New clinical trial designs for evaluation of antimicrobial agents

Guest speakers: David Paterson, Julie Marsh
Moderator: Thomas Snelling
Host: Astrid Pentz-Murr (GARDP)

27 May 2021
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The presentation will be followed by an interactive Q&A session.

If your question is addressed to a specific speaker, please include their name when submitting the question.

Please submit your questions via the ‘questions’ window. We will review all questions and respond to as many as possible after the presentation.
Today’s speakers

New clinical trial designs for evaluation of antimicrobial agents

David Paterson
Director
University of Queensland Centre for Clinical Research (Australia)

Julie Marsh
Biostatistical Lead
Wesfarmers Centre of Vaccines and Infectious Diseases, University of Western Australia (Australia)

Moderator:
Thomas Snelling
Professor of Infectious Diseases and Director of the Health and Clinical Analytics Lab
Sydney School of Public Health, University of Sydney (Australia)
David Paterson is an Infectious Diseases Physician with a major interest in AMR. He has worked clinically in three continents - North America, Europe and Australia. He is currently Director of the University of Queensland Centre for Clinical Research, Brisbane, Australia. He is the author of more than 500 peer-reviewed publications including those of the MERINO trials, which he leads.
Overview of innovations in clinical trials of antimicrobial agents

David Paterson
University of Queensland
What do we want to avoid in antibiotic development?
A Case Study: Achaogen
Plazomicin vs KPC producers

**A  Cumulative Probability of Survival**

<table>
<thead>
<tr>
<th>Days</th>
<th>Plazomicin</th>
<th>Colistin</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>0.10</td>
<td>0.20</td>
</tr>
<tr>
<td>50</td>
<td>0.20</td>
<td>0.40</td>
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<tr>
<td>40</td>
<td>0.30</td>
<td>0.50</td>
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<tr>
<td>30</td>
<td>0.40</td>
<td>0.60</td>
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<tr>
<td>20</td>
<td>0.50</td>
<td>0.80</td>
</tr>
<tr>
<td>10</td>
<td>0.60</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Hazard ratio for death:
Through day 28, 0.25 (95% CI, 0.05–1.19)
Through day 60, 0.47 (95% CI, 0.19–1.19)

**B  Increase in Serum Creatinine Concentration**

- **Magnitude of Increase**
  - ≥2.0 to <3.0 mg/dl
  - ≥1.5 to <2.0 mg/dl
  - ≥1.0 to <1.5 mg/dl
  - ≥0.5 to <1.0 mg/dl

- **No. of Patients with Increase**
  - Plazomicin: 2
  - Colistin: 1

- **No. of Patients with Increase/Total No. of Patients**
  - Plazomicin: 2/12
  - Colistin: 8/16
Achaogen Stock Price
The value proposition of clinical trials networks
The value proposition of investigator-initiated clinical trials conducted by networks

Investigator-initiated trials run by clinical trial networks provide net economic benefits to health systems
A self-improving, sustainable health care system

- **Clinical quality registries**
  - Measure treatment and outcomes
  - Identify variation

- **Research and clinical trials**
  - Generate hypotheses
  - Analyse and interpret variation
  - Test hypotheses
  - Generate evidence

- **Health care practice, policy and stewardship**
  - Monitor translation and adherence
  - Develop evidence-based guidelines

**Better outcomes, better value**

**Investigate**

**Measure**

**Implement**
Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance
A Randomized Clinical Trial

Patrick N. A. Harris, MBBS; Paul A. Tambyah, MD; David C. Lye, MBBS; Yin Mo, MBBS; Tau H. Lee, MBBS; Mesut Yilmaz, MD; Thamer H. Alenazi, MD; Yaseen Arabi, MD; Marco Falcone, MD; Matteo Bassetti, MD, PhD; Elda Righi, MD, PhD; Benjamin A. Rogers, MBBS, PhD; Souha Kanji, MD; Hasan Bhally, MBBS; Jon Iredell, MBBS, PhD; Marc Mendelson, MBBS, PhD; Tom H. Boyles, MD; David Looke, MBBS; Spiros Miyakis, MD, PhD; Genevieve Walls, MB, ChB; Mohammed Al Khamis, MD; Ahmed Zikri, PharmD; Amy Crowe, MBBS; Paul Ingram, MBBS; Nick Daneman, MD; Paul Griffin, MBBS; Eugene Athan, MBBS, MPH, PhD; Penelope Lorenc, RN; Peter Baker, PhD; Leah Roberts, BSc; Scott A. Beatson, PhD; Anton Y. Peleg, MBBS, PhD; Tiffany Harris-Brown, RN, MPH; David L. Paterson, MBBS, PhD; for the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)
MERINO Trial sites

More than 25 sites in 9 countries
Examples of trial networks in AMR

- US: Antibiotic Resistance Leadership Group (ARLG)
- European Clinical Research Alliance on Infectious Diseases (ECRAID)
- Wellcome Asian Drug Resistant Infections Clinical Research Network
What could MAMS, DOOR or PRACTical bring to clinical trials of antimicrobials?
<table>
<thead>
<tr>
<th>Year</th>
<th>Arm A - Standard of Care (SOC)</th>
<th>Arm B - SOC + zolendronic acid</th>
<th>Arm C - SOC + docetaxel</th>
<th>Arm D - SOC + celecoxib</th>
<th>Arm E - SOC + zolendronic acid + docetaxel</th>
<th>Arm F - SOC + zolendronic acid + celecoxib</th>
<th>Arm G - SOC + abiraterone</th>
<th>Arm H - SOC + radiotherapy</th>
<th>Arm J - SOC + emzalutamide</th>
<th>Arm K - SOC + metformin</th>
<th>Arm L - SOC + oestradiol patches</th>
</tr>
</thead>
<tbody>
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<td>Future comparison</td>
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</tbody>
</table>

- **Standard of care**
- **In development**
- **Closed to recruitment**
Cluster-Randomized, Crossover Trial of Head Positioning in Acute Stroke

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lying Flat (N=4676)</th>
<th>Sitting Up (N=5072)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./total no. (%)</td>
<td>no./total no. (%)</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levels of disability on the modified Rankin scale at 90 days*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 — No symptoms at all</td>
<td>745/4676 (15.9)</td>
<td>922/5072 (18.2)</td>
</tr>
<tr>
<td>1 — No clinically significant disability despite symptoms</td>
<td>1704/4676 (36.4)</td>
<td>1703/5072 (33.6)</td>
</tr>
<tr>
<td>2 — Slight disability</td>
<td>410/4676 (8.8)</td>
<td>438/5072 (8.6)</td>
</tr>
<tr>
<td>3 — Moderate disability requiring some help</td>
<td>711/4676 (15.2)</td>
<td>820/5072 (16.2)</td>
</tr>
<tr>
<td>4 — Moderately severe disability requiring assistance with daily living</td>
<td>444/4676 (9.5)</td>
<td>446/5072 (8.8)</td>
</tr>
<tr>
<td>5 — Severe disability, bed-bound, and incontinent</td>
<td>283/4676 (6.1)</td>
<td>326/5072 (6.4)</td>
</tr>
<tr>
<td>6 — Death</td>
<td>379/4676 (8.1)</td>
<td>417/5072 (8.2)</td>
</tr>
</tbody>
</table>
Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR)

Scott R. Evans,1 Daniel Rubin,2 Dean Follmann,3 Gene Pennello,4 W. Charles Huskins,5 John H. Powers,6,7 David Schoenfeld,8 Christy Chuang-Stein,9 Sara E. Cosgrove,10 Vance G. Fowler Jr,11 Ebbing Lautenbach,12 and Henry F. Chambers13
| Rank | Alive | How many of:  
1) Clinical Failure  
2) Infectious Complication  
3) SAE, or AE leading to study drug discontinuation | QoL |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>0 of 3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>1 of 3</td>
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<tr>
<td>3</td>
<td>Yes</td>
<td>2 of 3</td>
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<tr>
<td>4</td>
<td>Yes</td>
<td>3 of 3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>No (Death)</td>
<td>Any</td>
<td>Tiebreaker based on QoL score</td>
</tr>
</tbody>
</table>
Personalised randomised controlled trial designs—a new paradigm to define optimal treatments for carbapenem-resistant infections

A Sarah Walker*, Ian R White*, Rebecca M Turner, Li Yang Hsu, Tsin Wen Yeo, Nicholas J White, Mike Sharland*, Guy E Thwaites*
Flow diagram of PRACTical participants

1. Patients with serious known or highly likely carbapenem-resistant infection
2. Review list of all possible randomised treatments (table) and exclude on the basis of:
   - Unacceptable toxicity for the patient
   - Probable low efficacy (e.g., based on other susceptibilities or molecular mechanism)
   - Physician preference
3. Personalised randomisation list (containing a subset of all possible allocations)
4. Random allocation to one regimen on the personalised randomisation list
5. Treatment and follow-up as standard

*Figure 1: Proposed flow diagram of participants through the trial*
<table>
<thead>
<tr>
<th>Patient 1: moderate renal impairment (creatinine clearance &lt;40 mL/min)</th>
<th>Patient 2: history of myocardial infarction</th>
<th>Patient 3: meropenem MIC ≥ 64</th>
<th>Patient 4: ventilator-acquired or hospital-acquired pneumonia</th>
<th>Patient 5: Pseudomonas aeruginosa infection</th>
<th>Patient 6: known class B (NDM, IMP, VIM) infection</th>
<th>Patient 7: presence of 6S ribosomal RNA methyltransferases (encoding aminoglycoside resistance)*</th>
<th>Patient 8: presence of moderate to severe allergy to cephalosporins</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: piperacillin</td>
<td>No or maybe†</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>B: ceftazidime plus aztreonam</td>
<td>No or maybe†</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>C: cefepime</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>D: high-dose meropenem‡</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>E: polymyxin B with or without zidovudine</td>
<td>No or maybe†</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>F: high-dose meropenem‡ plus ertapenem</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>G: high-dose meropenem‡ plus imipenem</td>
<td>No or Maybe†</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>H: high-dose meropenem‡ plus polymyxin B with or without zidovudine</td>
<td>No or maybe†</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>I: high-dose meropenem‡ plus high-dose tigecycline</td>
<td>Maybe†</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>J: high-dose meropenem‡ plus fosfomycin</td>
<td>Maybe†</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>K: high-dose tigecycline‡ plus polymyxin B with or without zidovudine</td>
<td>No or maybe†</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>L: high-dose tigecycline‡ plus fosfomycin</td>
<td>Maybe†</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>M: fosfomycin plus polymyxin B with or without zidovudine</td>
<td>No or maybe†</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

MIC—minimum inhibitory concentration. NDM—New Delhi metallo-β-lactamase. IMP—imipenemase. VIM—Verona integron metallo-β-lactamase. *Based on plausibility as assessed by high MIC.
†Dose adjustments required in patients with renal impairment, which might or might not be assessed as feasible in an individual patient; patient weight or surface area and creatinine are important variables, given their likely effect on drug exposure to the treatment outcome. ‡By use of continuous or prolonged infusion (≥3 h), 2 g delivered every 8 h. §200 mg loading dose and 100 mg maintenance dose every 12 h.

Table: Example of possible regimens for personalised randomised trial design
Figure 2: Hypothetical ranking of regimens from a personalised randomisation list for a future individual patient after the trial. Efficacy ranking based on predicted probability of primary outcome for the personalised randomisation subset (table). I=high-dose meropenem plus high-dose tigecycline. D=high-dose meropenem. H=high-dose meropenem plus polymyxin B with or without zidovudine. F=high-dose meropenem plus ertapenem. B=ceftazidime plus avibactam. A=plazomicin.
PROS and CONS
The purpose of these innovations is to improve the efficiency of trials.

MAMS and PRACTical: will companies take the chance in being compared to multiple opponents?

PRACTical: statistical methods not yet in the public domain.

DOOR: could be easily manipulated.
Resist the Temptation of Response-Adaptive Randomization

Michael Proschan\textsuperscript{1,\textcircled{1}} and Scott Evans\textsuperscript{2}

\textsuperscript{1}Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases, Rockville, Maryland, USA, and \textsuperscript{2}Department of Biostatistics and Bioinformatics; Director, Biostatistics Center, Milken Institute School of Public Health, George Washington University, Washington, DC, USA
Response-adaptive randomization (RAR) has recently gained popularity in clinical trials. The intent is noble: minimize the number of participants randomized to inferior treatments and increase the amount of information about better treatments. Unfortunately, RAR causes many problems, including (1) bias from temporal trends, (2) inefficiency in treatment effect estimation, (3) volatility in sample-size distributions that can cause a nontrivial proportion of trials to assign more patients to an inferior arm, (4) difficulty of validly analyzing results, and (5) the potential for selection bias and other issues inherent to being unblinded to ongoing results. The problems of RAR are most acute in the very setting for which RAR has been proposed, namely long-duration “platform” trials and infectious disease settings where temporal trends are ubiquitous. Response-adaptive randomization can eliminate the benefits that randomization, the most powerful tool in clinical trials, provides. Use of RAR is discouraged.
Conclusions

- We all want trials to be less expensive, quicker and to study the AMR problem which they are designed to address.
- Clinical trial networks are clearly good for investigator initiated trials (including with industry sponsorship) and are emerging as an option for registrational trials.
- MAMS, adaptive trials and PRACTical can all make trials more “efficient”.
- DOOR can be considered as a primary superiority endpoint (or as a secondary exploratory endpoint).
Julie Marsh is an experienced statistical consultant who worked in the pharmaceutical industry for many years before returning to academia. She is the Lead Biostatistician in the Wesfarmers Centre of Vaccines and Infectious Diseases at the Telethon Kids Institute (TKI) and a Senior Research Fellow in the Adaptive Health Intelligence team, co-located in TKI and the University of Sydney. She specializes in Bayesian adaptive clinical trials and statistical methods for detecting adverse events following immunisation. Her role in the Australian Clinical Trial Alliance (ACTA) involves training and mentoring the next generation of statistical trialists.
Adaptive trials in vaccines & antimicrobial agents

Dr Julie Marsh

Wesfarmers Centre Vaccines & Infectious Diseases
• The need for efficient clinical trials
• Common adaptive trial features
• Decision making using Bayesian methods
• Adaptive trial governance & integrity
• Are Bayesian adaptive designs acceptable?
• Implementation challenges
The need for efficient clinical trials

- Unresponsive to consumer priorities
- Failure to translate trial results
  - considered non-applicable to specific patient
  - mismanagement commercial-academic
  - biases in design, management & reporting
- Failure to address heterogeneity & complexity of modern diseases

Heneghan et al. BMJ Evidence-Based Medicine 2017; 22:120-122
Bekelman et al. JAMA 2003; 289:454–65
The need for efficient trials ... to be able to

- Drop interventions that don’t improve outcomes
- Add new interventions when available
- Keep recruiting to avoid inconclusive results or stop trial if futile
- Allocate more participants to better interventions
- Evaluate interventions in sub-populations
- Increase/stop recruitment in sub-populations
- Evaluate over multiple concurrent treatments
- Change primary endpoint during the trial
Common adaptive trial features

Adaptive trials have the same features as non-adaptive trials except:

- Outcomes are repeatedly assessed on accumulating data over time
- Study design may be modified based on pre-specified rules
  - Sample size reassessment: *insurance policy*
  - Treatment selection: *promising candidates (risk/benefit)*
  - Seamless (combined data over stages/phases): *economical*
  - Response adaptive randomisation: *patient-centric/ethical*
  - Enrichment: *patient-centric/promising populations*
  - *Platform trial*: multiple treatments & populations evaluated simultaneously/efficiency
Sample size reassessment (SSR)

<table>
<thead>
<tr>
<th>Option 1: Conventional (non-adaptive) trial without SSR</th>
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<tbody>
<tr>
<td><strong>First interim analysis</strong></td>
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<tr>
<td>Experimental intervention</td>
</tr>
<tr>
<td>Standard of care (or placebo)</td>
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<tr>
<td><strong>Final analysis</strong></td>
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<tr>
<td>Original planned sample size</td>
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</table>

<table>
<thead>
<tr>
<th>Option 2: Adaptive clinical trial with SSR</th>
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<tbody>
<tr>
<td>Experimental intervention</td>
</tr>
<tr>
<td>Standard of care (or placebo)</td>
</tr>
<tr>
<td><strong>SSR</strong></td>
</tr>
<tr>
<td>Increased sample size target</td>
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</tbody>
</table>

Amended from Park et al. (2018)
Treatment selection (arm dropping)

Amended from Park et al. (2018)
Seamless design

Park et al. (2018)
Response adaptive randomisation

High dose allocation probability = 0

Parket al. (2018)
Enrichment design

Amended Park et al. (2018)
Beyond simple adaptive trial designs

- **Umbrella trial**
  - One population, many drugs

- **Basket trial**
  - Many populations, one drug

- **Platform trial**
  - Many populations, many drugs

Master protocol + domain appendices
Open-ended or even perpetual trial
With Bayesian methods, can share (borrow) information across drugs or populations
The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

The drug development enterprise is struggling. The development of new therapies is limited by high costs, slow progress, and a high failure rate, even in the late stages of development. Clinical trials are most commonly based on a “one population, one drug, one disease” strategy, in which the clinical trial infrastructure is created to test a single treatment in a homogeneous population.

This approach has been largely unsuccessful for multiple diseases, including sepsis, dementia, and stroke. Despite promising preclinical and early human trials, there have been numerous negative phase 3 trials of treatments for Alzheimer disease 1 and more than 40 negative phase 3 trials of neuroprotectants for stroke. 2 Effective treatments for such diseases will likely require combining treatments to affect multiple targets in complex cellular pathways and, perhaps, tailoring treatments to subgroups defined by genetic, proteomic, metabolomic, or other markers. 3

There has been increasing interest in efficient trial strategies designed to evaluate multiple treatments and benefits when evaluating potentially synergistic combination treatments (eg, treatment A, treatment B, treatment C, and all combinations) if the starting point is the testing of each treatment in isolation.

What Is a Platform Trial?
A platform trial is defined by the broad goal of finding the best treatment for a disease by simultaneously investigating multiple treatments, using specialized statistical tools for allocating patients and analyzing results. The focus is on the disease rather than any particular experimental therapy. A platform trial is often intended to continue beyond the evaluation of the initial treatments and to investigate treatment combinations, to quantify differences in treatment effects in subgroups, and to treat patients as effectively as possible within the trial. Although some of the statistical tools used in platform trials are frequently used in other settings and some less so, it is the integrated application of multiple tools that allows a platform trial to address its multiple goals. The Table summarizes the general differences be-
Platform Trials

Platform collects clinician assigned treatment and outcome data.
Decision making using Bayesian methods
## Decision making: Frequentist or Bayesian

<table>
<thead>
<tr>
<th>Frequentist</th>
<th>Bayesian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focus on null hypothesis</td>
<td>Focus on ‘updating’ prior beliefs</td>
</tr>
<tr>
<td>Probability of <strong>data</strong></td>
<td>Probability of <strong>hypothesis</strong></td>
</tr>
<tr>
<td>Analytical focus</td>
<td>Computational focus</td>
</tr>
<tr>
<td>Less flexible</td>
<td>More flexible</td>
</tr>
<tr>
<td>Poorly suited to sequential inference</td>
<td>Sequential inference a breeze</td>
</tr>
<tr>
<td>More familiar/routinely used</td>
<td>Less familiar</td>
</tr>
<tr>
<td>Software widely available</td>
<td>Requires specialised software</td>
</tr>
</tbody>
</table>

**Decision making**: Choose between Frequentist and Bayesian approaches based on their strengths and weaknesses. Frequentist methods focus on the null hypothesis and are less flexible, whereas Bayesian methods focus on updating prior beliefs and are more flexible, though they require specialized software.
Decision making using Bayesian methods

Trials in which key design parameters change during trial execution based upon a priori predefined rules and accumulating data from the trial to achieve goals of validity, scientific efficiency, and safety.
Consider a simple sample size reassessment trial with two arms: Treatment A and Treatment B

**Objective:** Is treatment B *superior* to A?

- $p_A$: proportion cured on treatment A
- $p_B$: proportion cured on treatment B

*Where difference, $d = p_B - p_A$*

**Null hypothesis** $H_0$: $d \leq 0$

**Alternate hypothesis** $H_1$: $d > 0$

B is superior if it has a higher cured rate than A
In a Bayesian framework, at each pre-specified time-point (interim):

- **Step 1**

  Calculate posterior distribution and estimate probability of alternate hypothesis ($H_1$) given the current data

  \[ \text{pr}(H_1 | \text{data}) = \text{pr}(d > 0) \]
Decision making using Bayesian methods

• Step 2

Compare this probability to a pre-defined threshold and follow protocol defined decision rules, e.g.

- **Superiority**: if probability that B has a higher cure rate than A is greater than 95% [given the current data], $pr(d>0) > 0.95$, then declare B superior (early stopping)

- **Futility**: if probability that B has a higher cure rate than A is less than 1% [given the current data], $pr(d>0) < 0.01$, then declare trial futility (early stopping)
Decision making using Bayesian methods

• **Step 3**
  Implement decision rule:

  - If maximum sample size met ➔ **STOP trial, complete follow-up and report final results**
  - If superiority or futility threshold met ➔ **STOP recruiting, complete follow-up & report results**
  - Otherwise ➔ **CONTINUE recruiting**
Response-Adaptive Randomisation (RAR)

Information gathering vs. optimising participant outcome

• **2 treatment arms**: optimal treatment allocation 1:1

• **>2 treatment arms**: consider RAR where treatment allocation is proportional to the current estimated cure rate, taking sample size and variability into account
  • Requires short time between recruitment and participant outcome, relative to overall trial recruitment period

• In a **superiority framework**, if none of the treatments are efficacious then MAMS (group sequential) designs slightly more efficient

• In a **non-inferiority framework**, it is less clear if RAR or MAMS designs are more efficient
Response-Adaptive Randomisation (RAR)

• By chance, higher B cure rate than true value: increased allocation to treatment B, faster return to true value

• By chance, lower A cure rate than true value: reduced allocation to treatment A, slower return to true value

• Current RAR algorithms tend to slightly under-estimate treatment estimates, but this is an active research area.
Adaptive trials governance & integrity
Adaptive Trial Governance

Trial Management Group
- Day-to-day delivery & conduct of the trial. Audits trial sites.
  - Not independent of trial
  - Blinded to interim summaries of safety & efficacy by intervention arm

Trial Steering Committee
- Executive decision making group that considers the interests of the trial, participants, funder/sponsor.
  - Communicates trial conclusions
  - Mixture of not independent & independent of trial
  - Blinded to interim summaries of safety & efficacy by intervention arm

Analytic Team
- Production & QC of safety & interim reports for DSMC
- Trial quality reviews for TMG
  - Not independent of trial
  - Generates unblinded interim summaries of safety & efficacy, inc. evaluation of trial decision criteria.

Data Safety & Monitoring Committee
- Review of interim safety & efficacy (incl. decision criteria, potential bias & trial governance).
- Recommends actions to TSC
  - Independent of trial
  - Unblinded to interim summaries of safety & efficacy, inc. progress of trial against decision criteria for adaptation or reporting conclusions.

Statistical Subcommittee
- Designs trial (incl. new domains & interventions in ongoing trial), writes protocol & SAP, & reviews potential sub-studies.
  - Blinded. Mixture independent/not Masked or Unblinded
Adaptive Trial Integrity (information flow)

**Trial Management Group**
1. Monitor safety
2. Monitor recruitment
3. Monitor trial & data quality
4. Trial administration

**Data Safety & Monitoring Committee**
- **Open Session**
- **Closed Session**
  - Restrict access to minutes from closed session

**Analytic Team**
1. Summarise safety data (risk)
2. Analyse efficacy data (benefit)
3. Evaluate decision rules (adapt/conclude)
4. Review post randomisation events
5. Restrict access to unblinded reports

**Blinded Report**

**Trial Steering Committee**
Executive decision making:
1. Safety communication: HREC, Sponsor, Sites...
2. Protocol amendments
3. Timing of publication of conclusions
4. Implementation of trial adaptations based on pre-specified rules
5. Assessment of data sharing requests

**Enrolment**
- Treatment allocation & pharmacokinetics

**Trial Data**

**Blinded Recommendations**

**Safety Updates**

**Published Conclusions**

Maintain current trial design or implement adaptations and/or protocol amendments
Are adaptive designs acceptable for vaccine and antimicrobial trials?
Key design considerations for adaptive clinical trials: a primer for clinicians

Kristian Thorlund,1,2 Jonas Haggstrom,2 Jay JH Park,1 Edward J Mills1,2

This article reviews important considerations for researchers who are designing adaptive clinical trials. These differ from conventional clinical trials because they allow and even enforce continual modifications to key components of trial design while data are being collected. This innovative approach has the potential to reduce resource use, decrease time to trial completion, limit allocation of participants to inferior interventions, and improve the likelihood that trial results will be scientifically or clinically relevant. Adaptive designs have mostly been used in trials evaluating drugs, but their use is spreading. The US Food and Drug Administration recently issued guidance on adaptive trial design, which highlighted several decision rules that have been rigorously examined via statistical simulations before the first trial participant is enrolled. The authors review important characteristics of adaptive trials and common types of study modifications and provide a practical guide, illustrated with a case study, to aid investigators who are planning an adaptive clinical trial.

Adaptive clinical trials can be completed sooner than trials with conventional (non-adaptive) designs. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recently released guidance on adaptive designs for licensing. But little guidance exists on how investigators should proceed when designing and planning an adaptive clinical trial. We outline and discuss common characteristics and study modifications of adaptive trials and provide a practical planning guide for designing and interpreting adaptive clinical trials.
Definition: A document containing the governing rules for the platform trial, such as patient eligibility, randomization rules, endpoints, the overarching statistical model and rules for study arm graduation. The protocol specifies all generic elements of the APT, rather than those related to a specific non-constant feature, such as a particular experimental arm or study region.
How acceptable are adaptive trial designs?

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-CoV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor: BioNTech
Study Conducted By: Pfizer
Study Intervention Number: PF-07002048
Study Intervention Name: RNA-Based COVID-19 Vaccines
US IND Number: 19736
EudraCT Number: 2020-002641-42
Protocol Number: C4591001
Phase: 1/2/3
Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

1.2. Schema

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>For each vaccine candidate (4:1 randomization active/placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: 18-55 y</td>
<td>Age: 65-85 y</td>
</tr>
<tr>
<td>Low-dose-level 2-dose group (n=15)</td>
<td>Low-dose-level 2-dose group (n=15)</td>
</tr>
<tr>
<td>IRC (safety)</td>
<td>IRC (safety)</td>
</tr>
<tr>
<td>after Dose 1</td>
<td>after Dose 1</td>
</tr>
<tr>
<td>Mid-dose-level 2-dose group (n=15)</td>
<td>Mid-dose-level 2-dose group (n=15)</td>
</tr>
<tr>
<td>IRC (safety)</td>
<td>IRC (safety)</td>
</tr>
<tr>
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<td>after Dose 1</td>
</tr>
<tr>
<td>IRC choice of group(s) for Phase 2/3 (safety &amp; immunogenicity after Doses 1 and 2)</td>
<td></td>
</tr>
</tbody>
</table>

Phase 2/3

Safety and Immunogenicity analysis of Phase 2 data (first 80 participants) by unblinded team (these participants will also be included in Phase 3 analyses)

Single vaccine candidate

Age: 516
(1:1 randomization active/placebo)

Abbreviation: IRC = internal review committee
How acceptable are adaptive trial designs?
How acceptable are adaptive trial designs?

https://www.remapcap.org/
How acceptable are adaptive trial designs?

Incorporating Adult Evidence Into Pediatric Research and Practice
Bayesian Designs to Expedite Obtaining Child-Specific Evidence

The need for child-specific knowledge acquisition through high-quality clinical trials is clear. Due to differences in drug metabolism or pathophysiology, children may respond differently than adults to various therapies, even when used to treat the same disease. FDA guidance has been drafted on these innovative designs, allowing for adult trials to be completed, and through an expert-driven process of weighting the prior distribution based on clinical relevance, initiate the pediatric study. FDA guidance has been drafted on these innovative designs, allowing for adult trials to be completed, and through an expert-driven process of weighting the prior distribution based on clinical relevance, initiate the pediatric study. Need to answer research questions for adults and children in parallel.
How acceptable are adaptive trial designs?

Clinical Infectious Diseases

When to know when you are not always able

Resist the Temptation of Randomization

Michael Proschan* and Scott Evans

Abstract

Background: Adaptive participant benefit of clinical trials is a design that allows
changes to the treatment received by patients enrolled in the trial. Such designs may
reduce sample size or the enrollment of patients that are enrolled in ongoing trials.

Response-adaptive randomization (RAR) is a form of adaptive randomization in which
the probability of participants randomized to intervention b is increased if b is more
effective than a, which reduces the number of participants randomized to less
effective group a. The RAR causes many problems, including:
inaccurate sample-size distributions that can cause an overestimation of the
true effect size, which can lead to inappropriate conclusions, and 
problems that result from the process of randomization.

Main text: In this paper, we discuss the issues associated with RAR and
how it can be used to improve the efficiency of clinical trials.

Conclusion: Adaptive randomization is a powerful tool that can improve the
efficiency of clinical trials. However, it is important to carefully consider
the potential benefits and drawbacks of using adaptive designs.

Keywords: randomized controlled trials; adaptive designs; response-adaptive randomization; temporal trend; platform trials; frequentist approach; Bayesian approach.
How acceptable are adaptive trial designs?

Common criticisms of adaptive trials

- Temporal changes & non-concurrent controls: complex modelling time effects
- RAR: inefficiency & bias in treatment effect estimation: minimise by delaying time until start of RAR, fixing comparator arm allocation and weighting response-adaptive allocation on both treatment response and information
- Potential for selection & operational bias: trial governance & integrity document
- More resources needed to initiate trial but may be resource saving overall
- Shortage of researchers with training/skills to implement adaptive trials
- Greater statistical burden and shortage of statisticians with appropriate skills
- Knowledge gap: Ethics committees and Data Safety & Monitoring Committees

Global need for training and capacity building

Recommendation: START SIMPLE
Adaptive trials implementation challenges
Adaptive trial implementation challenges

- Short term endpoint
- Explicit model for outcomes
- Bayesian sharing
- Availability & quality of data
- Adaptive randomisation
- Sharing of control groups
- Decision criteria
- Trial simulation
- Data office
Additional resources

https://adaptivehealthintelligence.org.au/resources

https://www.berryconsultants.com/library/
How to submit your questions

If your question is addressed to a specific speaker, please include their name when submitting the question.

The presentation will be followed by an interactive Q&A session.

Please submit your questions via the ‘questions’ window. We will review all questions and respond to as many as possible after the presentation.
Today’s speakers

New clinical trial designs for evaluation of antimicrobial agents

**David Paterson**  
*Director*  
University of Queensland Centre for Clinical Research (Australia)

**Julie Marsh**  
*Biostatistical Lead*  
Wesfarmers Centre of Vaccines and Infectious Diseases, University of Western Australia (Australia)

**Moderator:**  
Thomas Snelling  
*Professor of Infectious Diseases and Director of the Health and Clinical Analytics Lab*  
Sydney School of Public Health, University of Sydney (Australia)
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REVIVE webinar

10 June, 15:30-17:00 CEST

Openly accessible resources for the global antimicrobial R&D community

Speakers:
- Eva Garmendia, Uppsala Antibiotic Center (Sweden)
- David Jenkins, BSAC (UK)
- Astrid Pentz-Murr, GARDP (Switzerland)

Registration link and more information will be available on:
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Thank you for joining us