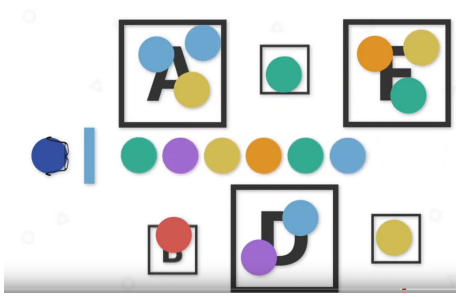
What are adaptive trials?

Adaptive features can include:

- Response adaptive randomisation with multiple treatment options
  - At each interim, assign higher proportion to treatments based on the probability of that treatment being best



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What are adaptive trials?

Adaptive features can include:

- Adding/dropping treatment arms
  - New treatments discovered
  - Drop treatments if they are clearly not best or harmful
- Subgroup evaluations
  - Use Bayesian borrowing across similar groups (e.g. we can still learn by understanding what works in similar patient subtypes)

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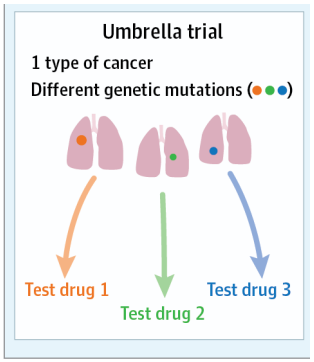
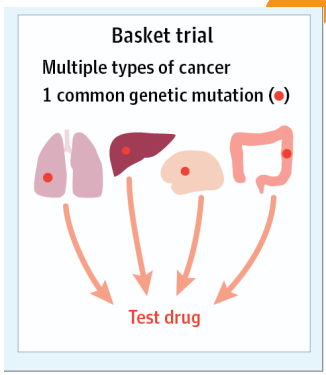
3. What are platform trials?

What are platform trials?





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What are platform trials?

A platform trial is a clinical trial with a single master protocol in which multiple treatments are evaluated simultaneously.

Efficiencies of platform clinical trials: A vision of the future.
Saville & Berry. Clinical Trials 2016 13(3)

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What are platform trials?

- Scott Berry a statistician and leader in adaptive trials:
  - Platform trials are like sports stadiums
  - Provide infrastructure for multiple teams to compete
  - Flexibility for playing multiple sports

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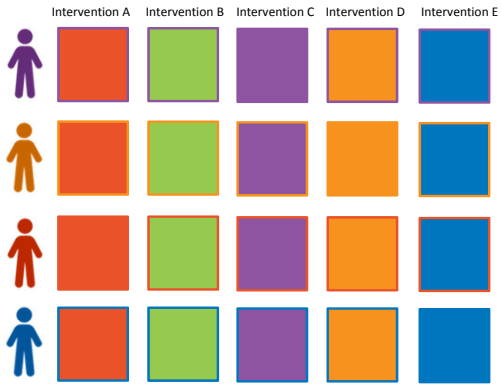
What are platform trials?



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What are platform trials?

- Any number of treatment combinations
- Treatments can be added or removed
- Any number of subgroups (though there may be a limit if population of interest is small)
- No maximum sample size (perpetual study)
- Frequent analyses
- Predefined decision rules for adaptation
- Treatment assignment controlled my central statistical model and accruing patient data

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What are platform trials?

Use when:

- Outcomes are available fairly quickly (not helpful if outcomes take years to measure)
- There is large uncertainty for relative efficacy, adverse event rates, variability of patient population etc.
- Multiple treatment options and/or differences in treatment response
- New biomarkers/therapies available
- Able to secure buy-in of stakeholders

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4. How to use adaptive features in trial design

Adaptive features

Response adaptive randomisation

- Example: **BEAT CF** (Bayesian Evidence Adaptive Treatment in Cystic Fibrosis)
- What is the optimal management of CF exacerbations?

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Adaptive features

- RAR can be informed by simulations (run thousands of theoretical trials to simulate rate of trial success/failure)
- At each interim ask: What is the probability this treatment is best compared to all other treatments being evaluated?
- Assign more future participants to better performing treatments and less participants to treatments that are clearly not best
- Can start with a burn in period of equal allocation (good if high variance in initial stages)
- Can simulate conservative/aggressive RAR strategies to see how trial design performs

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Adaptive features

Example design:

Domain A: Primary antibiotics
1. A1
2. A2
3. A3
4. A4

Domain B: Adjunct antibiotics
1. B1
2. B2
3. B3
4. B4

Patient Subgroups:
1. High FEV_1 w/o pseudomonas
2. High FEV_1 w pseudomonas
3. Low/ mod FEV_1

FEV_1 = Forced Expiratory Volume in 1 sec. Common measure of lung function

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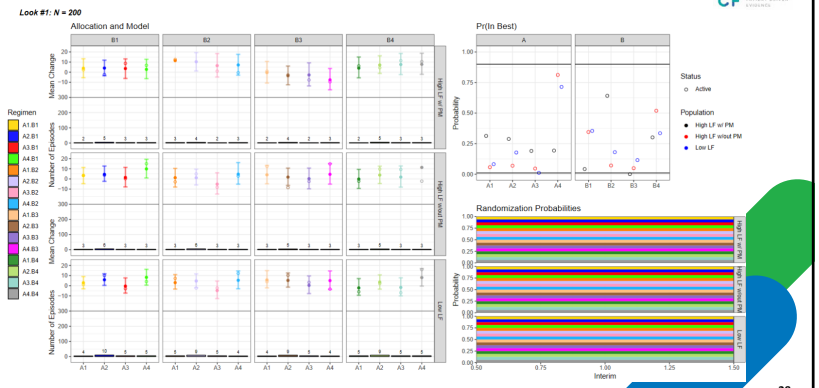
Adaptive features



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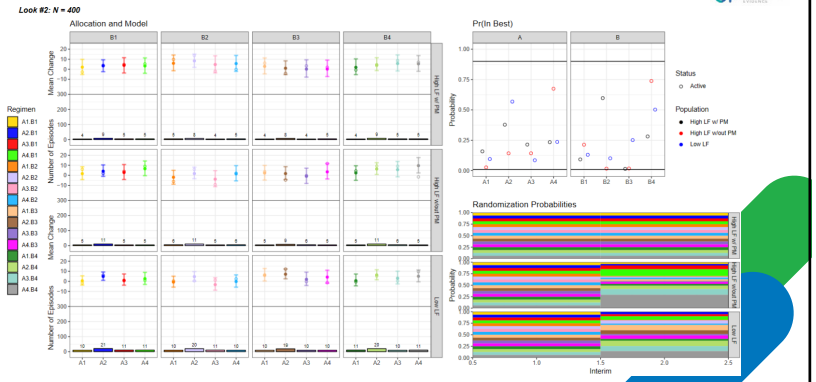
Adaptive features



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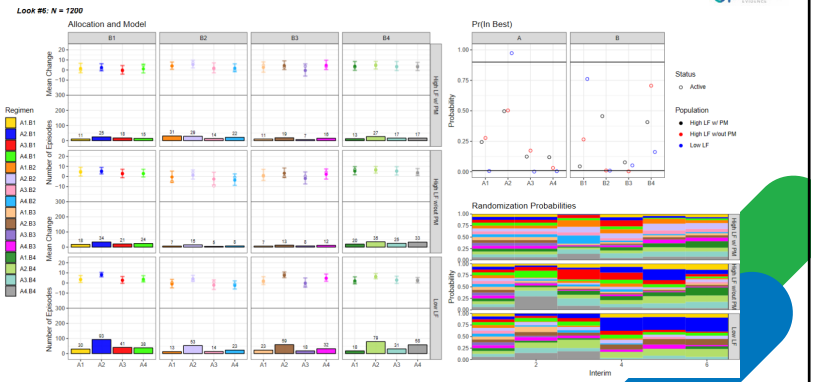
Adaptive features



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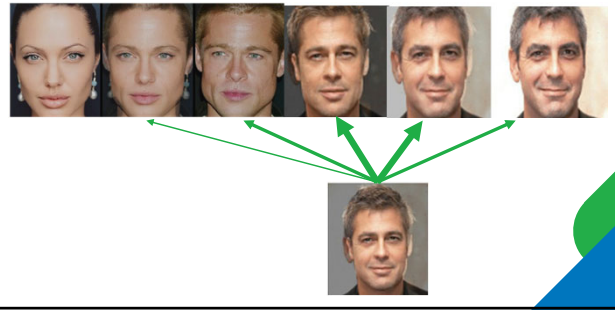
Adaptive features

Subgroup analysis with Bayesian borrowing

- Can learn from similar patient subgroups



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Adaptive features

Third Level

Prior on mean and variance of response rates

μ σ^2

Second Level

Population of response rates

σ^2 μ R_1, R_2, R_3

First Level

Group response rate

R_1 R_2 R_3

Type A Type B Type C

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5. Suggestions for implementation

Suggestions for implementation

Design

- Take your time to consult with statisticians, clinicians and consumers to design trial
- Adaptive designs take longer to design (need to prespecify adaptations and provide simulations supporting design)

Funding

- Educating ethics committees, clinicians and funders on novel designs like platform trials to increase understanding and funding opportunities
- MRFF schemes appear good for novel methods

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Suggestions for implementation

Funding

Trial you propose:

The money you are funded:

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Suggestions for implementation

Funding

- Continuous education to increase understanding and funding opportunities (e.g. ethics committees, clinicians, funders and community)
- May need pilot funding for proof of concept first
- MRFF schemes appear good for novel trial design methods

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Suggestions for implementation

Approval

- Ethics/scientific committees may be skeptical/ignorant of novel designs
- Concerns about:
  - Bayesian inference
  - Adaptive features (misunderstanding of how they work)
  - Digital infrastructure and security (Platform trials are best implemented with electronic data capture)

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Suggestions for implementation

Approval

- Ethics/scientific committees may be skeptical/ignorant of novel designs
- Concerns about:
  - Bayesian inference
  - Adaptive features (misunderstanding of how they work)
  - Digital infrastructure and security (Platform trials are best implemented with electronic data capture)
- Enquire whether committee has any prior history of review or submission of an adaptive trial
- May need to consult with committee prior to submission

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Suggestions for implementation

Approval

- Ethics submission in step-wise fashion:
  - Phase 1: Observational platform (core protocol)
  - Phase 2: Randomisation to different treatments (domain-specific appendices)
- Consider governance requirements for multi-site trials

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Suggestions for implementation

Digital support

- Computing power for trial simulations (simulations are essential to optimise your design)
- Need electronic data capture to enable response adaptive randomisation
- Good for embedding adaptive trials in routine care
- Takes time to build modules to support aspects of trial design

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Suggestions for implementation

Understanding

- Engage with a team with track record in adaptive trials
  - Adaptive Health Intelligence, Telethon Kids Institute
  - Health and Clinical Analytics, University of Sydney

- High statistical support and workload required throughout process

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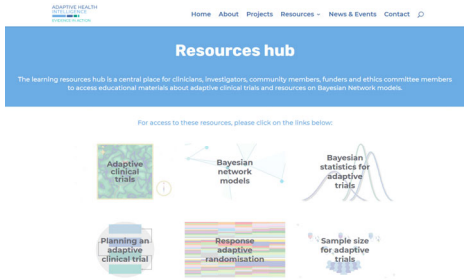
Suggestions for implementation

Resources

- Resources available on https://adaptivehealthintelligence.org.au



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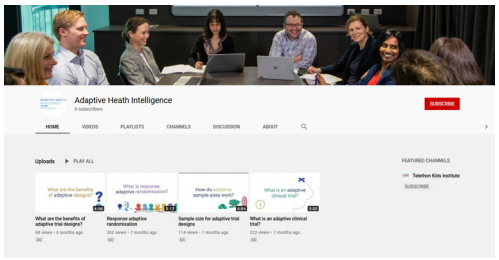
Suggestions for implementation

Resources

- Videos on YouTube: https://www.youtube.com/channel/UC_J-y_3Nrdcd2Irj3Rxzw9Q



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Suggestions for implementation

Resources

- Reach out to our team to discuss your trial ideas:

adaptivehealth@telethonkids.org.au

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Summary

- Efficient trial designs design can decrease financial and opportunity costs
  - Response adaptive randomisation, flexible stopping rules and Bayesian borrowing can make trials more efficient to answer more questions with multiple treatment options
- What's needed:
  - High level coordination, governance
  - Expertise in simulation and Bayesian analysis
  - Time/effort for building the best design
  - Digital infrastructure to support implementation

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Questions?

Upcoming Research Skills Seminars:

22 May 12:30 Knowledge Translation
Dr Fenella Gill / Dr Tobias Schoep

5 Jun 12:30 Introductory Biostatistics
Dr Julie Marsh

*Full 2020 Research Skills seminar schedule in back of handouts

Please give us feedback!

A survey is included in the back of your handout or complete it online via:
https://is.gd/adaptivetrials2020

Researcheducationprogram@health.wa.gov.au

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ADDITIONAL NOTES AND RESOURCES

USEFUL WEBSITES

- https://adaptivehealthintelligence.org.au
- https://www.berryconsultants.com/library/
- https://clinicaltrialsalliance.org.au/topics/innovative-trial-design/

ADDITIONAL READING

- Saville B & Berry S. Efficiencies of platform clinical trials: A vision of the future. Clin Trials 2016;13(3):358-66. doi: 10.1177/1740774515626362
- Berry S, Connor J & Lewis R. The Platform Trial: An Efficient Strategy for Evaluating Multiple Treatments. The Platform Trial: An Efficient Strategy for Evaluating Multiple Treatments. JAMA. 2015; 313(13). doi: 10.1001/jama.2015.2316.
- Schultz A, Saville B, Marsh J & Snelling T. An introduction to clinical trial design. Paediatric Respiratory Reviews. 2019; 32: 30-35. https://doi.org/10.1016/j.prrv.2019.06.002
- Schultz A, Marsh J, Saville B et al., Trial Refresh: A Case for an Adaptive Platform Trial for Pulmonary Exacerbations of Cystic Fibrosis. Frontiers in Pharmacology. 2019; 10:301. doi: 10.3389/fphar.2019.00301/full
- Book: Berry S, Carlin B, Lee J & Muller P. Bayesian Adaptive Methods for Clinical Trials. 2010. Chapman & Hall/CRC Biostatistics Series. Taylor & Francis Group. ISBN-13: 978-1439825488

GUIDELINES

- FDA Guidelines: Adaptive Designs for Clinical Trials of Drugs and Biologics 2019. https://www.fda.gov/media/78495/download

https://cahs.health.wa.gov.au/ResearchEducationProgram/