New clinical trial designs for evaluation of antimicrobial agents

Guest speakers: David Paterson, Julie Marsh

Moderator: Thomas Snelling

Host: Astrid Pentz-Murr (GARDP)

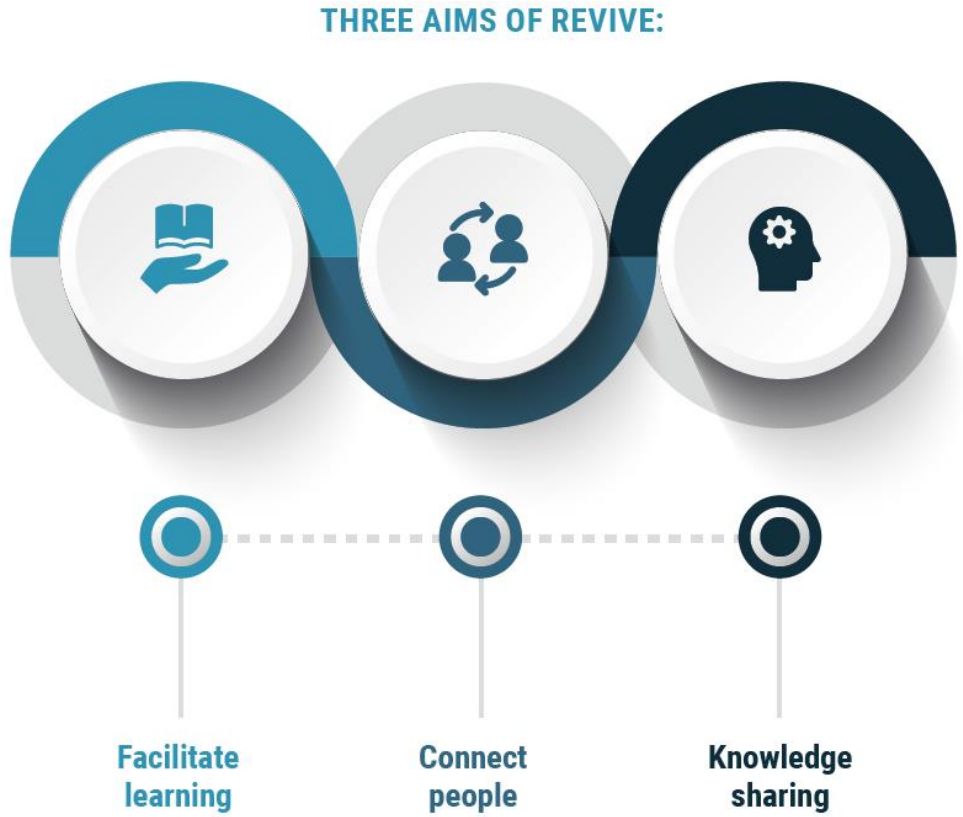
27 May 2021

GARDP

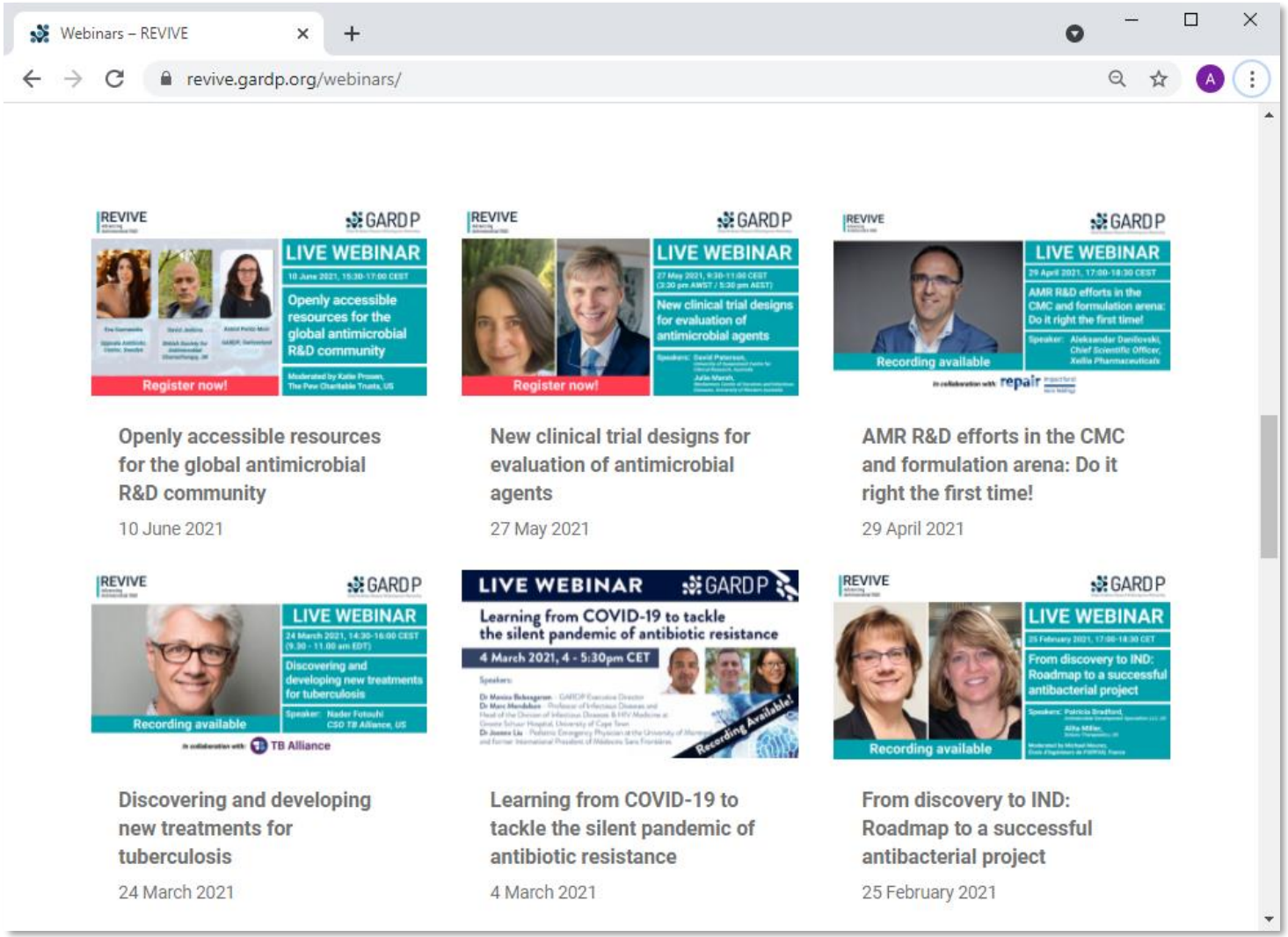
Global Antibiotic Research & Development Partnership

REVIVE

An online space to connect and support the antimicrobial discovery, research, and development community



Webinar recordings



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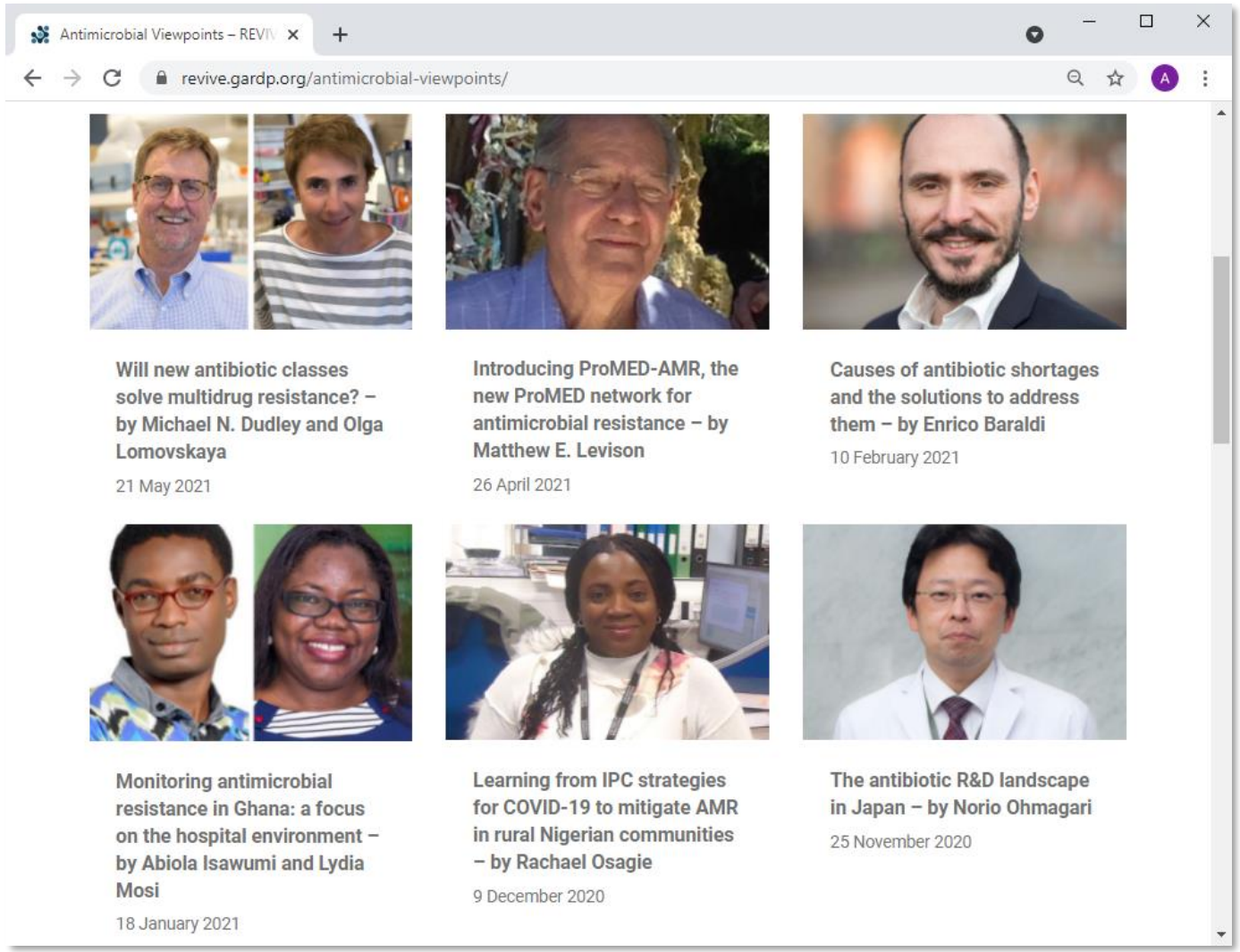
Antimicrobial Viewpoints



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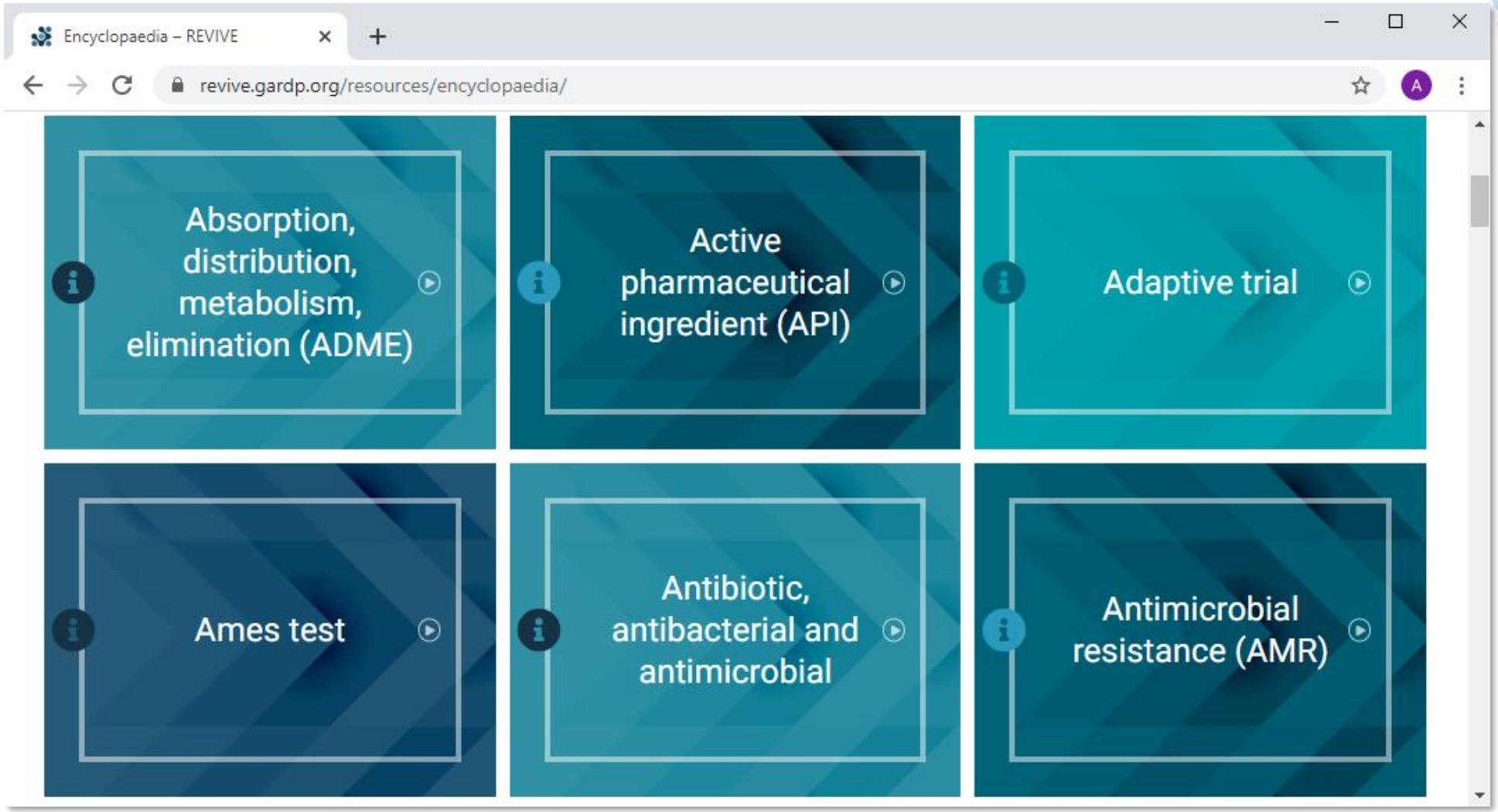
Antimicrobial Encyclopaedia



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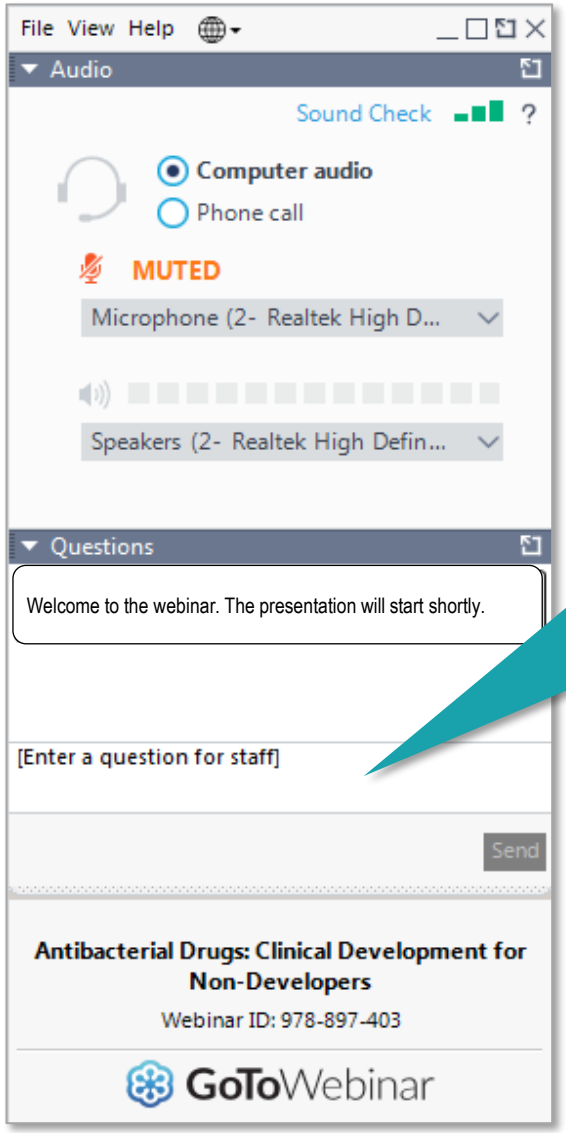
How to submit your questions

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)

David Paterson

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.

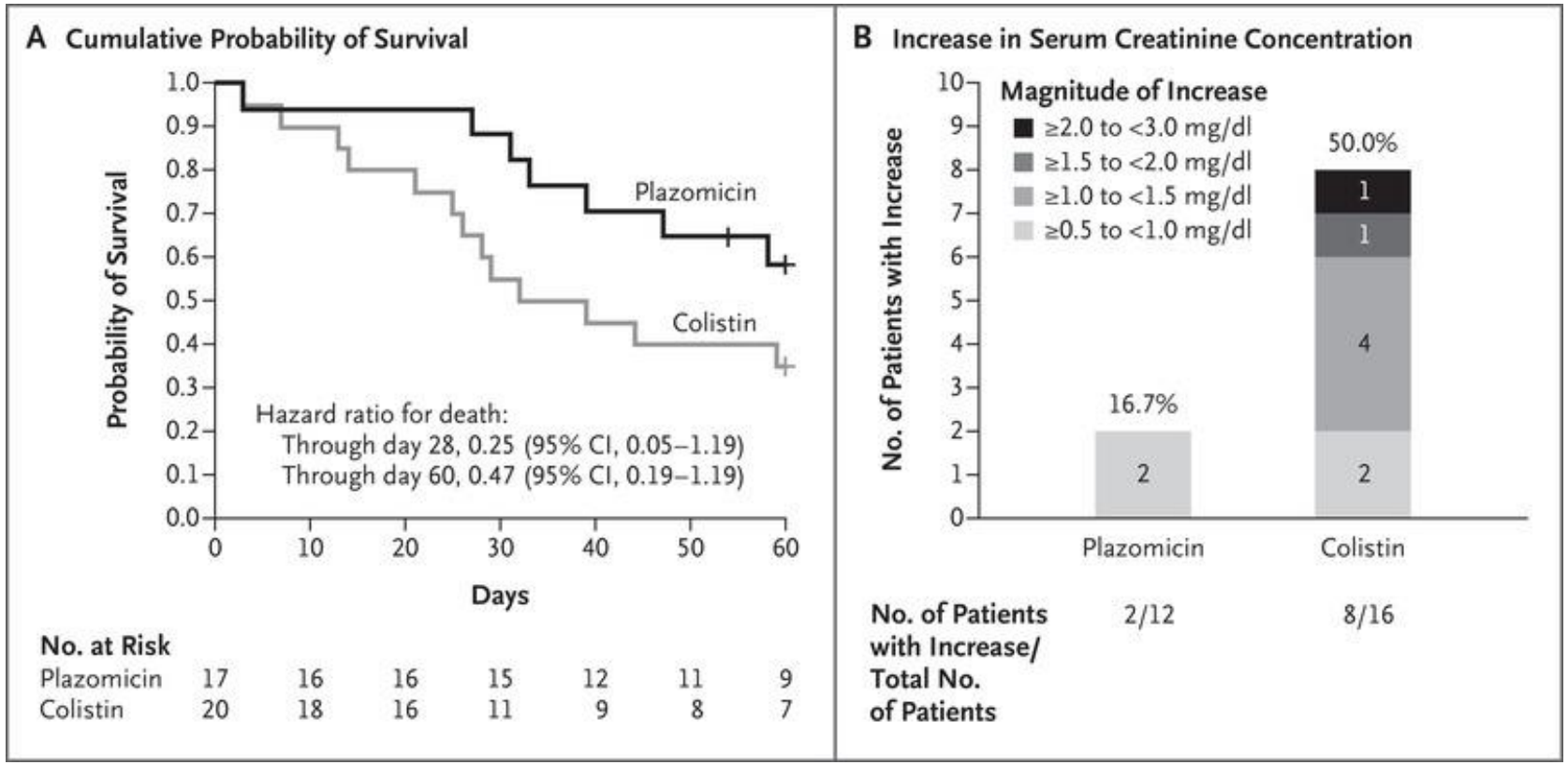
Overview of innovations in clinical trials of antimicrobial agents

David Paterson
University of Queensland

What do we want to avoid in antibiotic development?

A Case Study: Achaogen

Plazomicin vs KPC producers

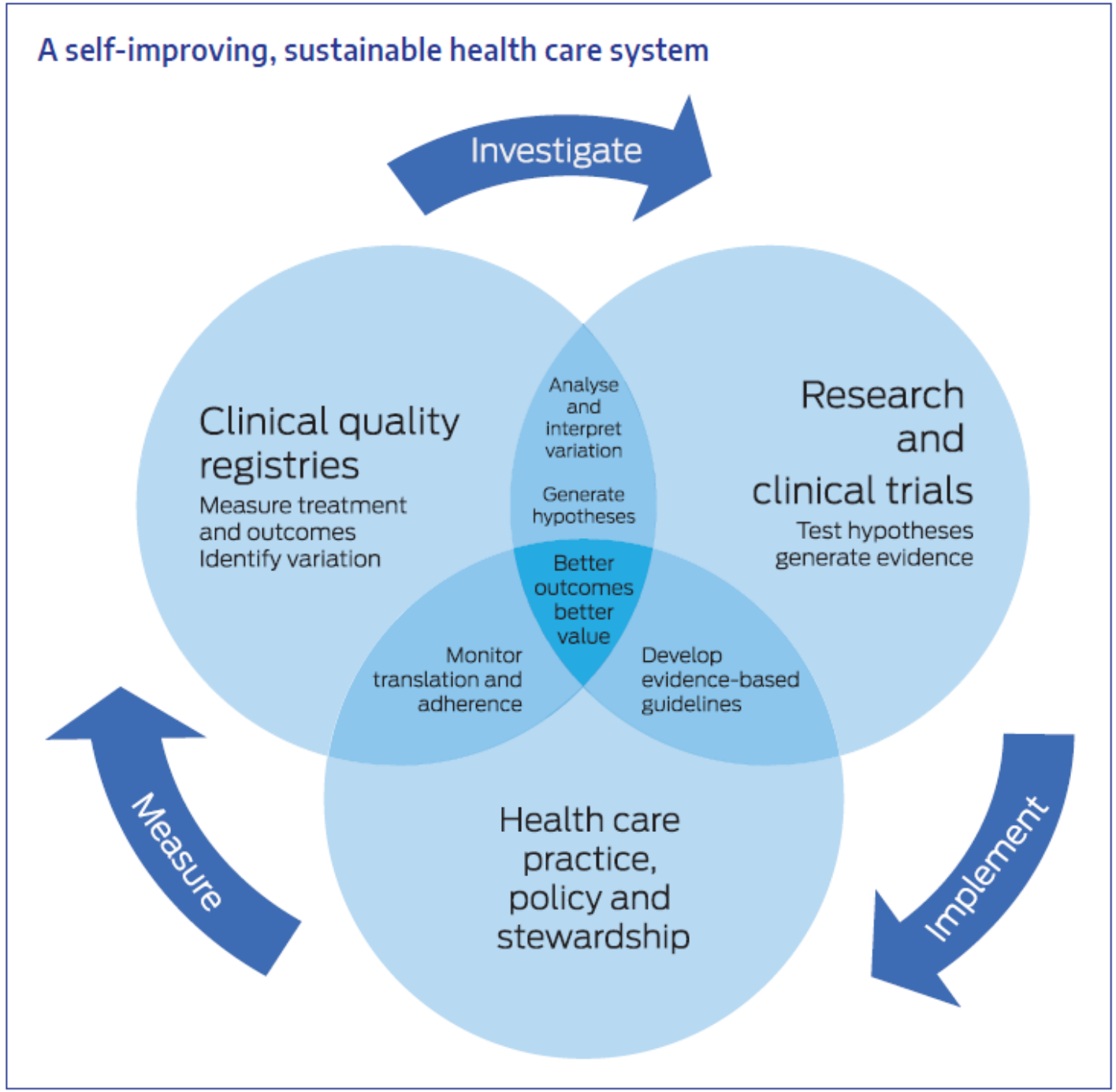


Achaogen Stock Price

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
Investigate
Clinical quality registries
Measure treatment and outcomes
Identify variation
Research and clinical trials
Test hypotheses generate evidence
Health care practice, policy and stewardship
Analyse and interpret variation
Generate hypotheses
Better outcomes better value
Monitor translation and adherence
Develop evidence-based guidelines
Measure
Implement

Research

JAMA | Original Investigation

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 Kanj, 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)

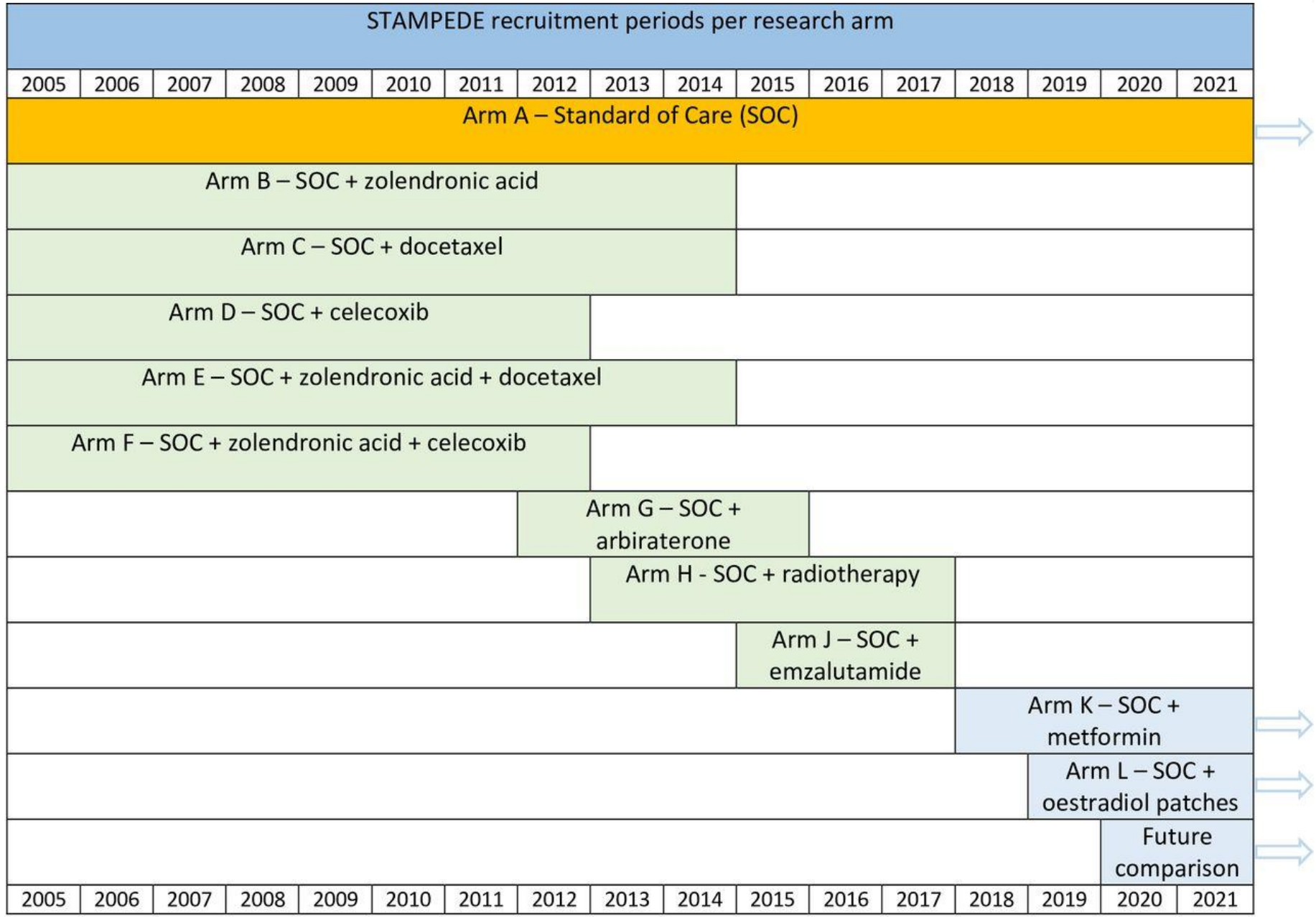
MERINO Trial sites

More than 25 sites in 9 countries

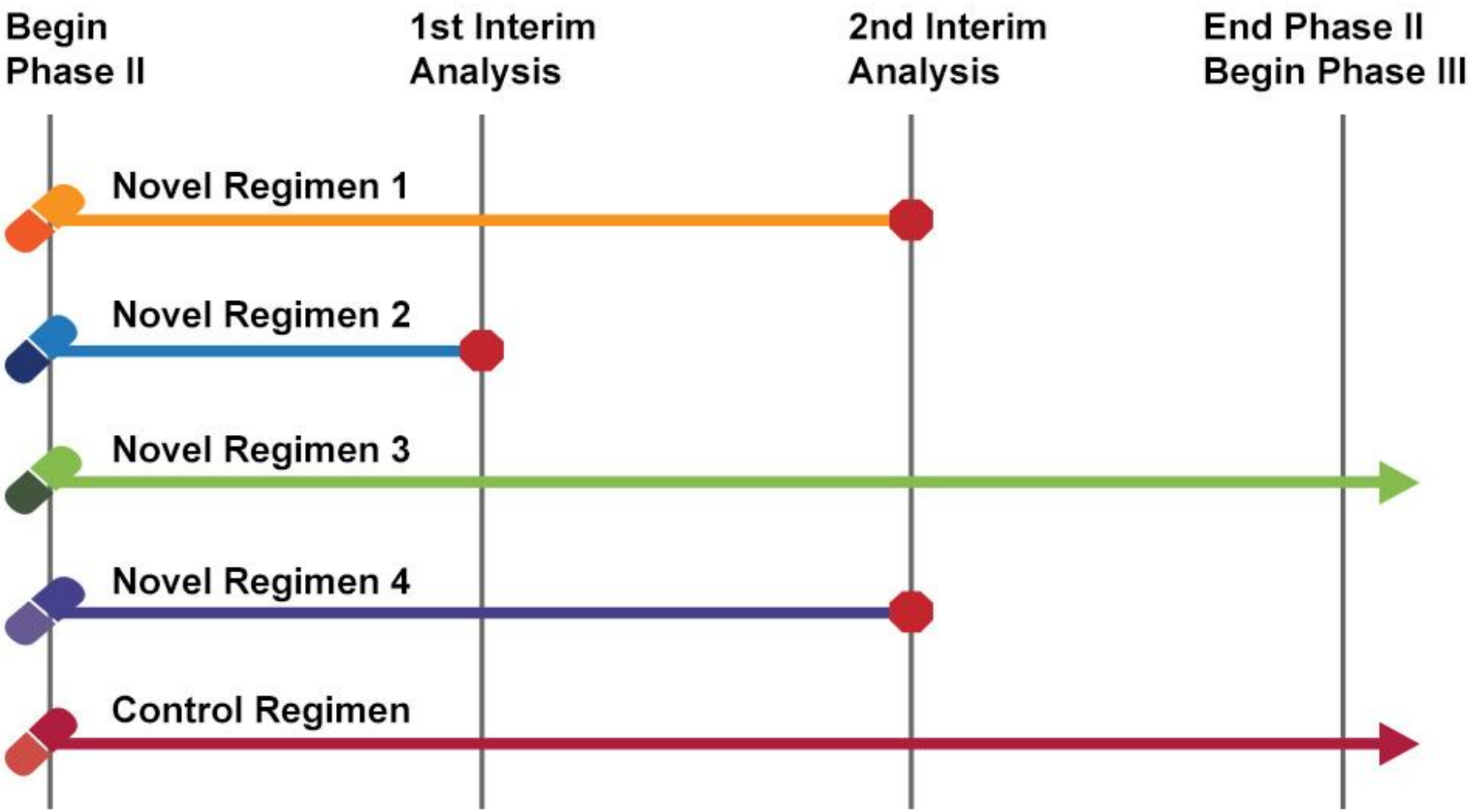
Examples of trial networks in AMR

- 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?


STAMPEDE recruitment periods per research arm
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
Arm A – Standard of Care (SOC)
Arm B – SOC + zolendronic acid
Arm C – SOC + docetaxel
Arm D – SOC + celecoxib
Arm E – SOC + zolendronic acid + docetaxel
Arm F – SOC + zolendronic acid + celecoxib
Arm G – SOC + arbiraterone
Arm H - SOC + radiotherapy
Arm J – SOC + emzalutamide
Arm K – SOC + metformin
Arm L – SOC + oestradiol patches
Future comparison
Standard of care
In development
Closed to recruitment

Multi-arm multi-stage (MAMS) design



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cluster-Randomized, Crossover Trial of Head Positioning in Acute Stroke

C.S. Anderson, H. Arima, P. Lavados, L. Billot, M.L. Hackett, V.V. Olavarría, P. Muñoz Venturelli, A. Brunser, B. Peng, L. Cui, L. Song, K. Rogers, S. Middleton, J.Y. Lim, D. Forshaw, C.E. Lightbody, M. Woodward, O. Pontes-Neto, H.A. De Silva, R.-T. Lin, T.-H. Lee, J.D. Pandian, G.E. Mead, T. Robinson, and C. Watkins, for the HeadPoST Investigators and Coordinators*

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

Clinical Infectious Diseases Advance Access published July 14, 2015

INVITED ARTICLE

HEALTHCARE EPIDEMIOLOGY

Robert A. Weinstein, Section Editor

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. Chambers[13]

Rank	Alive	How many of: 1) Clinical Failure 2) Infectious Complication 3) SAE, or AE leading to study drug discontinuation	QoL
1	Yes	0 of 3	Tiebreaker based on QoL score
2	Yes	1 of 3	
3	Yes	2 of 3	
4	Yes	3 of 3	
5	No (Death)	Any	

PRACTical

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 particpants

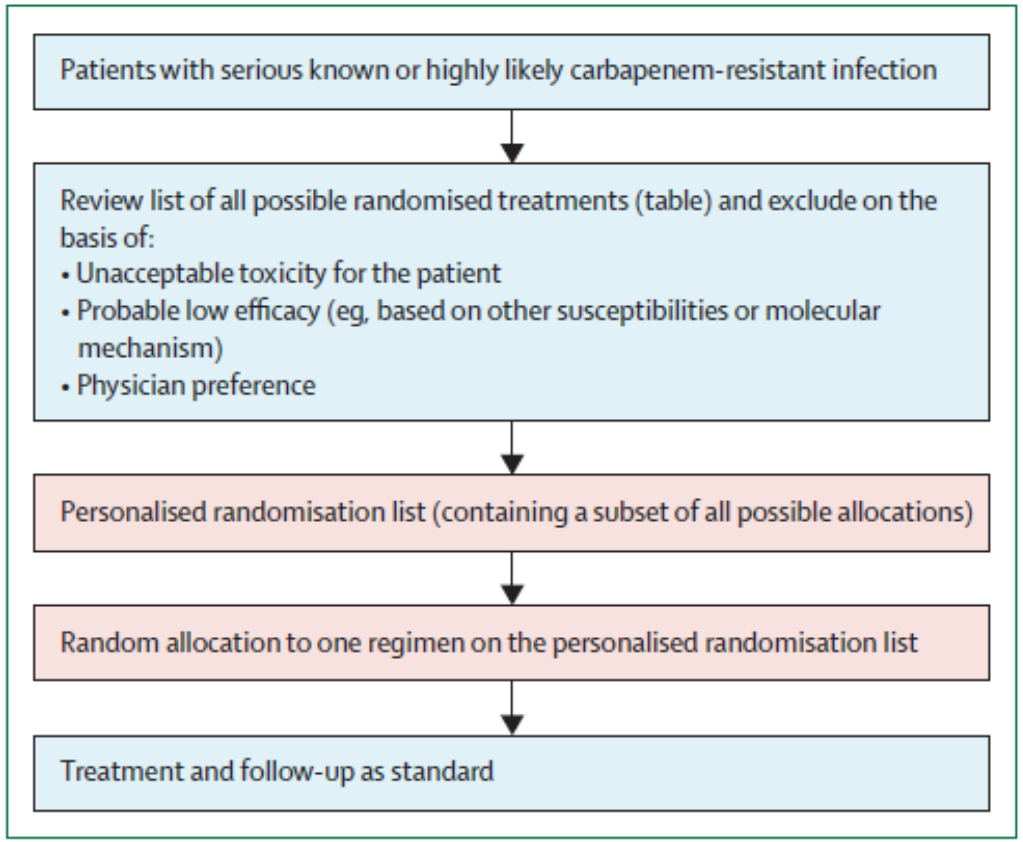


Figure 1: **Proposed flow diagram of participants through the trial**

	Patient 1: moderate renal impairment (creatinine clearance <40mL/min)	Patient 2: history of myocardial infarction	Patient 3: meropenem MIC ≥64	Patient 4: ventilator-acquired or hospital-acquired pneumonia	Patient 5: *Pseudomonas aeruginosa* infection	Patient 6: known class B (NDM, IMP, VIM) infection	Patient 7: presence of 6S ribosomal RNA methyltransferases (encoding aminoglycoside resistance)*	Patient 8: history of moderate to severe allergy to cephalosporins
A: plazomicin	No or maybe†	Yes	Yes	Yes	Yes	No	No	Yes
B: ceftazidime plus avibactam	No or maybe†	Yes	Yes	Yes	Yes	No	Yes	No
C: cefiderocol	Maybe†	Yes	Yes	Yes	Yes	Yes	Yes	No
D: high-dose meropenem‡	Maybe†	Yes	No	Yes	Yes	Yes	Yes	Yes
E: polymyxin B with or without zidovudine	No or maybe†	Yes	Yes	No	Yes	Yes	Yes	Yes
F: high-dose meropenem‡ plus ertapenem	Maybe†	Yes	No	Yes	No	Yes	Yes	Yes
G: high-dose meropenem‡ plus imipenem	No or Maybe†	Yes	No	Yes	Yes	Yes	Yes	Yes
H: high-dose meropenem‡ plus polymyxin B with or without zidovudine	No or maybe†	Yes	No	No	Yes	Yes	Yes	Yes
I: high-dose meropenem‡ plus high-dose tigecycline	Maybe†	No	No	Yes	No	Yes	Yes	Yes
J: high-dose meropenem‡ plus fosfomycin	Maybe†	Yes	No	Yes	Yes	Yes	Yes	Yes
K: high-dose tigecycline§ plus polymyxin B with or without zidovudine	No or maybe†	No	Yes	No	No	Yes	Yes	Yes
L: high-dose tigecycline§ plus fosfomycin	Maybe†	No	Yes	Yes	No	Yes	Yes	Yes
M: fosfomycin plus polymyxin B with or without zidovudine	No or maybe†	Yes	Yes	No	Yes	Yes	Yes	Yes

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**

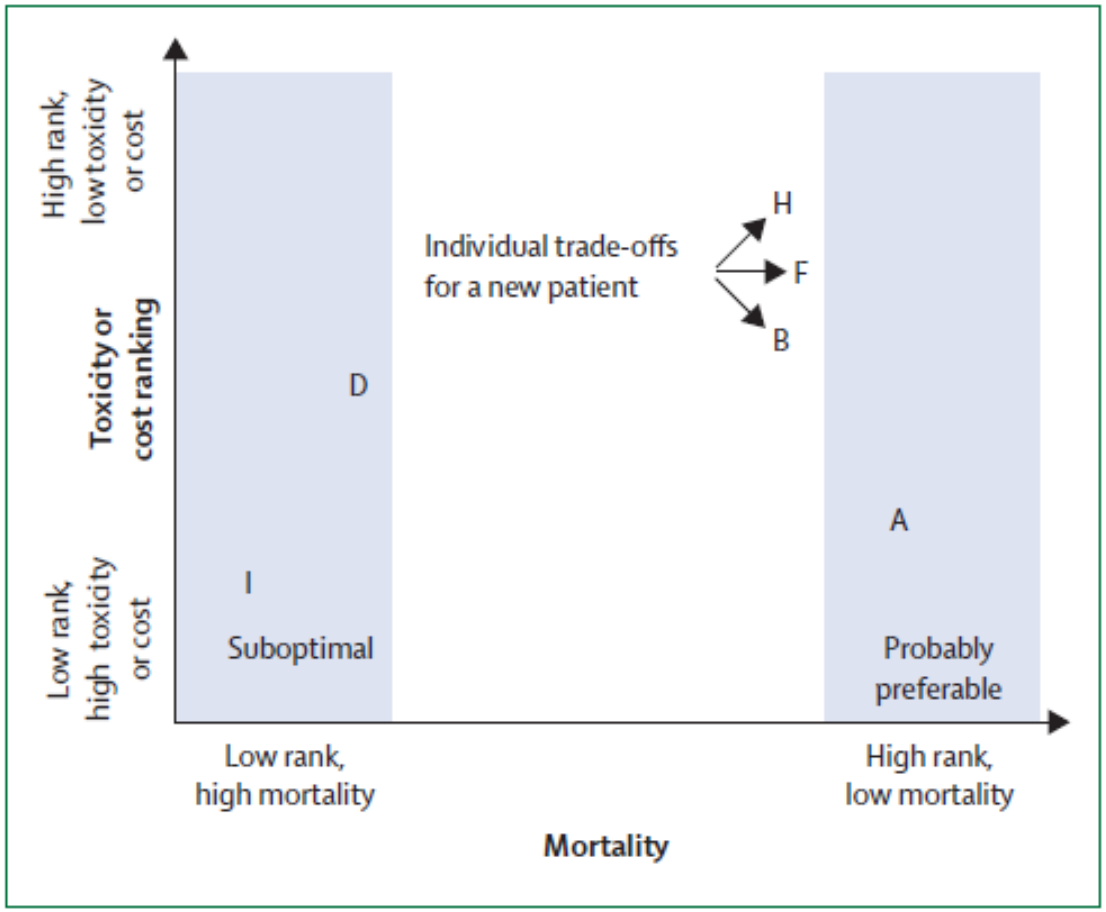


Figure 2: **Hypothetical ranking of regimens from a personalised randomisation list for a future individual patient after the trial**
Efficacy ranking based on predicted probability of primary outcome for the personalised randomisation subset (table). I=high-dose meropenem plus high-dose tigecycline. 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

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

Clinical Infectious Diseases

INVITED ARTICLE

INNOVATIONS IN DESIGN, EDUCATION AND ANALYSIS (IDEA): Victor De Gruttola and Scott R. Evans, Section Editors

Resist the Temptation of Response-Adaptive Randomization

Michael Proschan[1] **and Scott Evans**[2]

[1]Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases, Rockville, Maryland, USA, and [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

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

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ADAPTIVE HEALTH INTELLIGENCE
EVIDENCE IN ACTION

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- 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

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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*

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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

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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*

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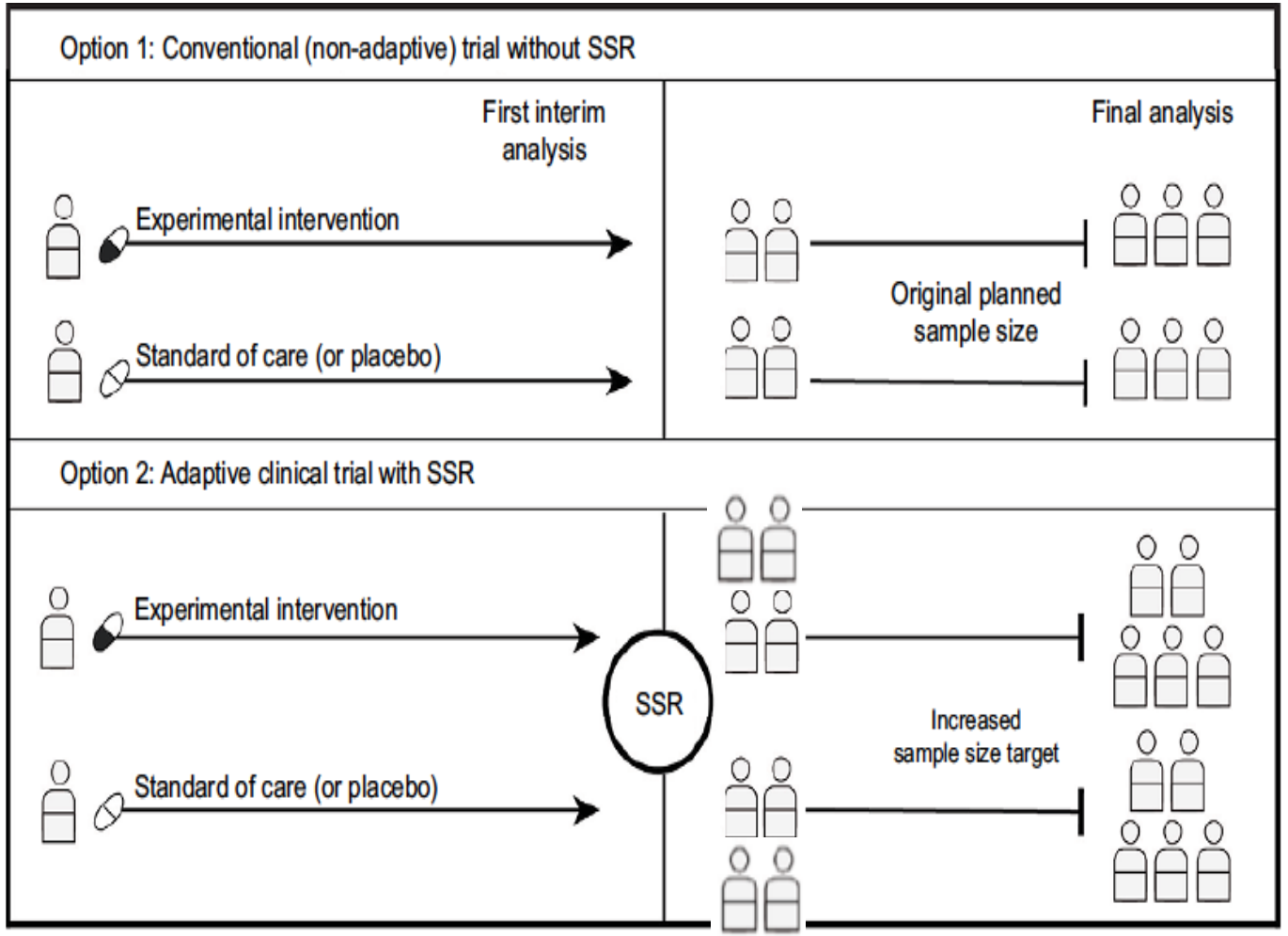
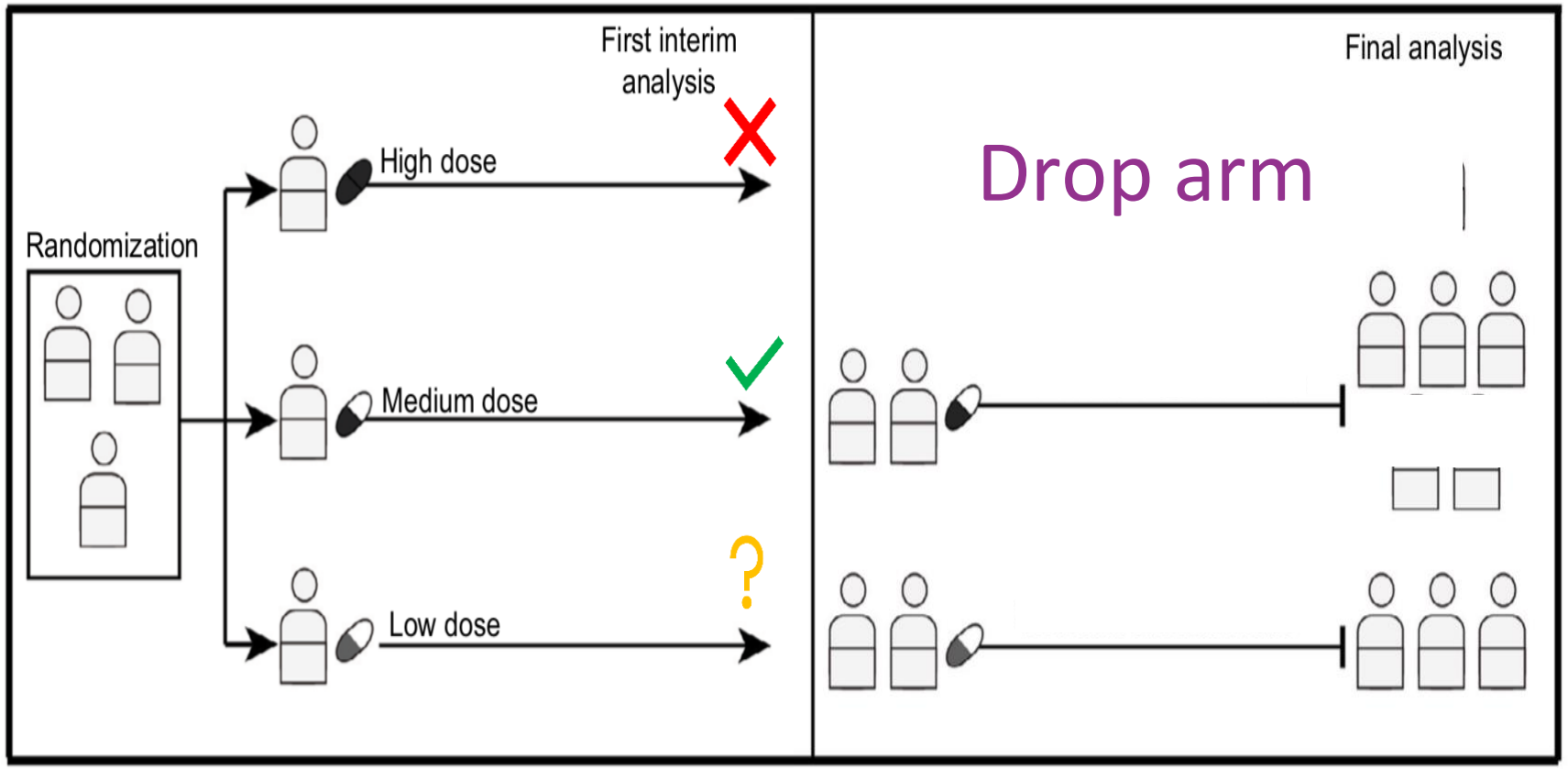
Sample size reassessment (SSR)



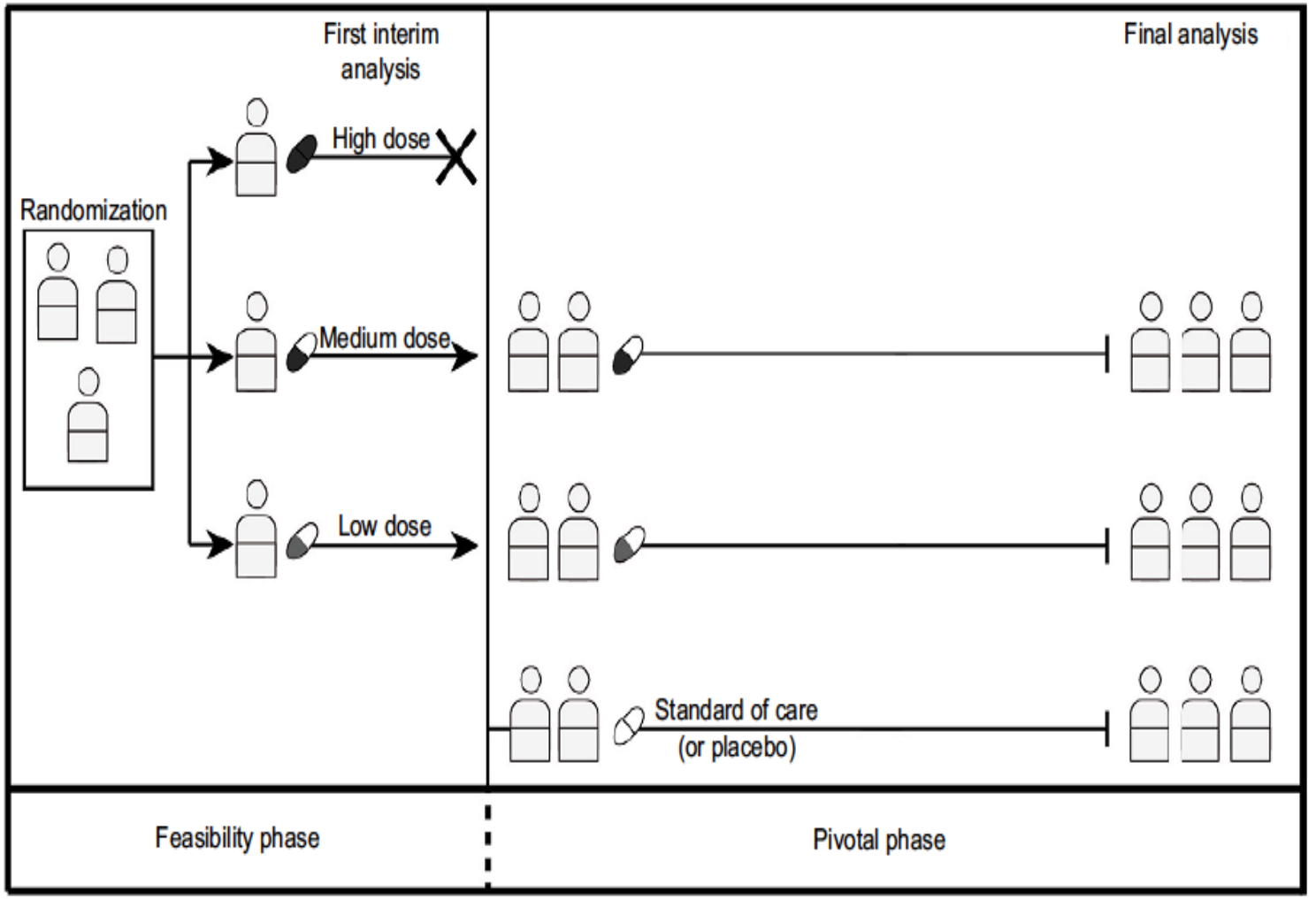
Amended from Park et al. (2018)

Treatment selection (arm dropping)



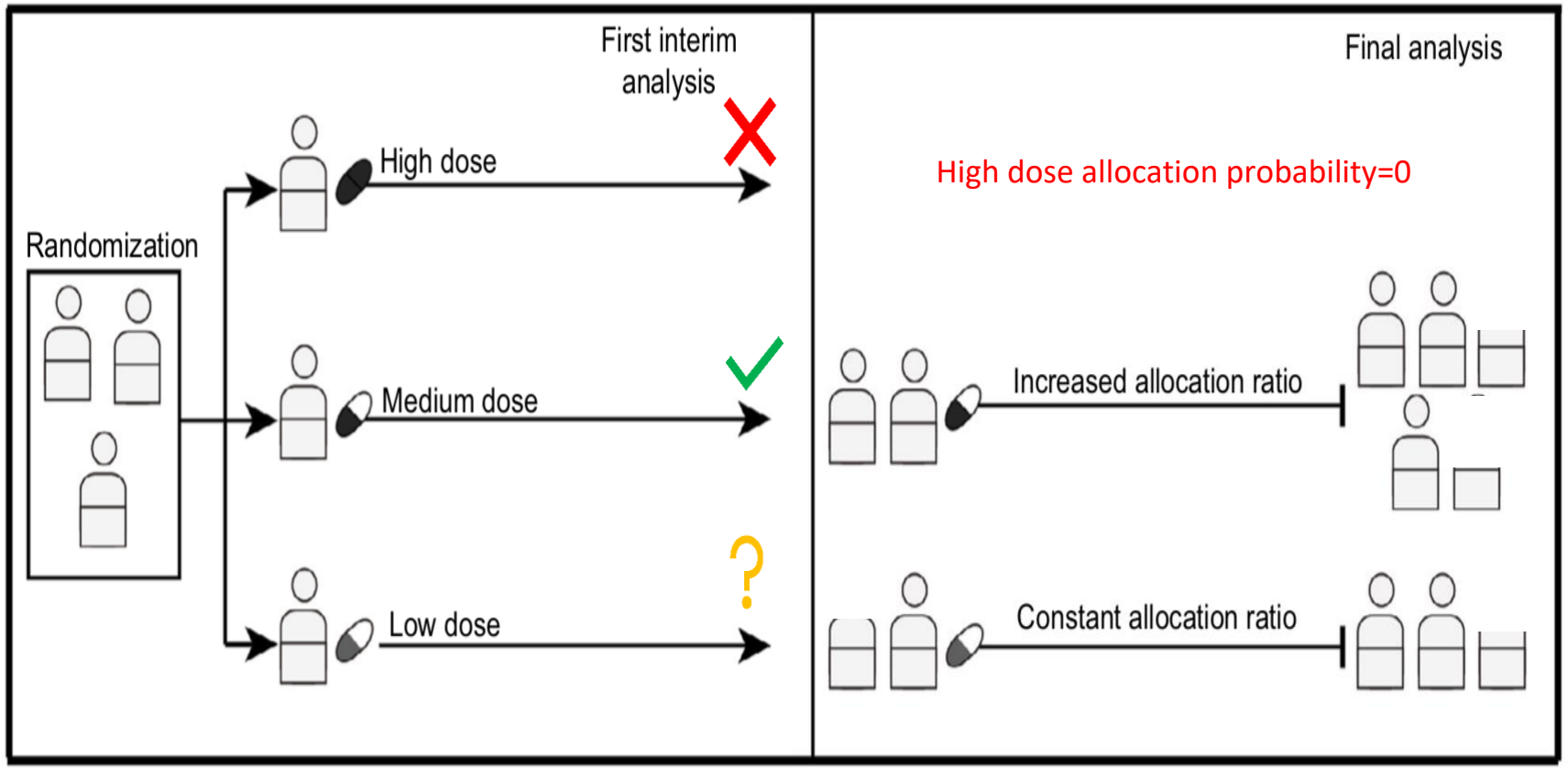
Amended from Park et al. (2018)

Seamless design



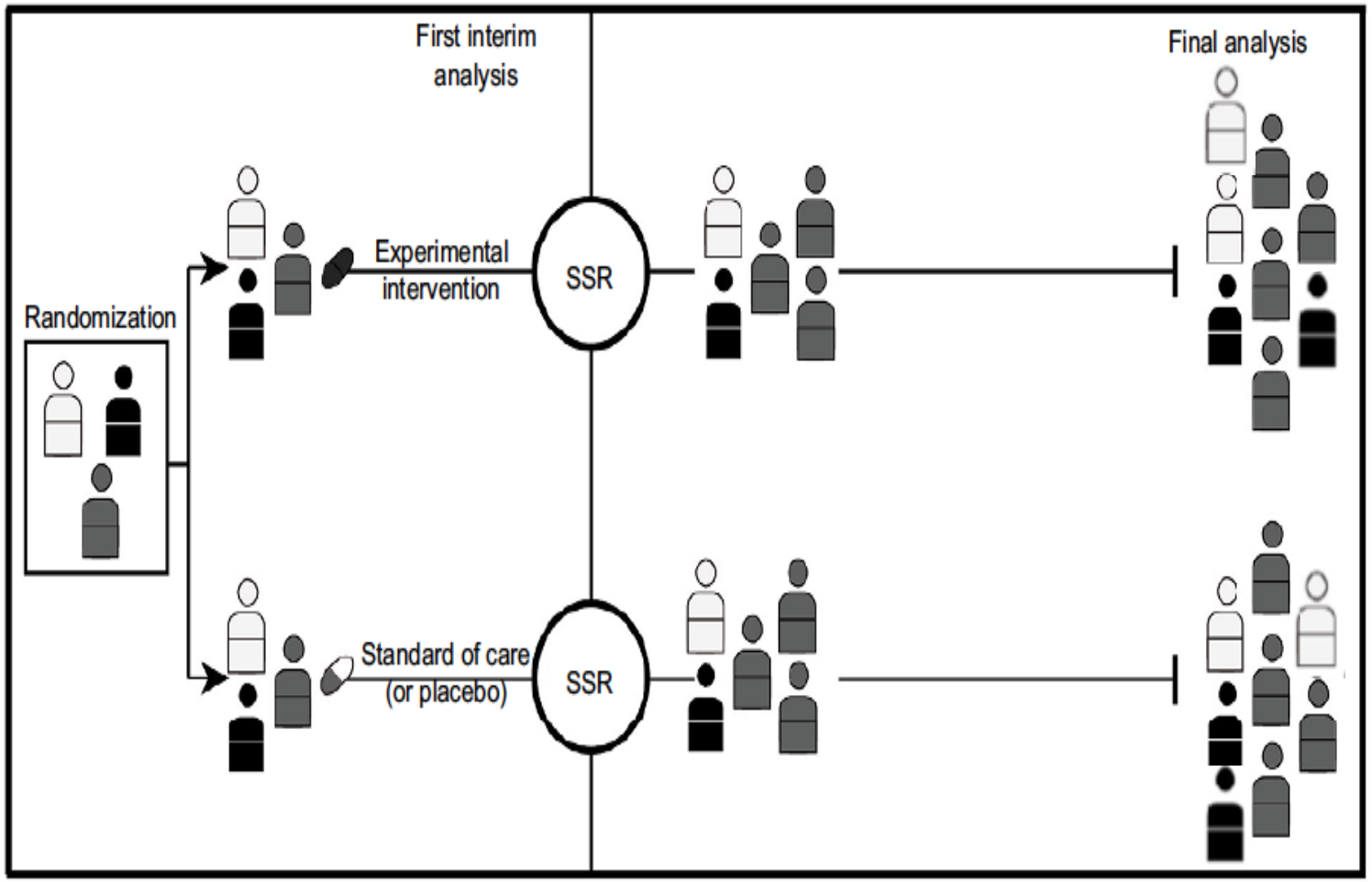
Park et al. (2018)

Response adaptive randomisation



Park et al. (2018)

Enrichment design



Amended Park et al. (2018)

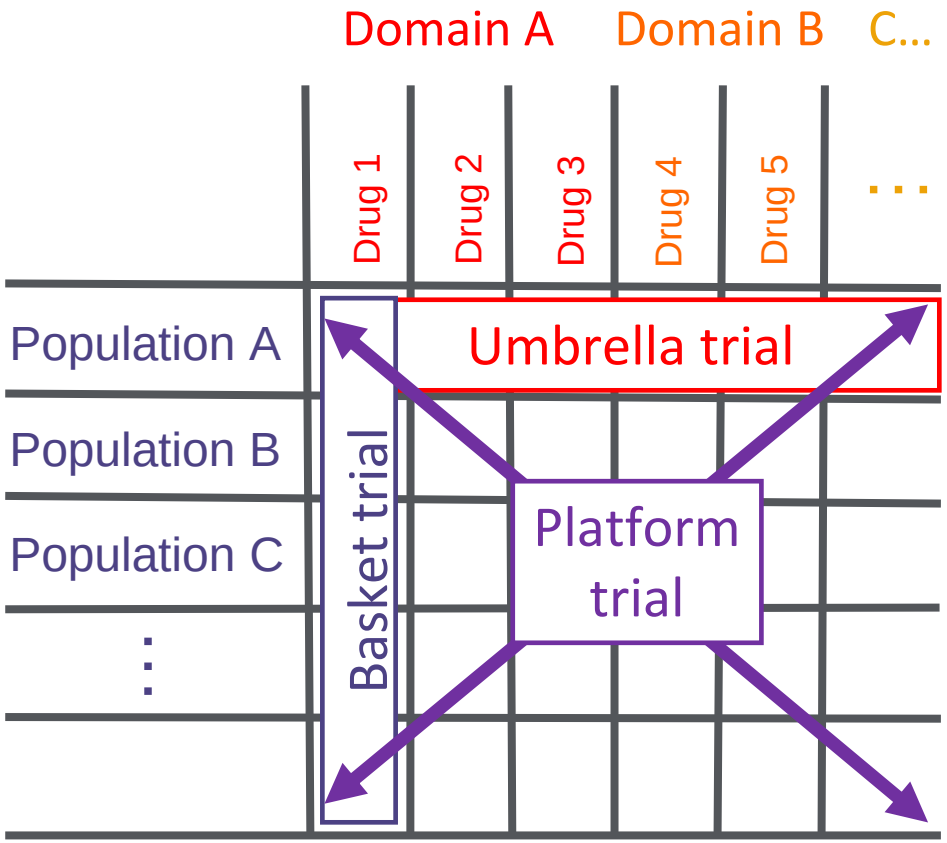
Beyond simple adaptive trial designs

- **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



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VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

Scott M. Berry, PhD
Berry Consultants LLC, Austin, Texas; and Department of Biostatistics, University of Kansas Medical Center, Kansas City.

Jason T. Connor, PhD
Berry Consultants LLC, Austin, Texas; and University of Central Florida College of Medicine, Orlando.

Roger J. Lewis, MD, PhD
Department of Emergency Medicine, Harbor-UCLA Medical Center, Torrance, California; and Berry Consultants LLC, Austin, Texas.

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.

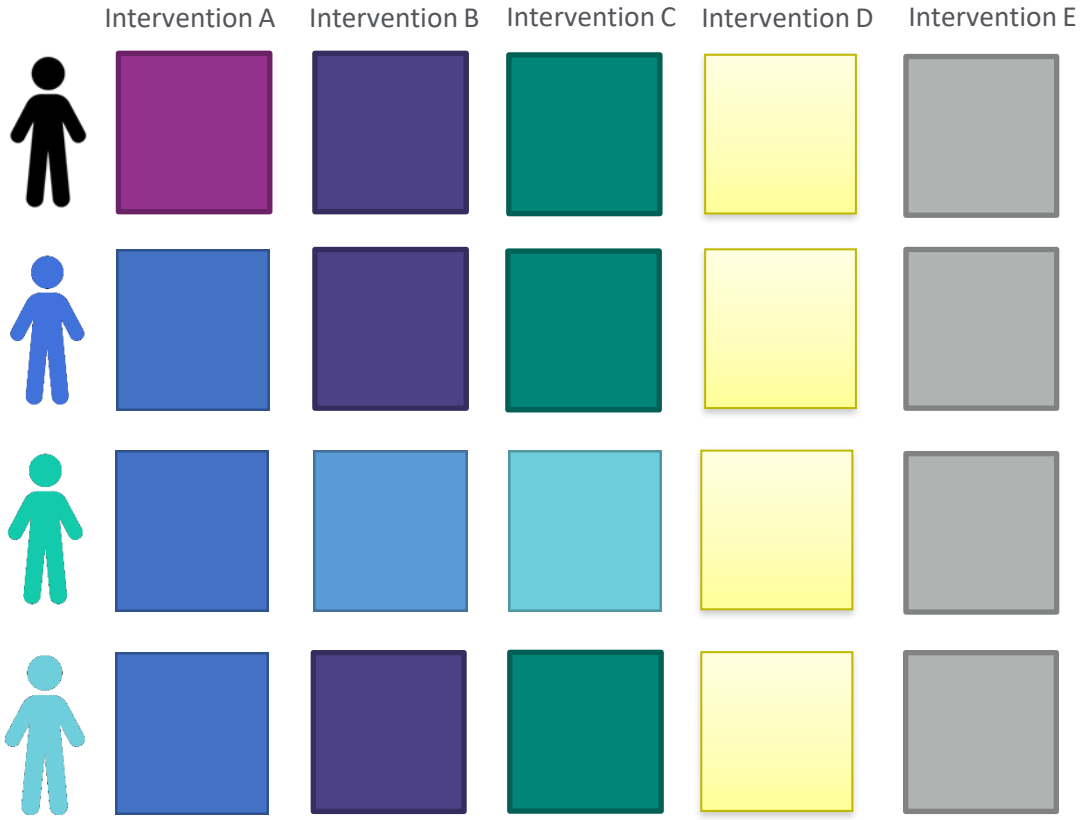
This approach has been largely unsuccessful for multiple diseases, including sepsis, dementia, and stroke. Despite promising preclinical and early human trials, there have been numerous negative phase 3 trials of treatments for Alzheimer disease[1] and more than 40 negative phase 3 trials of neuroprotectants 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



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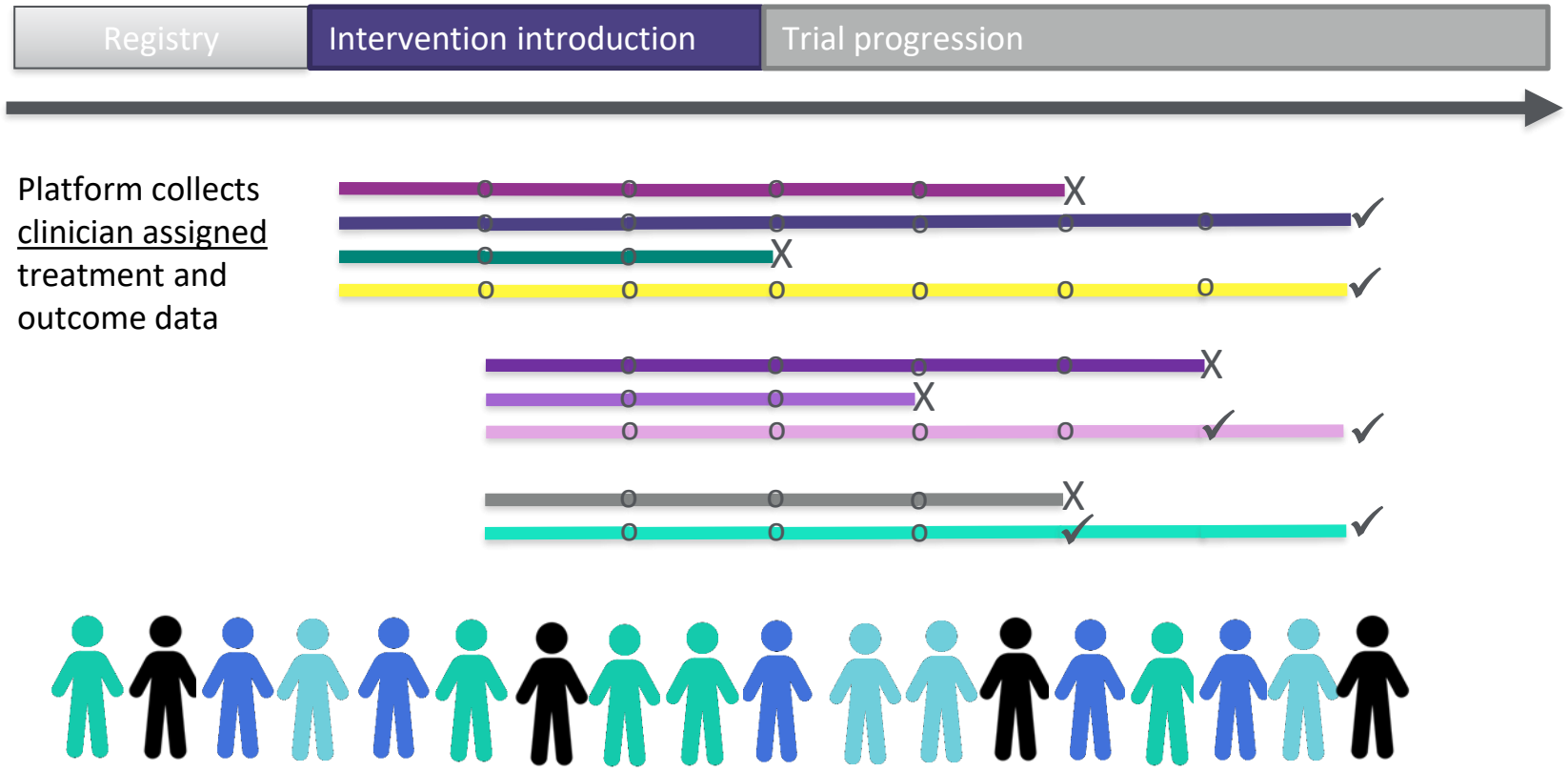
Platform Trials



Decision making using Bayesian methods

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Decision making: Frequentist or Bayesian

Frequentist	Bayesian
Focus on null hypothesis	Focus on ‘updating’ prior beliefs
Probability of **data**	Probability of **hypothesis**
Analytical focus	Computational focus
Less flexible	More flexible
Poorly suited to sequential inference	Sequential inference a breeze
More familiar/routinely used	Less familiar
Software widely available	Requires specialised software

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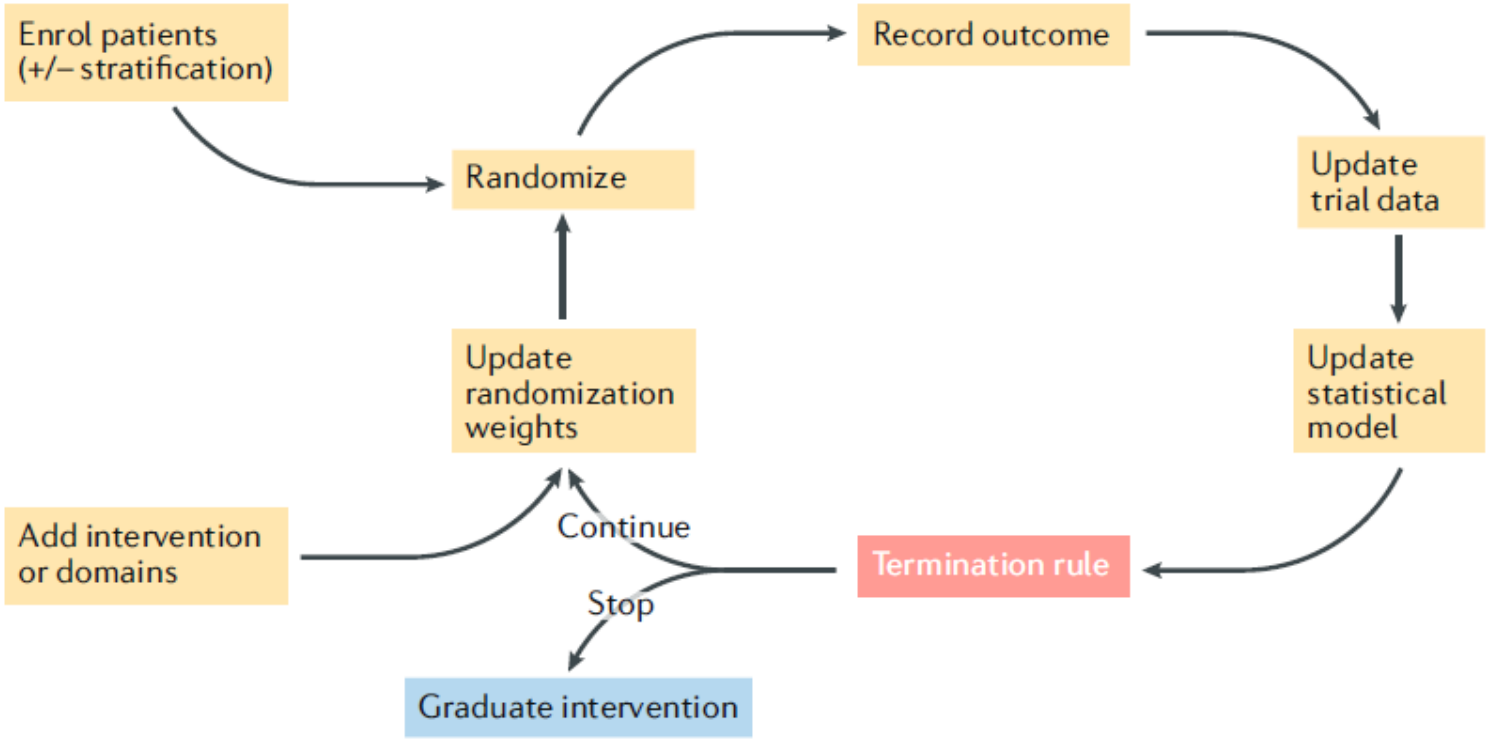
Decision making using Bayesian methods



Roger J. Lewis. *https://www.berryconsultants.com/wp-content/uploads/2012/09/An-Overview-of-Bayesian-Adaptive-Clinical-Trial-Design.pdf*

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Decision making using Bayesian methods

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

Decision making using Bayesian methods

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

i.e. $pr(H_1|data)=pr(d>0)$

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)*

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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

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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

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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.

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Adaptive trials governance & integrity

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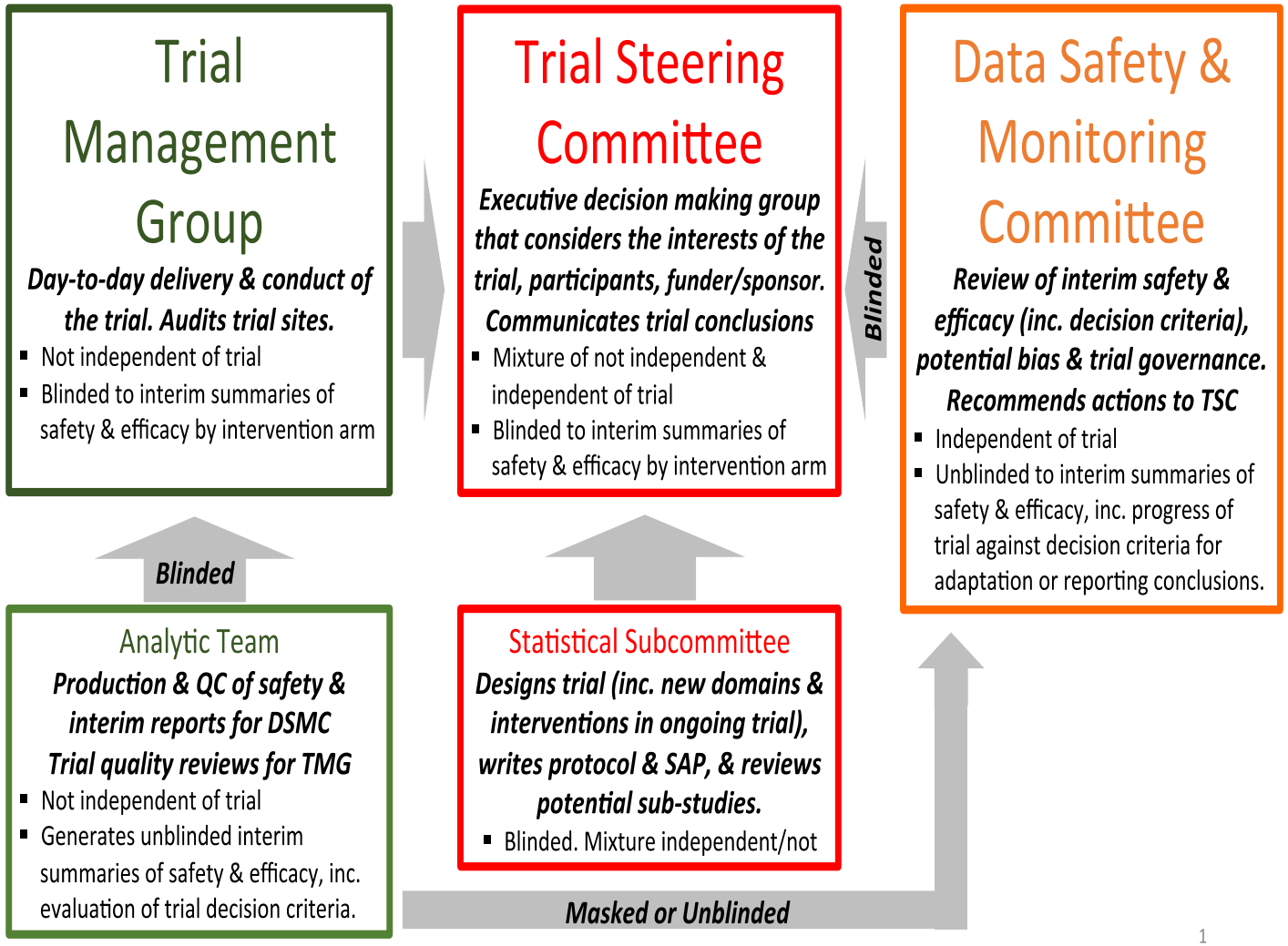
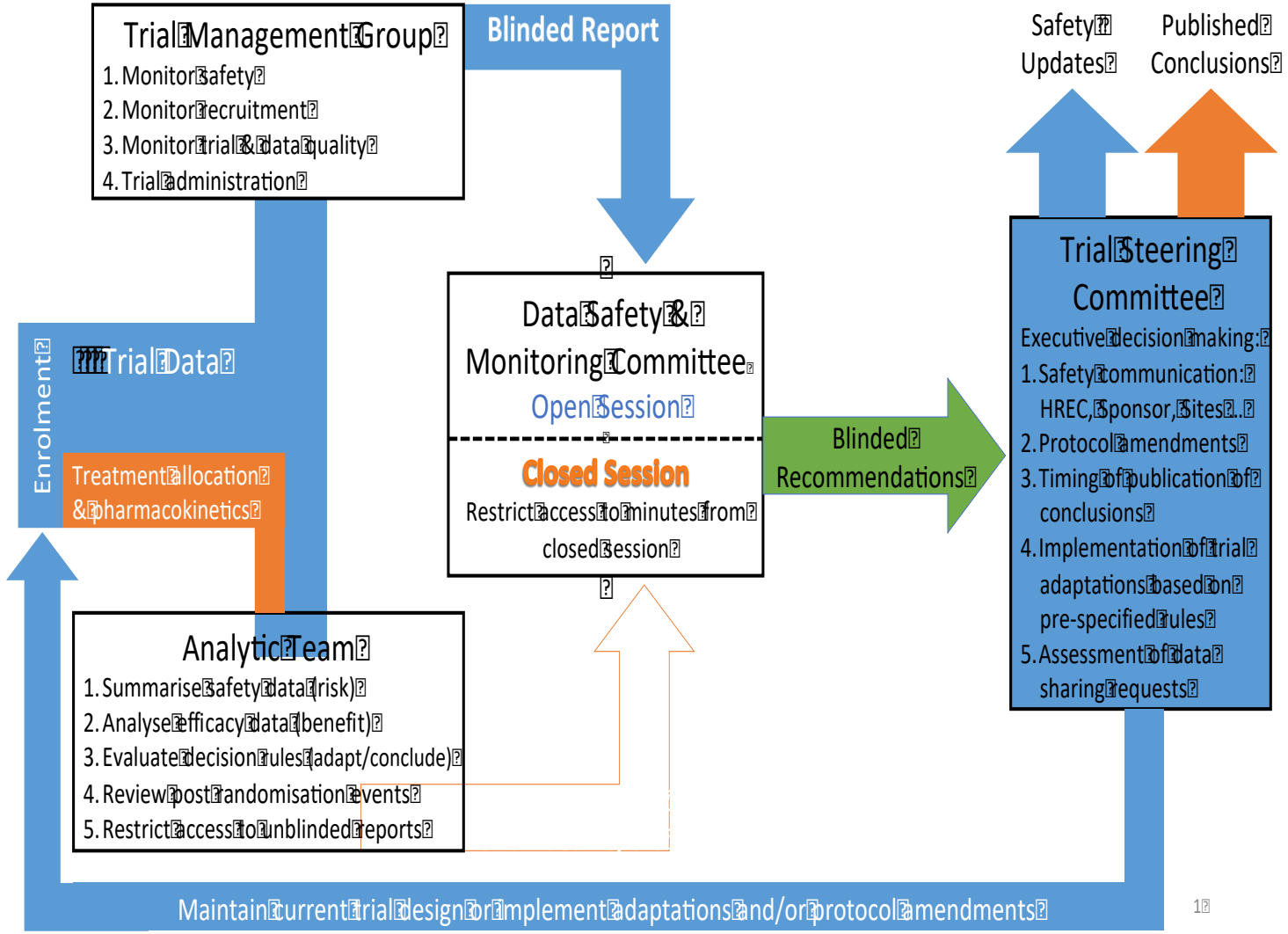
Adaptive Trial Governance



1

Adaptive Trial Integrity (information flow)



Are adaptive designs acceptable for vaccine and antimicrobial trials?

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Key design considerations for adaptive clinical trials: a primer for clinicians

Kristian Thorlund,[1,2] Jonas Haggstrom,[2] Jay JH Park,[1] Edward J Mills[1,2]

[1]Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University, Ontario, Canada

[2]The Bill and Melinda Gates Foundation, Seattle, Washington, USA

Correspondence to: EJ Mills
millsej@mcmaster.ca

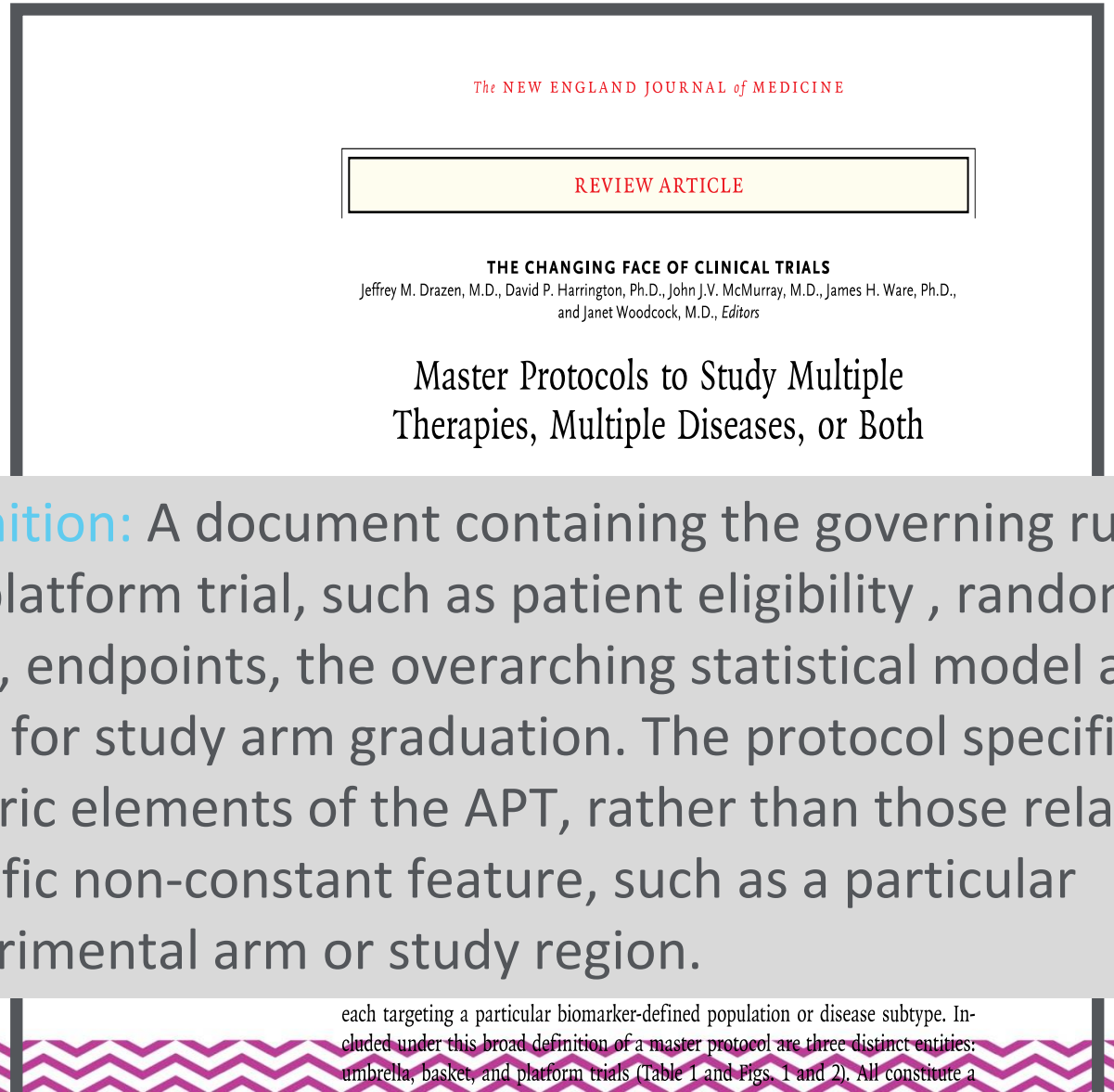
Cite this as: *BMJ* 2018;360:k698
http://dx.doi.org/10.1136/bmj.k698

Accepted: 20 December 2017

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 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.[1 2] 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.

How acceptable are adaptive trial designs?



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

each targeting a particular biomarker-defined population or disease subtype. Included under this broad definition of a master protocol are three distinct entities: umbrella, basket, and platform trials (Table 1 and Figs. 1 and 2). All constitute a

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?

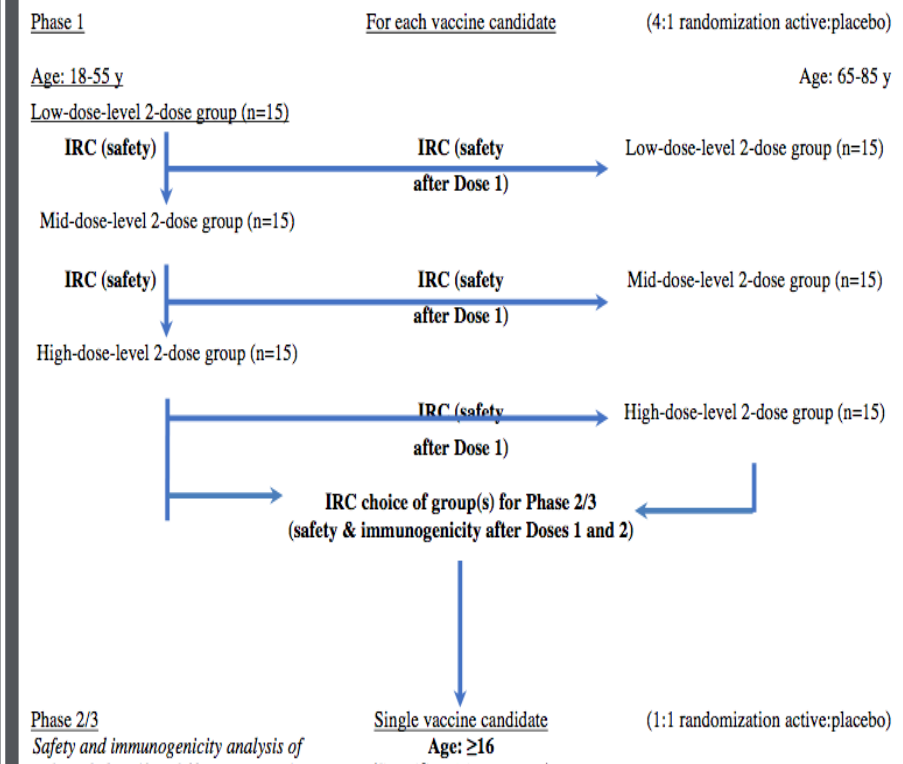
PF-07302048 (BNT162 RNA-Based COVID-19 Vaccines)
Protocol C4591001

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-07302048
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



Abbreviation: IRC = internal review committee.

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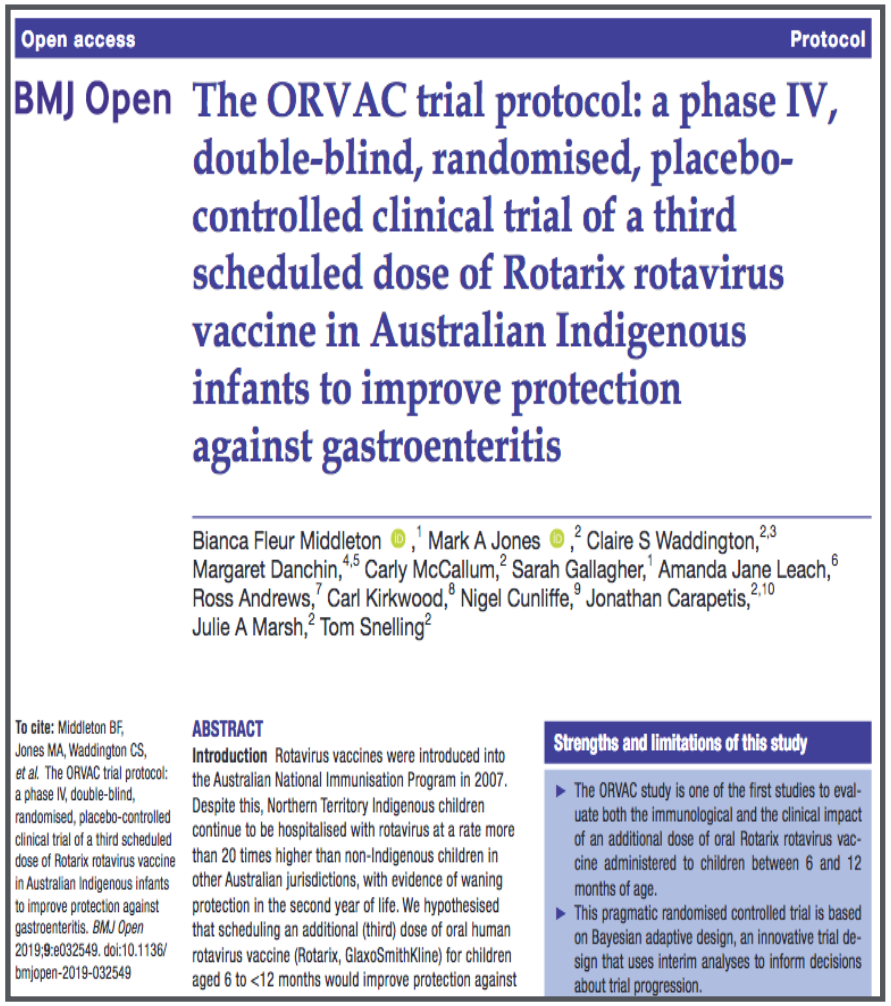
How acceptable are adaptive trial designs?



Open access Protocol

BMJ Open

The ORVAC trial protocol: a phase IV, double-blind, randomised, placebo-controlled clinical trial of a third scheduled dose of Rotarix rotavirus vaccine in Australian Indigenous infants to improve protection against gastroenteritis

Bianca Fleur Middleton ,[1] Mark A Jones ,[2] Claire S Waddington,[2,3] Margaret Danchin,[4,5] Carly McCallum,[2] Sarah Gallagher,[1] Amanda Jane Leach,[6] Ross Andrews,[7] Carl Kirkwood,[8] Nigel Cunliffe,[9] Jonathan Carapetis,[2,10] Julie A Marsh,[2] Tom Snelling[2]

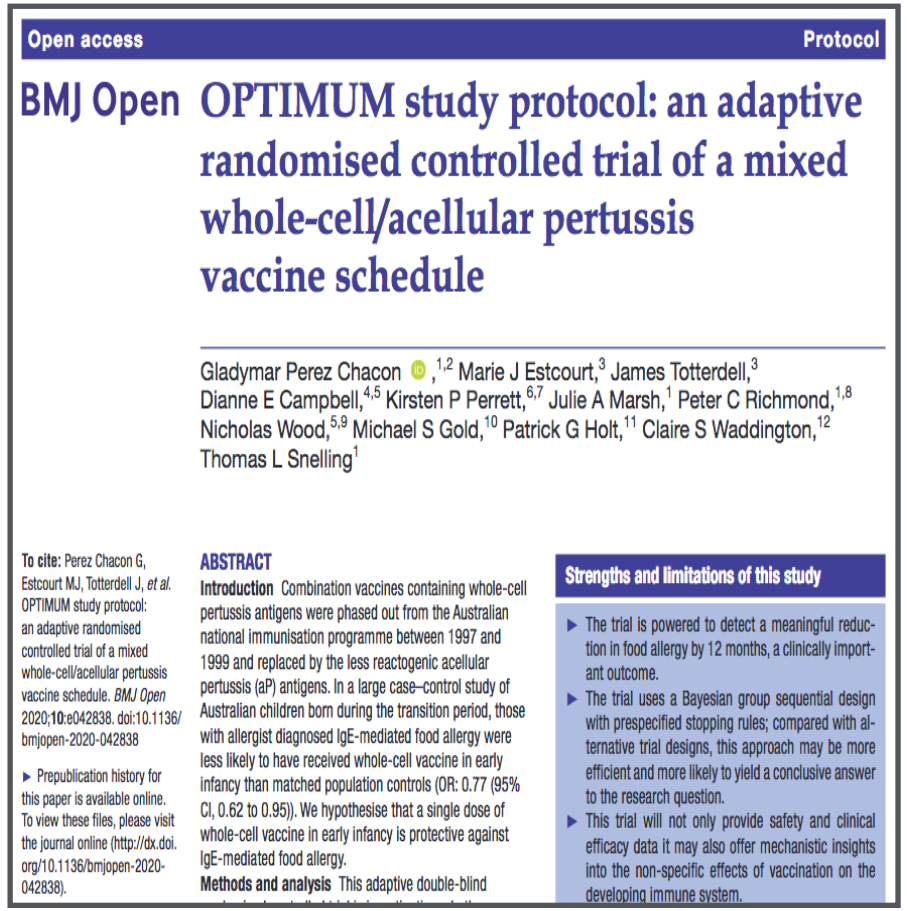
To cite: Middleton BF, Jones MA, Waddington CS, *et al*. The ORVAC trial protocol: a phase IV, double-blind, randomised, placebo-controlled clinical trial of a third scheduled dose of Rotarix rotavirus vaccine in Australian Indigenous infants to improve protection against gastroenteritis. *BMJ Open* 2019;**9**:e032549. doi:10.1136/bmjopen-2019-032549

ABSTRACT

Introduction Rotavirus vaccines were introduced into the Australian National Immunisation Program in 2007. Despite this, Northern Territory Indigenous children continue to be hospitalised with rotavirus at a rate more than 20 times higher than non-Indigenous children in other Australian jurisdictions, with evidence of waning protection in the second year of life. We hypothesised that scheduling an additional (third) dose of oral human rotavirus vaccine (Rotarix, GlaxoSmithKline) for children aged 6 to <12 months would improve protection against

Strengths and limitations of this study

- The ORVAC study is one of the first studies to evaluate both the immunological and the clinical impact of an additional dose of oral Rotarix rotavirus vaccine administered to children between 6 and 12 months of age.
- This pragmatic randomised controlled trial is based on Bayesian adaptive design, an innovative trial design that uses interim analyses to inform decisions about trial progression.



Open access Protocol

BMJ Open

OPTIMUM study protocol: an adaptive randomised controlled trial of a mixed whole-cell/acellular pertussis vaccine schedule

Gladymar Perez Chacon ,[1,2] Marie J Estcourt,[3] James Totterdell,[3] Dianne E Campbell,[4,5] Kirsten P Perrett,[6,7] Julie A Marsh,[1] Peter C Richmond,[1,8] Nicholas Wood,[5,9] Michael S Gold,[10] Patrick G Holt,[11] Claire S Waddington,[12] Thomas L Snelling[1]

To cite: Perez Chacon G, Estcourt MJ, Totterdell J, *et al*. OPTIMUM study protocol: an adaptive randomised controlled trial of a mixed whole-cell/acellular pertussis vaccine schedule. *BMJ Open* 2020;**10**:e042838. doi:10.1136/bmjopen-2020-042838

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-042838).

ABSTRACT

Introduction Combination vaccines containing whole-cell pertussis antigens were phased out from the Australian national immunisation programme between 1997 and 1999 and replaced by the less reactogenic acellular pertussis (aP) antigens. In a large case–control study of Australian children born during the transition period, those with allergist diagnosed IgE-mediated food allergy were less likely to have received whole-cell vaccine in early infancy than matched population controls (OR: 0.77 (95% CI, 0.62 to 0.95)). We hypothesise that a single dose of whole-cell vaccine in early infancy is protective against IgE-mediated food allergy.

Methods and analysis This adaptive double-blind

Strengths and limitations of this study

- The trial is powered to detect a meaningful reduction in food allergy by 12 months, a clinically important outcome.
- The trial uses a Bayesian group sequential design with prespecified stopping rules; compared with alternative trial designs, this approach may be more efficient and more likely to yield a conclusive answer to the research question.
- This trial will not only provide safety and clinical efficacy data it may also offer mechanistic insights into the non-specific effects of vaccination on the developing immune system.

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REMAP-CAP

Home About REMAP-CA

REMAP-CAP

A Randomised, Embedded, Multi-factorial, Adaptive Platform

13,401
Patient randomisations

12,04
Patient randomisat
suspected or prove

7,393
Total patients

6,58
Patients with suspect
COVID-19

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 22, 2021 VOL. 384 NO. 16

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators*

ABSTRACT

BACKGROUND

The efficacy of interleukin-6 receptor antagonists in critically ill patients with coronavirus disease 2019 (Covid-19) is unclear.

METHODS

We evaluated tocilizumab and sarilumab in an ongoing international, multifactorial, adaptive platform trial. Adult patients with Covid-19, within 24 hours after starting organ support in the intensive care unit (ICU), were randomly assigned to receive tocilizumab (8 mg per kilogram of body weight), sarilumab (400 mg), or standard care (control). The primary outcome was respiratory and cardiovascular organ support–free days, on an ordinal scale combining in-hospital death (assigned a value of −1) and days free of organ support to day 21. The trial uses a Bayesian statistical model with predefined criteria for superiority, efficacy, equivalence, or futility. An odds ratio greater than 1 represented improved survival, more organ support–free days, or both.

The members of the writing committee (A.C. Gordon, P.R. Mouncey, F. Al-Beidh, K.M. Rowan, A.D. Nichol, Y.M. Arabi, D. Annane, A. Beane, W. van Bentum-Puijk, L.R. Berry, Z. Bhimani, M.J.M. Bonten, C.A. Bradbury, F.M. Brunkhorst, A. Buzgau, A.C. Cheng, M.A. Detry, E.J. Duffy, L.J. Estcourt, M. Fitzgerald, H. Goossens, R. Haniffa, A.M. Higgins, T.E. Hills, C.M. Horvat, F. Lamontagne, P.R. Lawler, H.L. Leavis, K.M. Linstrum, E. Litton, E. Lorenzi, J.C. Marshall, F.B. Mayr, D.F. McAuley, A. McGlothlin, S.P. McGuinness, B.J. McVerry, S.K. Montgomery, S.C. Morpeth, S. Murthy, K. Orr, R.L. Parke, J.C. Parker, A.E. Patanwala, V. Pettilä, E. Rademaker, M.S. Santos, C.T. Saunders, C.W. Seymour, M. Shankar-Hari,

https://www.remapcap.org/

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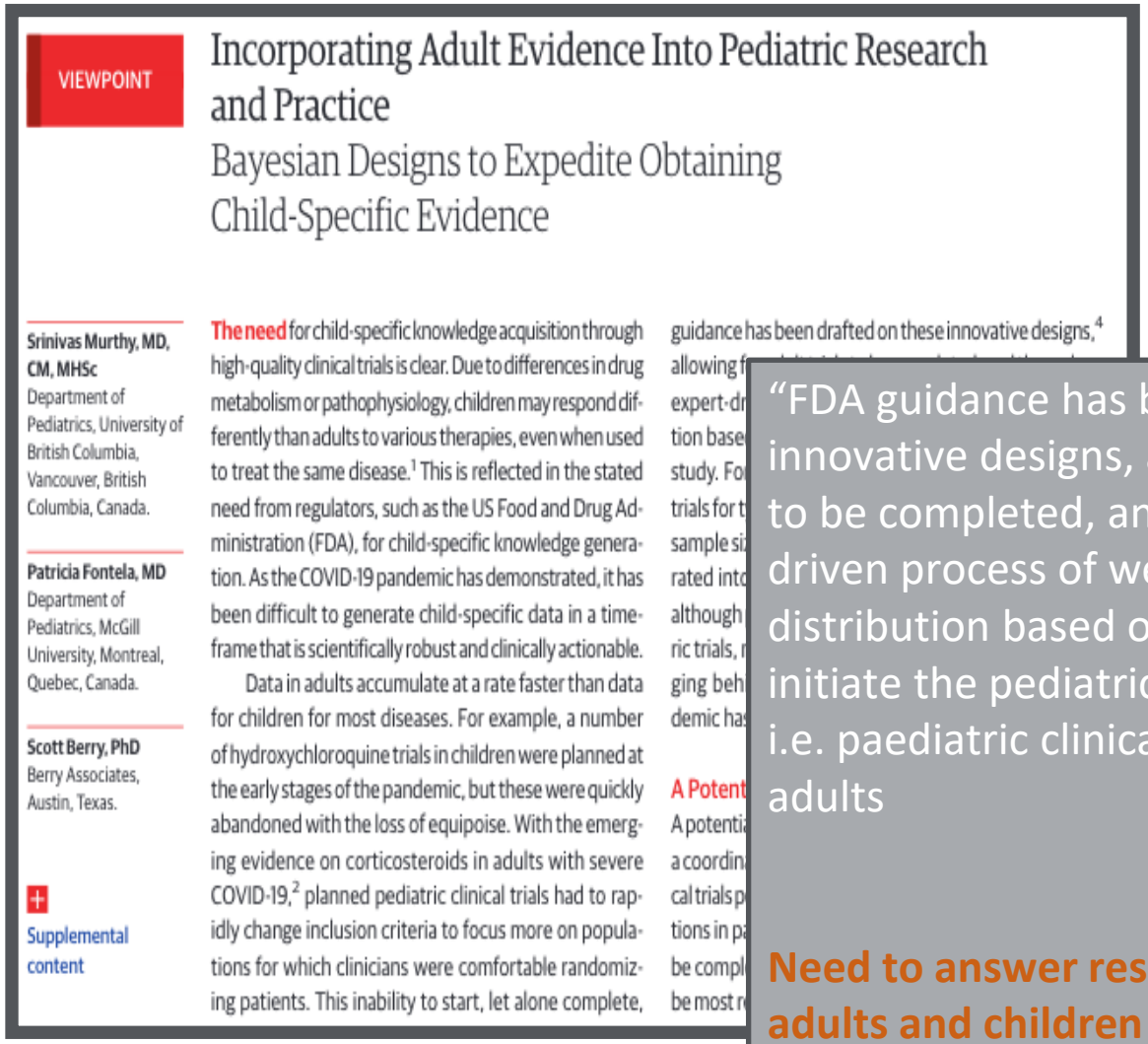
How acceptable are adaptive trial designs?



VIEWPOINT

Incorporating Adult Evidence Into Pediatric Research and Practice

Bayesian Designs to Expedite Obtaining Child-Specific Evidence

Srinivas Murthy, MD, CM, MHSc
Department of Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada.

Patricia Fontela, MD
Department of Pediatrics, McGill University, Montreal, Quebec, Canada.

Scott Berry, PhD
Berry Associates, Austin, Texas.

Supplemental content

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.[1] This is reflected in the stated need from regulators, such as the US Food and Drug Administration (FDA), for child-specific knowledge generation. As the COVID-19 pandemic has demonstrated, it has been difficult to generate child-specific data in a timeframe that is scientifically robust and clinically actionable.

Data in adults accumulate at a rate faster than data for children for most diseases. For example, a number of hydroxychloroquine trials in children were planned at the early stages of the pandemic, but these were quickly abandoned with the loss of equipoise. With the emerging evidence on corticosteroids in adults with severe COVID-19,[2] planned pediatric clinical trials had to rapidly change inclusion criteria to focus more on populations for which clinicians were comfortable randomizing patients. This inability to start, let alone complete,

guidance has been drafted on these innovative designs,[4]

"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."
i.e. paediatric clinical trial lags behind adults

Need to answer research questions for adults and children in parallel

JAMA April 26, 2021 Online

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How acceptable are ad

Wason *et al. BMC Medicine* (2019) 17:152
https://doi.org/10.1186/s12916

OPINION

When to k
are not alw

James M. S. Wason[1,2*]

Abstract

Background: Adaptive
participant benefit of
used to make changes
patients are enrolled t
size or the enrolment
their use in many clini
provide little efficiency
In our experience, facto
in methodological pap
actually are.

Main text: In this pap
situations when the ou
when increased practic

Conclusion: Adaptive
investigators to be aware that they do not always provide an advantage. There should always be careful consideration of the potential benefits and disadvantages of an adaptive design.

Clinical Infectious Diseases

INVITED ARTICLE

INNOVATIONS IN DESIGN, EDUCATI

Resist the Tempta
Randomization

Michael Proschan[1] and Scott Evans[2]

[1]Mathematical Statistician, Biostatistics Research Branch
Director, Biostatistics Center, Milken Institute School of

Response-adaptive randomization (RA
of participants randomized to inferio
RAR causes many problems, including
sample-size distributions that can cau
validly analyzing results, and (5) the p
problems of RAR are most acute in th
infectious disease settings where temp
randomization, the most powerful tool in clinical trials, provides. Use of RAR is discouraged.

Keywords. response-adaptive randomization; temporal trend; platform trials; frequentist approach; Bayesian approach.

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Platform Trials — Beware the Noncomparable Control Group

TO THE EDITOR: The coronavirus disease 2019 (Covid-19) pandemic has highlighted the crucial role of randomized trials in guiding clinical practice and the need for designs that provide rapid evaluation of multiple interventions. Multigroup randomized clinical trials in which multiple experimental treatment groups are compared with a single control group allow for an efficient use of resources in that a separate control group does not need to be generated for each comgroup could bias the results of a trial is provided in Figure 1. Consider the decline in in-hospital mortality from Covid-19 that occurred over a 2-month period in the spring of 2020[2] and a hypothetical trial that compared a control treatment with an ineffective new agent that was not included in the randomization until the second month. If comparisons were made between the patients who received the control treatment during the 2-month period (April–May 2020) and

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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

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Adaptive trials implementation challenges

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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

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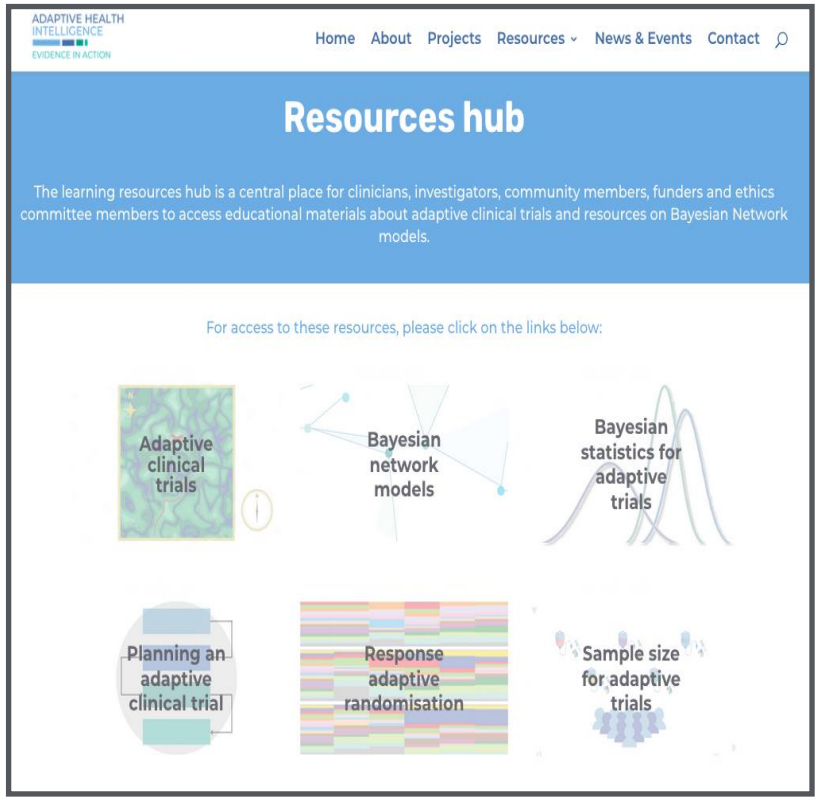
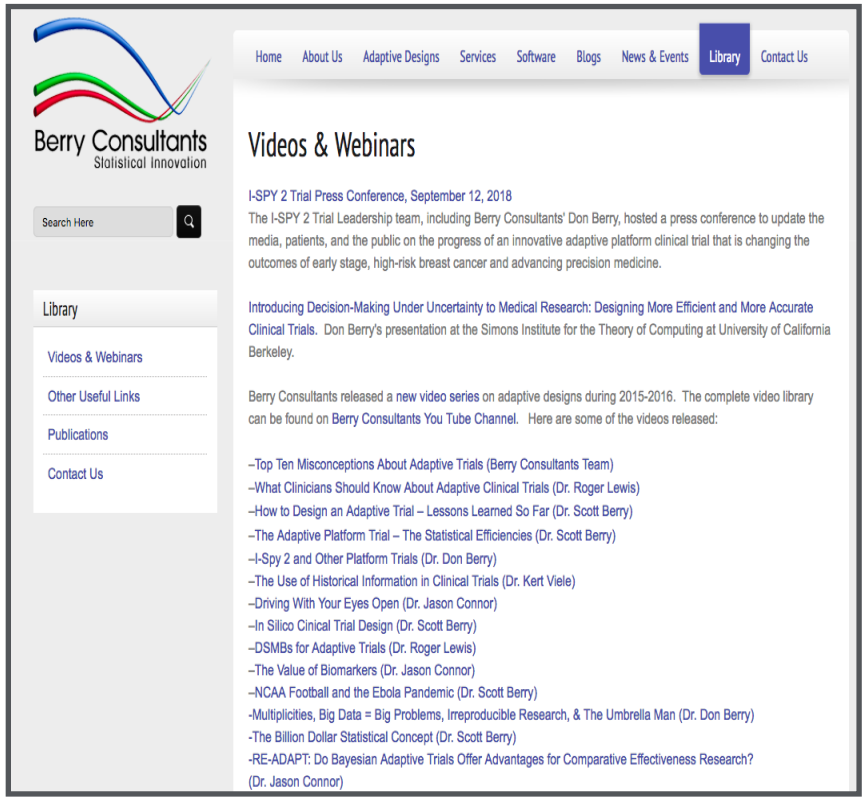
Additional resources

https://adaptivehealthintelligence.org.au/resources



https://www.berryconsultants.com/library/



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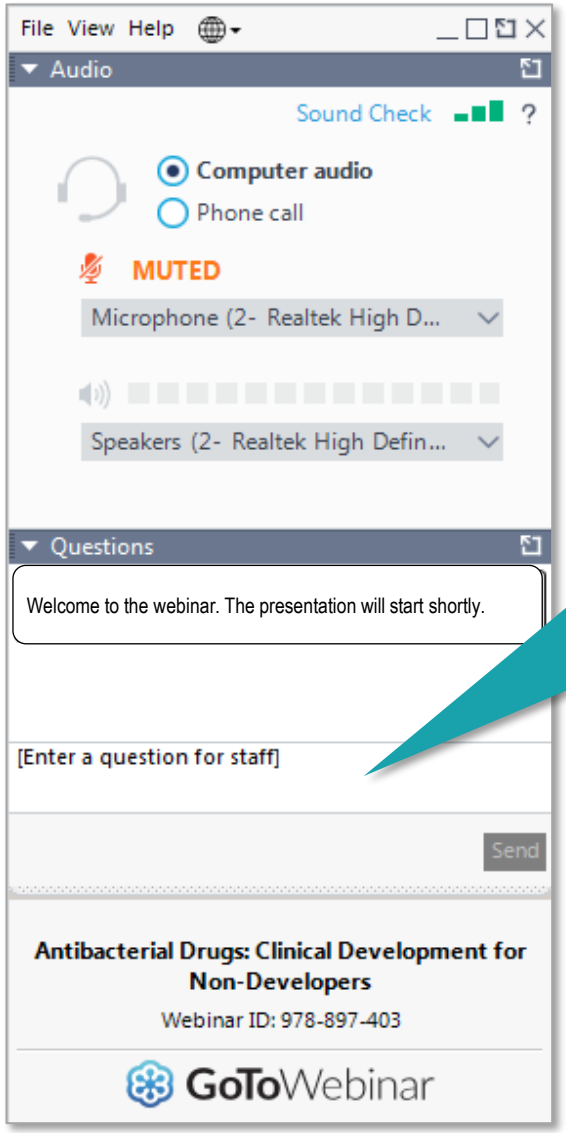
How to submit your questions

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)

Join us for our next webinar

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:
revive.gardp.org/webinars

Thank you for joining us