How to Design an Adaptive Platform Trial

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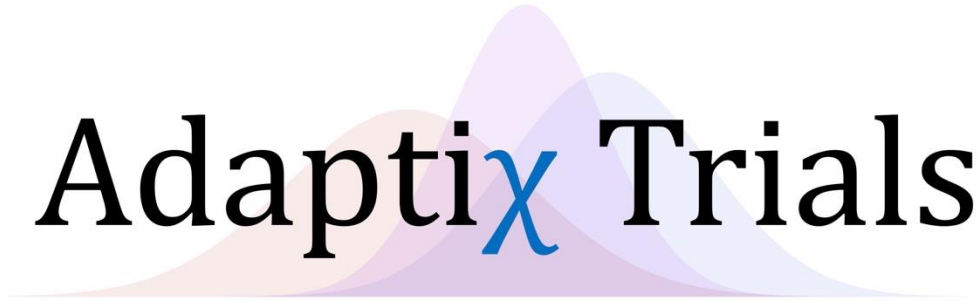

Summary

- Basics of a platform trial
- Where to start?
  - Skeleton designs
  - Cost, sample size, & funding
- Virtual trial design
  - Computer simulations as a design tool
  - Role of statisticians
- Platform trial organization

VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

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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.

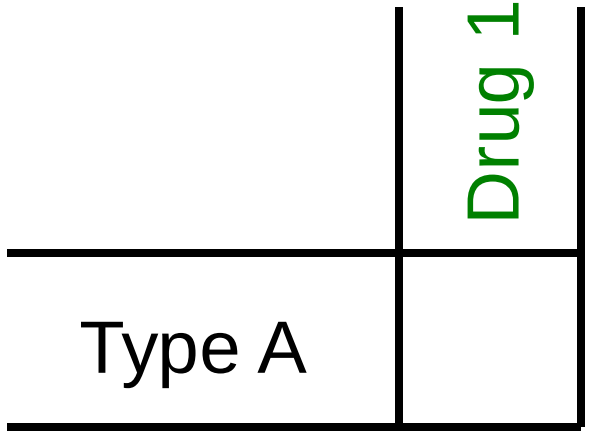
This approach has been largely unsuccessful for multiple diseases, including sepsis, dementia, and stroke. Despite promising preclinical and early human trials, there have been numerous negative phase 3 trials of treatments for Alzheimer disease[1] and more than 40 negative phase 3 trials of neuroprotectants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

Traditional Trial: Focus on Treatment

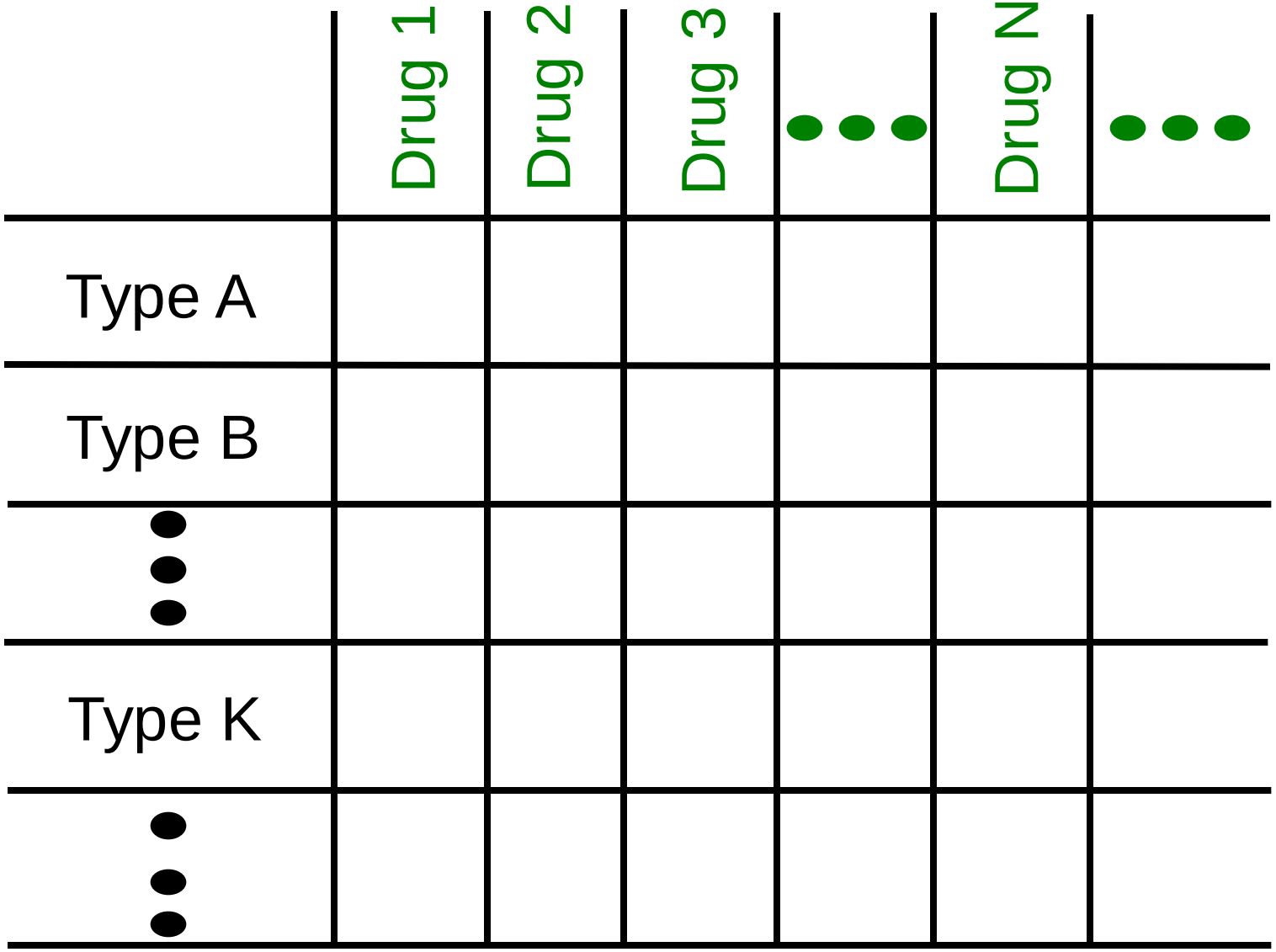


"Standard Trial: Single treatment,
Homogeneous patients, Single question "

Biomarkers & Personalized Medicine

- Complex Diseases
  - Biomarker development and personalized medicine are leading to a future in which the vast majority of diseases are “rare” diseases
  - Slow, large scale clinical trials with a single hypothesis within a single disease impractical to conduct
- Complex Treatments
  - “Which treatment or combination of treatments is best for each type of patient?”
  - Not easily addressed with traditional trial design

Platform Trial Designs



Adaptive Platform Trials

- Master Protocol
- Focus is on the Disease
  - “What is the best treatment for a unique patient with this disease?
- Typical Innovations
  - Response Adaptive Randomization (RAR)
  - Patient heterogeneity (hierarchical modeling)
  - Combination treatments
  - Allow treatments to be added through course of trial
  - Graduation/Removal, “Perpetual” trials
  - Statistical Modeling

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

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N Engl J Med 2017;377:62-70.
DOI: 10.1056/NEJMra1510062

HIGH-QUALITY EVIDENCE IS WHAT WE USE TO GUIDE MEDICAL PRACTICE. The standard approach to generating this evidence — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. As a result, important clinical questions go unanswered. The conduct of "precision medicine" trials to evaluate targeted therapies creates challenges in recruiting patients with rare genetic subtypes of a disease. There is also increasing interest in performing mechanism-based trials in which eligibility is based on criteria other than traditional disease definitions. The common denominator is a need to answer more questions more efficiently and in less time.

A methodologic innovation responsive to this need involves coordinated efforts to evaluate more than one or two treatments in more than one patient type or disease within the same overall trial structure.[1-4] Such efforts are referred to as master protocols, defined as one overarching protocol designed to answer multiple questions. Master protocols may involve one or more interventions in multiple diseases or a single disease, as defined by current disease classification, with multiple interventions, 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

2023 FDA Draft Guidance

Master Protocols for Drug and Biological Product Development

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Scott N. Goldie at 301-796-2055, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2023
Biostatistics / Clinical / Medical

Article

CLINICAL TRIALS

Clinical Trials
2016, Vol. 13(3) 358–366

DOI: 10.1177/1740774515626362
ctj.sagepub.com
SAGE

Efficiencies of platform clinical trials: A vision of the future

Benjamin R Saville[1,2] and Scott M Berry[1,3]

Abstract

Background: A "platform trial" is a clinical trial with a single master protocol in which multiple treatments are evaluated simultaneously. Adaptive platform designs offer flexible features such as dropping treatments for futility, declaring one or more treatments superior, or adding new treatments to be tested during the course of a trial.

Methods: A simulation study explores the efficiencies of various platform trial designs relative to a traditional two-arm strategy.

Results: Platform trials can find beneficial treatments with fewer patients, fewer patient failures, less time, and with greater probability of success than a traditional two-arm strategy.

Conclusion: In an era of personalized medicine, platform trials provide the innovation needed to efficiently evaluate modern treatments.

Potential Features of a Platform Trial

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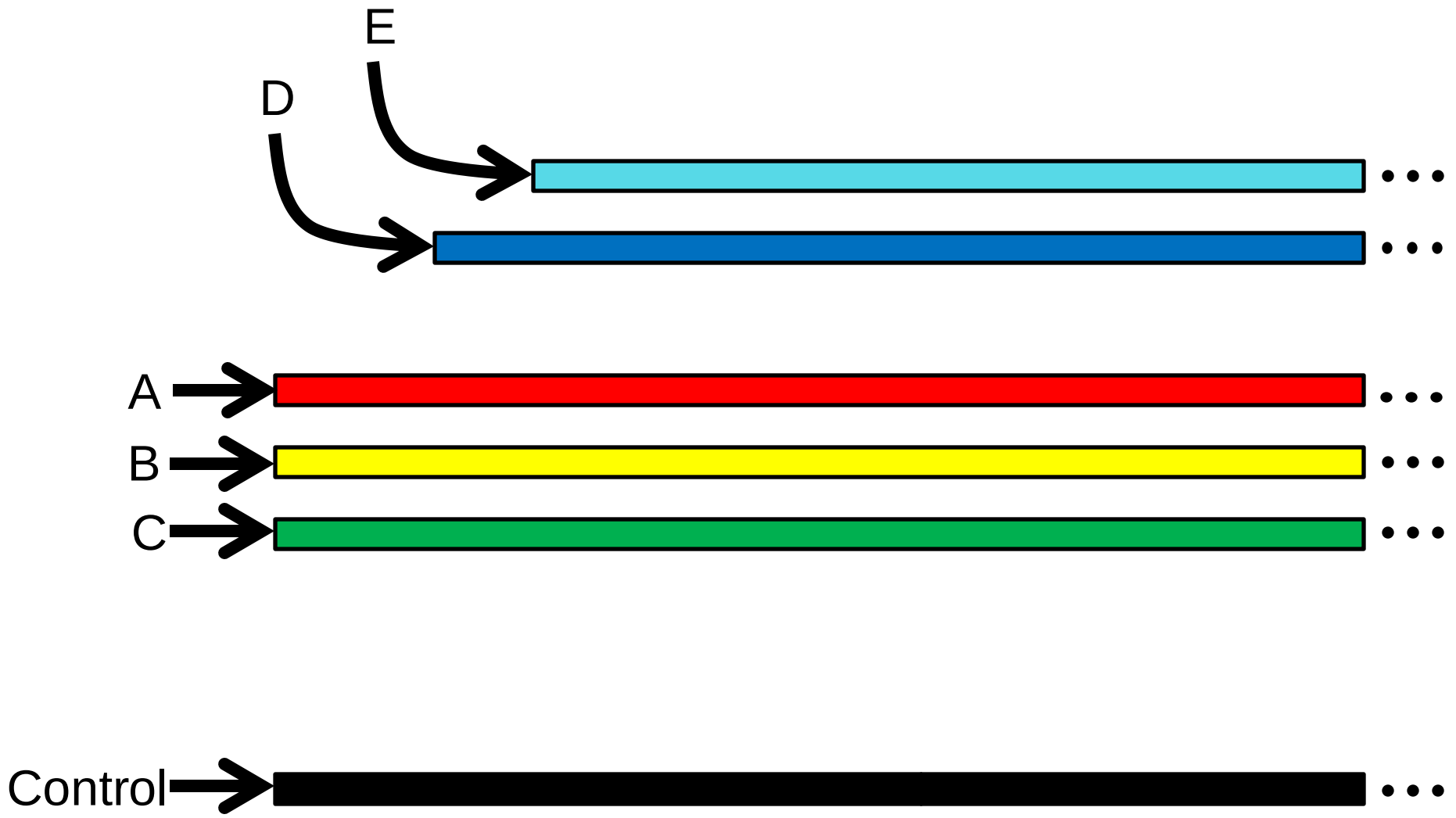

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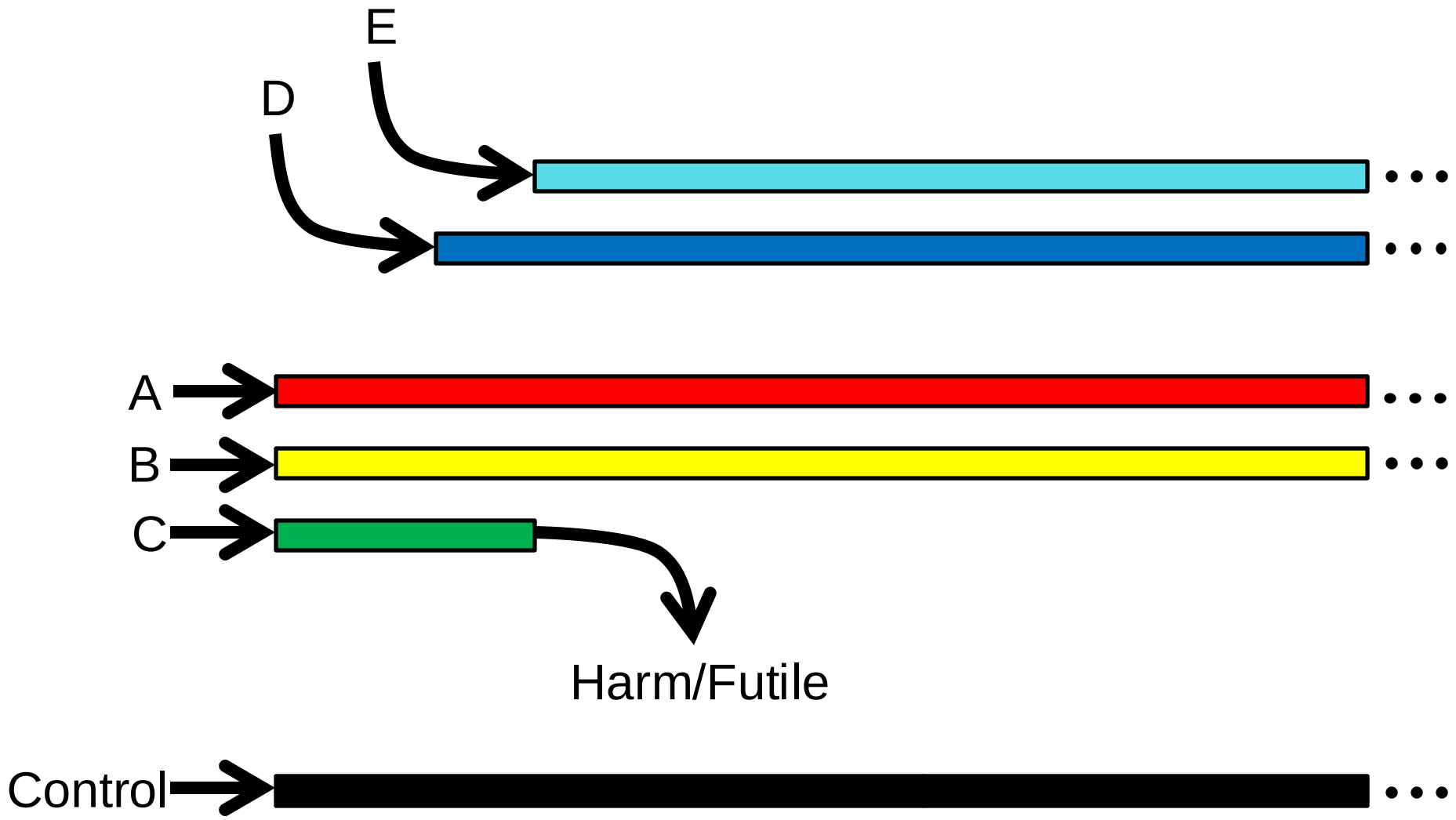

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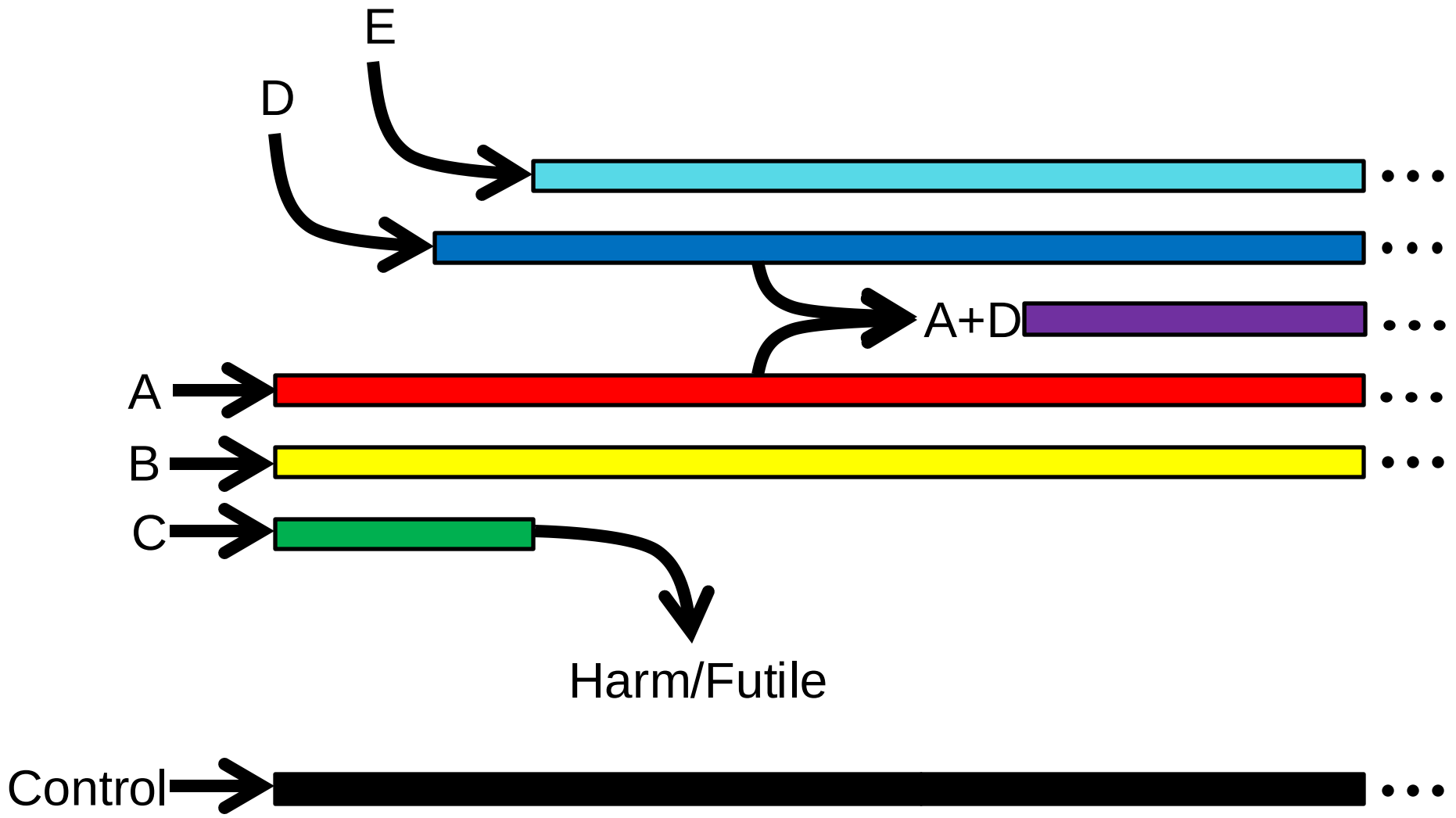

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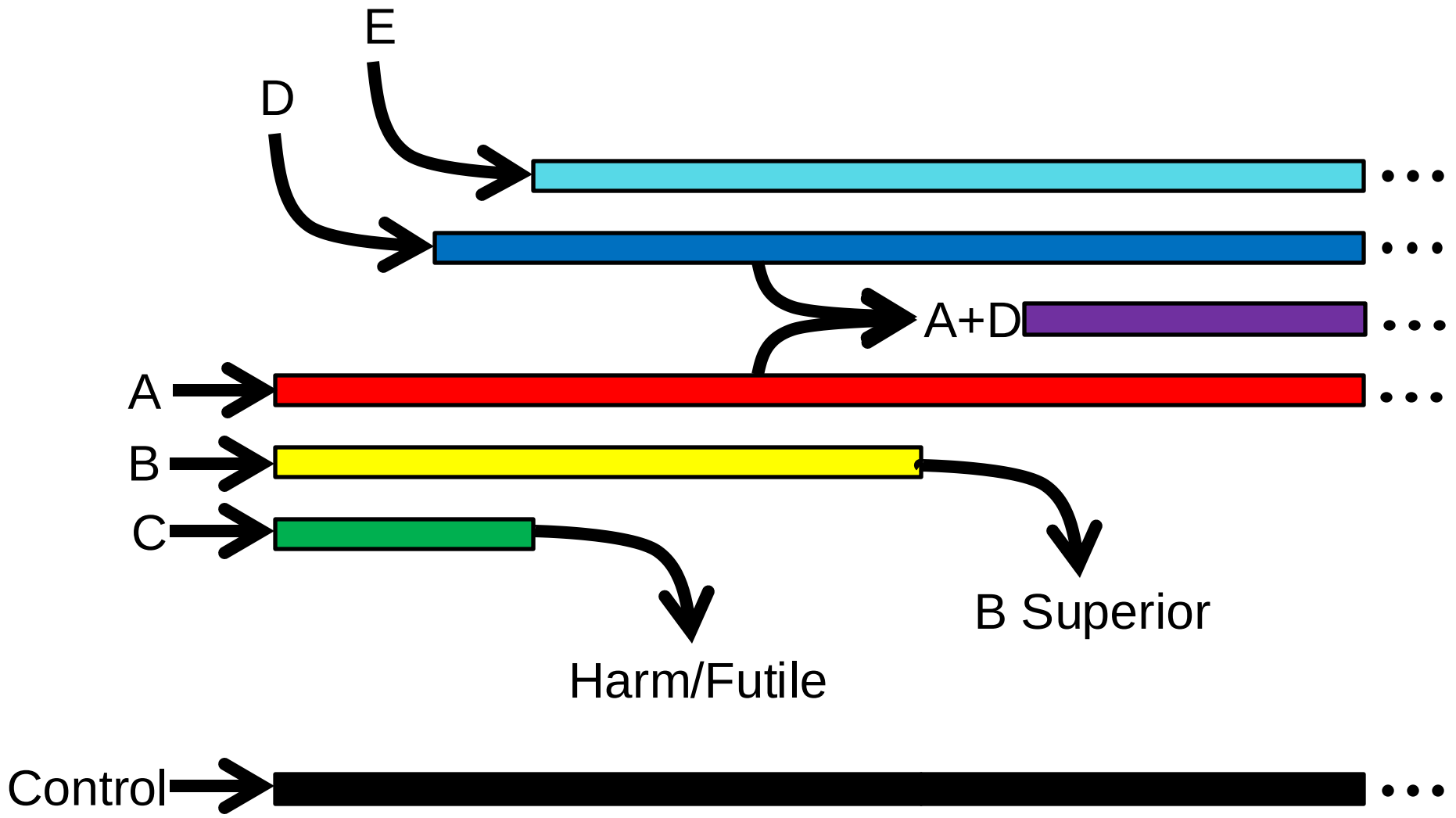

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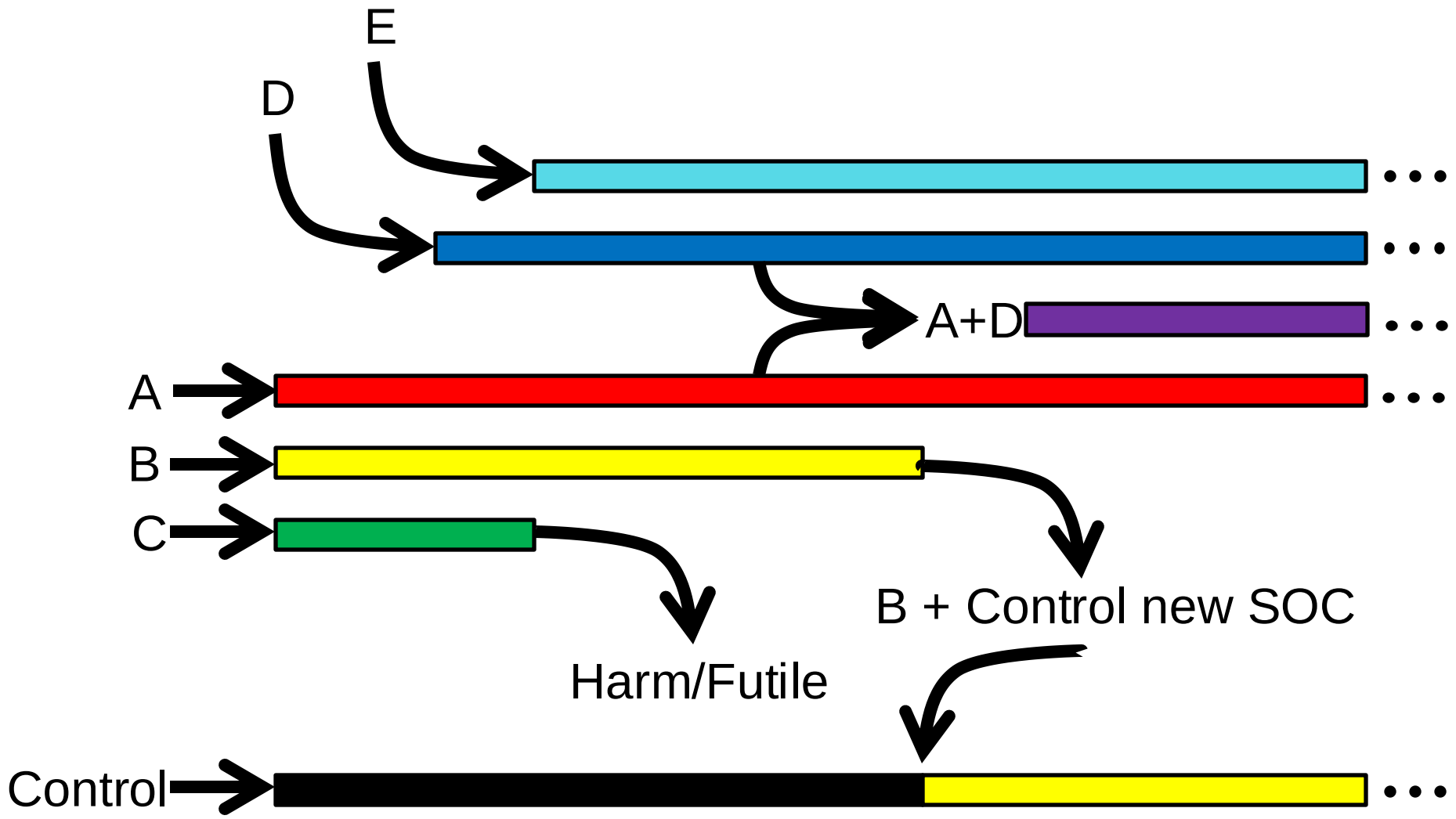


Thanks to Roger Lewis for figure (Berry Consultants)

Platform Trials are Happening

- Cancer
  - I-SPY2 in Breast Cancer
  - GBM AGILE in Glioblastoma multiforme
  - LUNG-MAP in Lung Cancer
  - PANCAN in Pancreatic Cancer
- Neurology
  - EPAD: European Prevention of Alzheimer's Dementia
  - DIAN: Dominantly Inherited Alzheimer's Network
  - P2P: Path to Prevention in Parkinson's
  - Healey ALS Platform Trial, Phase 2/3 with 7+ drugs
- Respiratory
  - PrecISE in pediatric Asthma
  - BEAT-CF in Cystic Fibrosis
- Acute Ischemic Stroke (STEP)

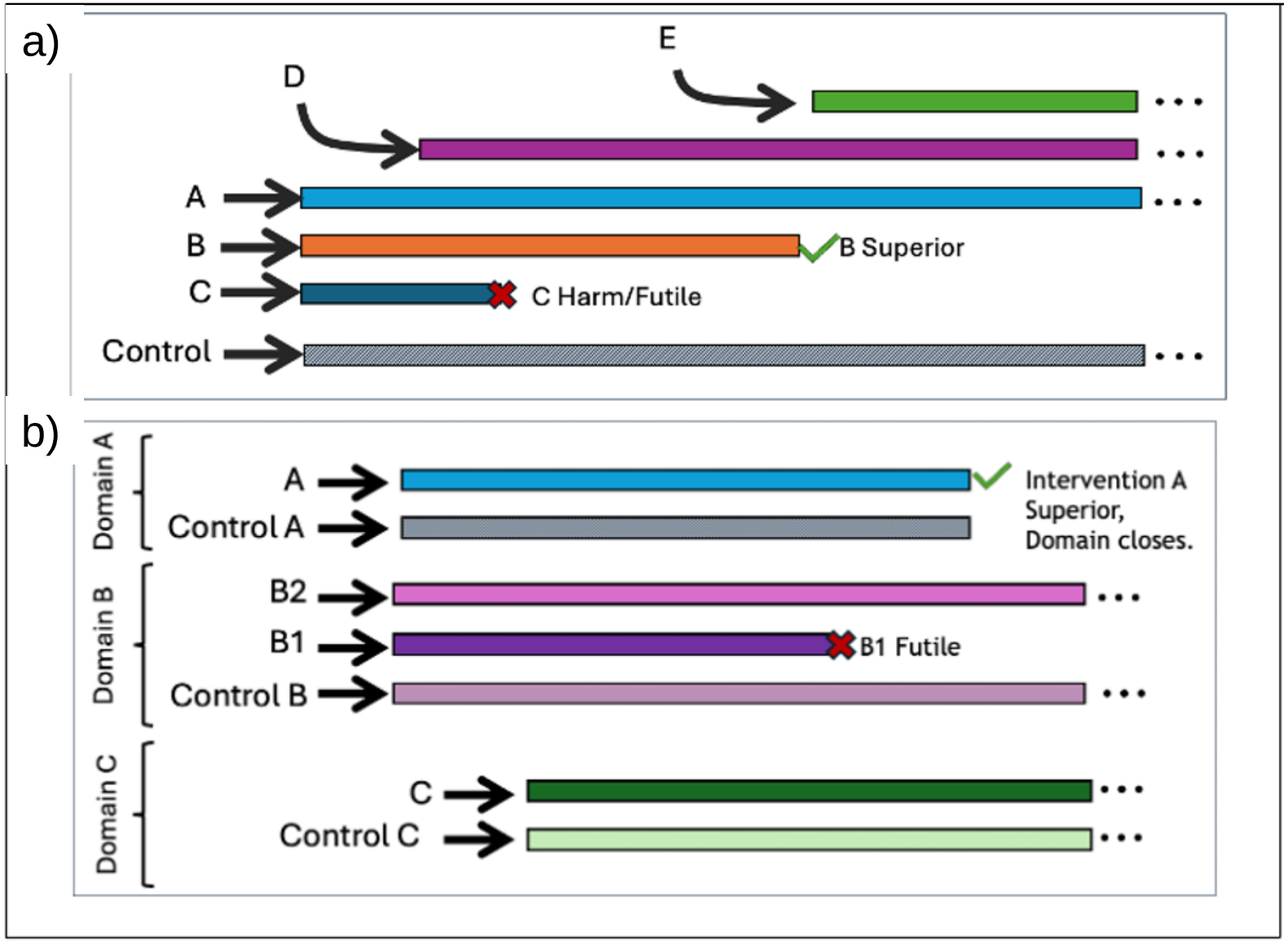
Platform Trials are Happening

- Infectious diseases
  - Gates Foundation sponsored Ebola design
  - NIH Ebola design
  - PREPARE: European Consortium for Disease Preparedness
    - Pandemic flu, Butler at al Lancet, Jan 2020
    - REMAP CAP (Community Acquired Pneumonia) ongoing, REMAPCAP.org
  - SNAP in Staphylococcus aureus
- COVID-19
  - REMAP-COVID by International consortium critical care trial
  - PRINCIPLE/PANORAMIC in UK, pre-hospital trial
  - RECOVERY in UK
  - ACTT by NIAID -- the Remdesivir trial
  - SOLIDARITY by WHO, 4 arms
  - ISPY-COVID: UCSF & WISDOM Network, Phase 2
  - ACTIV by NIH

Where Do We Start?

- Start with the disease
  - Bring together clinical experts, clinical trialists, and statisticians for brainstorming
- Primary objectives/questions
  - Comparative effectiveness of existing treatments?
  - Screen experimental treatments quickly in a Phase 2 setting?
  - Demonstrate substantial evidence of effectiveness (Phase 3)?
  - Seamless phase 2/3 designs?
    - Platform intended to screen therapies, which graduate to phase 3

Possible Structures



Thanks to Liz Lorenzi for figure (Berry Consultants)

Patient Populations

- Eligibility criteria
  - Traditional: as inclusive as possible in population we expect to see benefit
  - More complicated in a platform trial
- Target population depends on research questions and treatments
  - Would different treatments target different populations?
  - How to handle differences in eligibility criteria by treatment?
  - Biomarkers/subgroups?

Example: Platform Trial in Heart Failure

- Conversations initiated by Heart Failure Collaboratory
  - Consortium of stakeholders committed to improving the ecosystem of heart failure clinical trials
  - Public-private partnership with FDA, industry, academics
- Initial large meetings introducing the concept
  - Feedback and ideas
  - Objectives, funding, industry partners, etc.
- Subsequent smaller, focused meetings
  - Develop initial skeleton designs

Example: Skeleton Designs

- With smaller groups, can narrow in on more specific questions
- Statistician can elicit various skeleton designs that may address the relevant questions
  - Researchers may all have different ideas of what a platform trial is, and what it looks like in HF
  - Need concrete proposals to get reactions

Skeleton 1: Evaluate Drugs by Subgroups

Treatment	Male		Female	
	Age <60	Age >60	Age <60	Age >60
1) SGLT2 + MRA				
2) SGLT2 + ARNI				
3) SGLT2 + GLP1A				
4) SGLT2 + BB				
5) SGLT2 + MRA + ARNI				
6) SGLT2				
7) SGLT2 + Iron (if iron deficient)				

- One Domain: Drug (in HFpEF)
- Randomize to one of 6 treatment arms
  - (One of 7 treatment arms if iron deficient)
  - Either specify type of drug (e.g. specific BB); or let clinician choose

- Potential for response adaptive randomization by subgroup
- 7*2*2=28 cells (hierarchical modeling)
- Question Answered:
  What is the best treatment arm by subgroup?

Skeleton 2: Evaluate Combinations of Drugs

ARNI	Beta Blockers	GLP1A (Yes)		GLP1A (No)	
		MRA (yes)	MRA (no)	MRA (yes)	MRA (no)
ARNI (yes)	BB (yes)				
	BB (no)				
ARNI (no)	BB (yes)				
	BB (no)				

- Background for all: SGLT2
- Each patient receives multiple randomizations (one from each Domain)
- Adaptively drop arms or combinations
- Response adaptive randomization by combination

- Hierarchical modeling for interactions
- Could be expanded to evaluate subgroups (age, sex, etc.)
- 2*2*2*2 = 16 combinations
- Question Answered

  What is the best combination of drugs? (perhaps by subgroup)

Skeleton 3: Evaluate Multiple Domains

Domain 1: BB	Domain 2: ARNI		Domain 3: MRA		
	ARNI (1)	ARNI (none)	MRA (1)	MRA (2)	MRA (none)
BB (1)					
BB (2)					
BB (none)					

Domain 4: Sodium Restriction	Domain 5: Cardiac Rehab/Exercise	
	Yes	No
Yes		
No		

- Background for all: SGLT2
- Each patient receives multiple randomizations (one in each Domain)
- Adaptively drop arms or combinations
- Potential response adaptive randomization by combination

- Hierarchical modeling for interactions
- Could be expanded to evaluate subgroups (age, sex, etc.)
- 3*2*3*2*2= 72 combinations
- Questions Answered
  - Within each domain: is (A) better than (B)?
  - What is the best combination of Domains? (perhaps by subgroup)

Cost/Funding

- Narrowing in on a skeleton design, attention often turns to funding, sample size, and cost
- What are the primary endpoints?
  - Primary analysis models
- Who would be interested in funding this?
  - Disease specific organizations? (e.g. American Heart Association)
  - Government grants?
  - Private companies?
- How much is this going to cost?
  - Depends on sample size
  - Depends on design

Sample Size

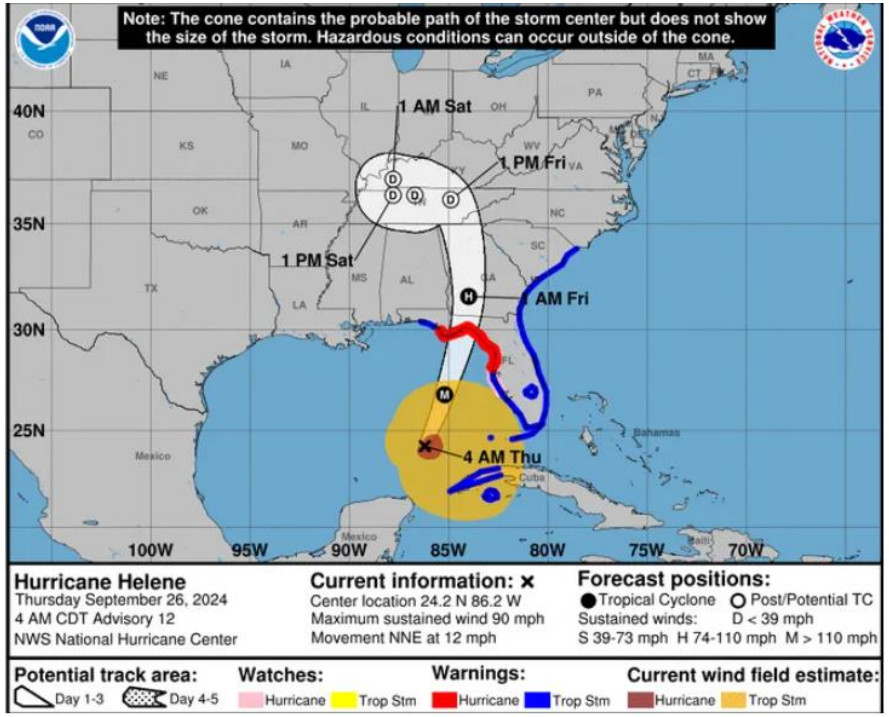
- Traditional power calculations for primary questions of interest
  - Focus on 1-2 primary endpoints
  - Single questions, no adaptations, etc.
  - Revise/re-calibrate skeleton designs
  - Make go/no-go decisions on feasibility of platform trial
- Use to secure trial funding
  - At a minimum, we need funding for trial design

Virtual Trial Simulations

- Simulations are typically required to understand the full performance and characteristics of a platform trial
  - Many questions
  - Many adaptations
- Need some initial funding in place for simulation work
  - Not a simple power calculation!
  - Several months of effort

Virtual Trial Simulations

- We are inundated with “simulations” being used as predictions
- This is common for PK/PD scientists – predict what will happen in humans



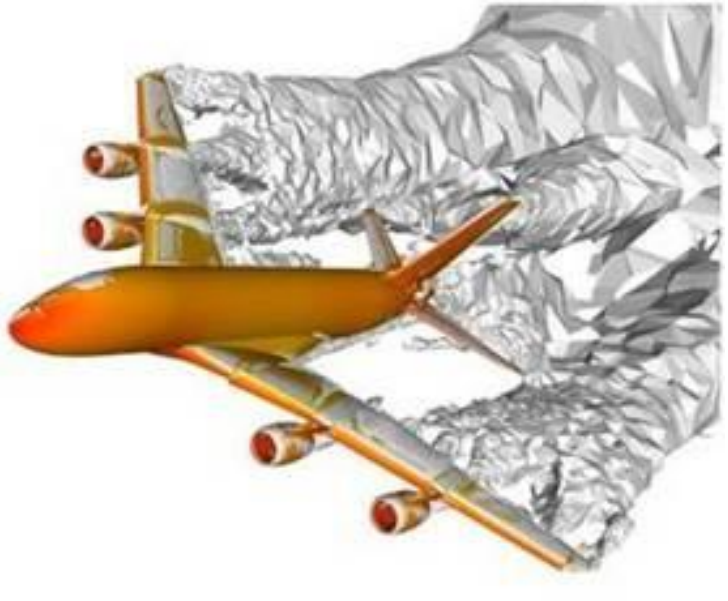
Hurricane Helene’s latest forecasted path, as of Thursday morning, Sept. 26, 2024. *National Hurricane Center*

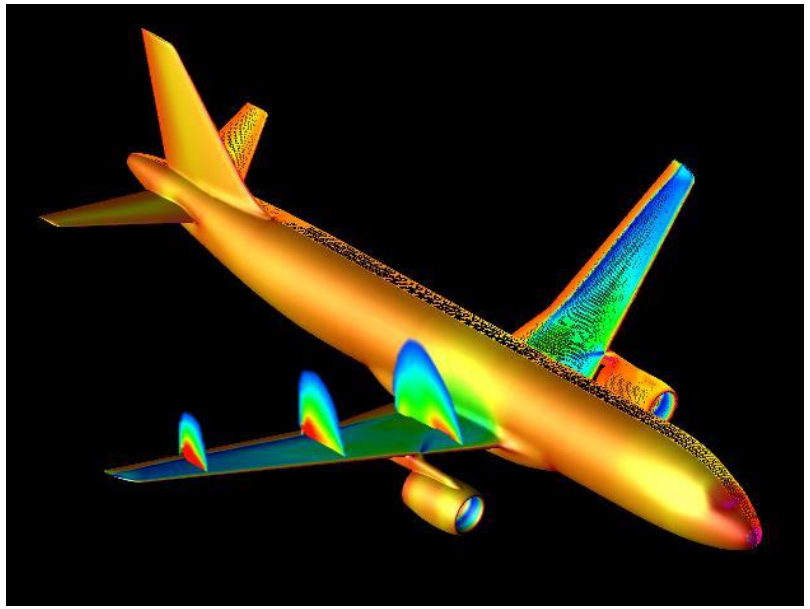
EA Sports

- This is not how simulations are used in creating virtual trial designs

Virtual Trial Simulations

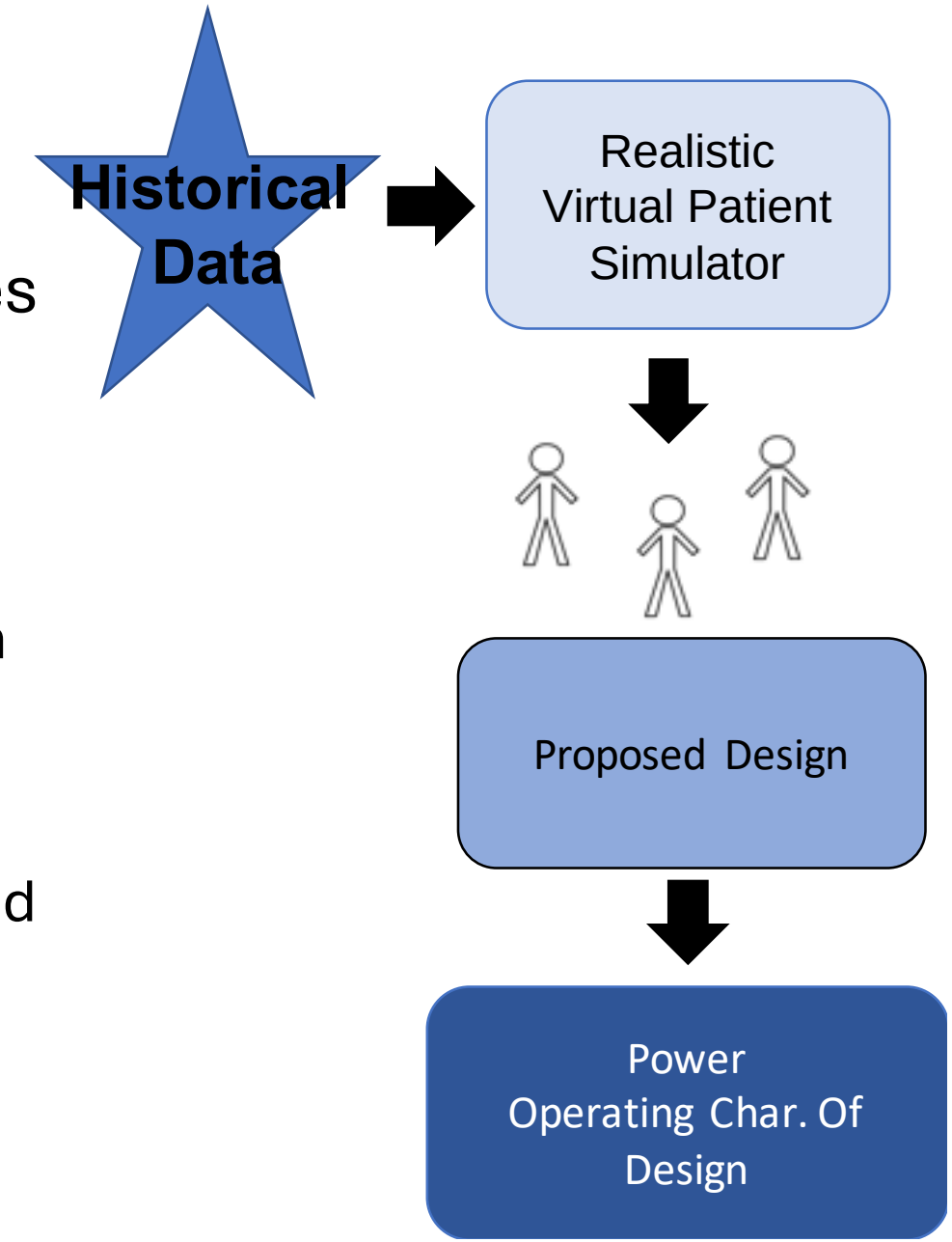
- Clinical trial design is more like building an airplane
- We simulate the behavior of a design to find its performance on various metrics
  - A complex mathematical calculation as opposed to a prediction system
  - Allows fully vetting the design as an instrument to learn about a medical therapy





Virtual Trial Simulation

1. Start with simulating patient outcomes
   - Historical data is valuable resource!
2. Build a complete trial
   - Typically start with a fixed trial
   - Various complexity, depending on skeleton
   - Compare endpoints and analyses
3. Introduce/apply adaptations
   - Interim analyses, patient accrual, staggered regimen entry, etc.
4. Repeat for 1,000s of trials & summarize performance



Design Iterations

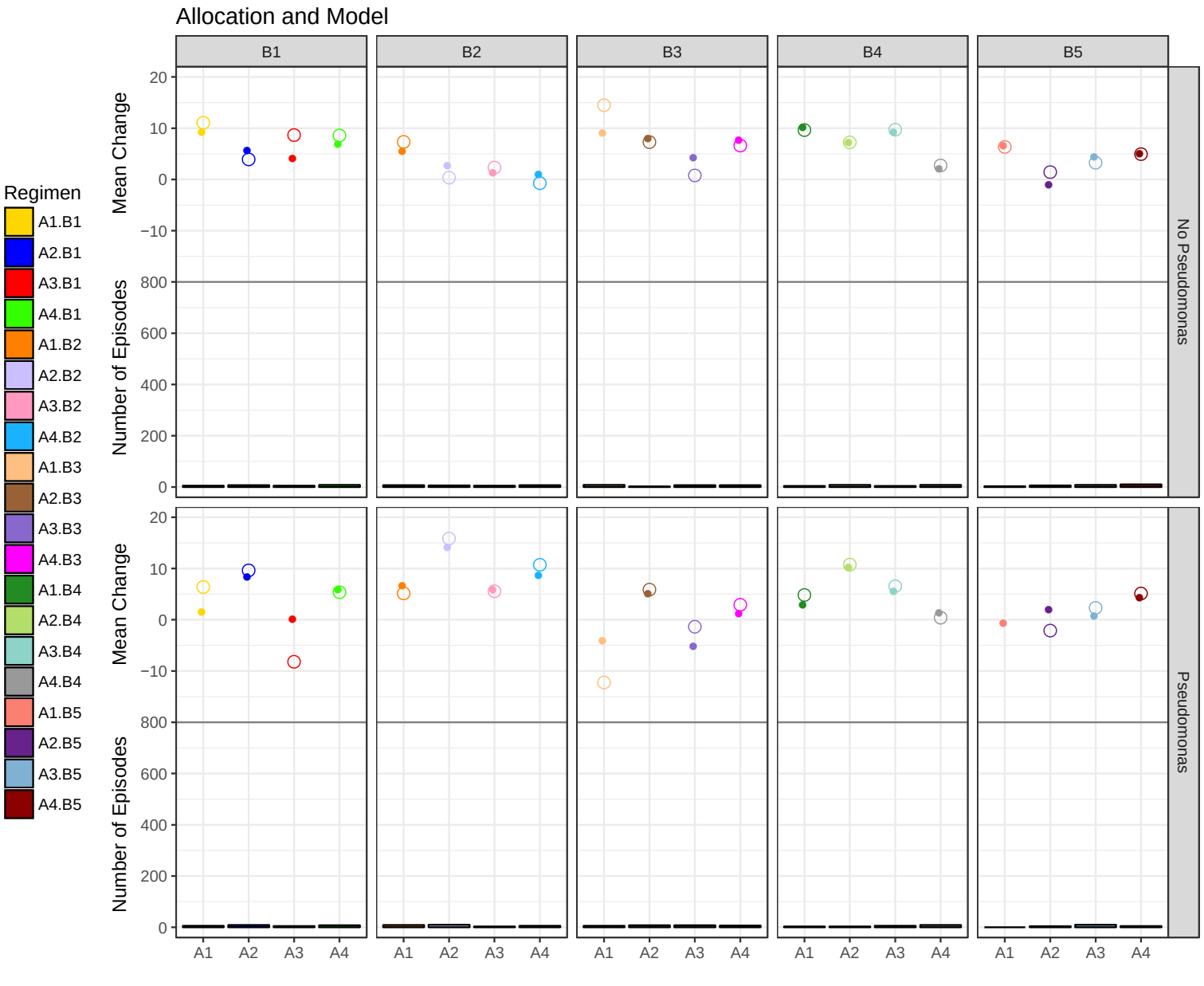
- We don’t expect to get the perfect platform trial on our first attempt
  - We don’t expect to get perfect airplane on first virtual design either
- We need iterations!
  - This is a natural process of trial design
- Statistician simulates virtual trials, shows simulation output to trial team
  - Feedback, reactions, revisions
  - Revise & re-run simulations
  - Repeat

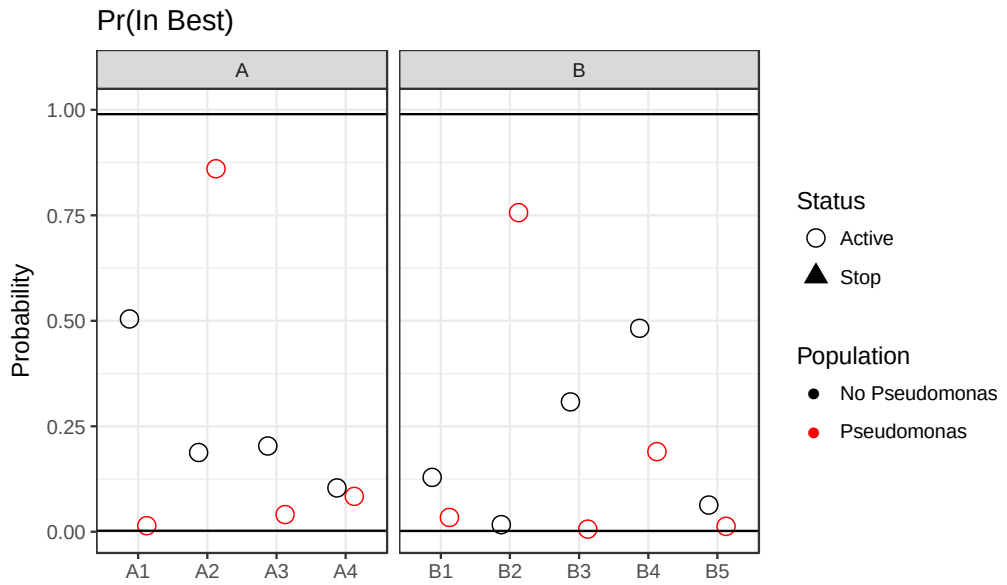
Design Iterations

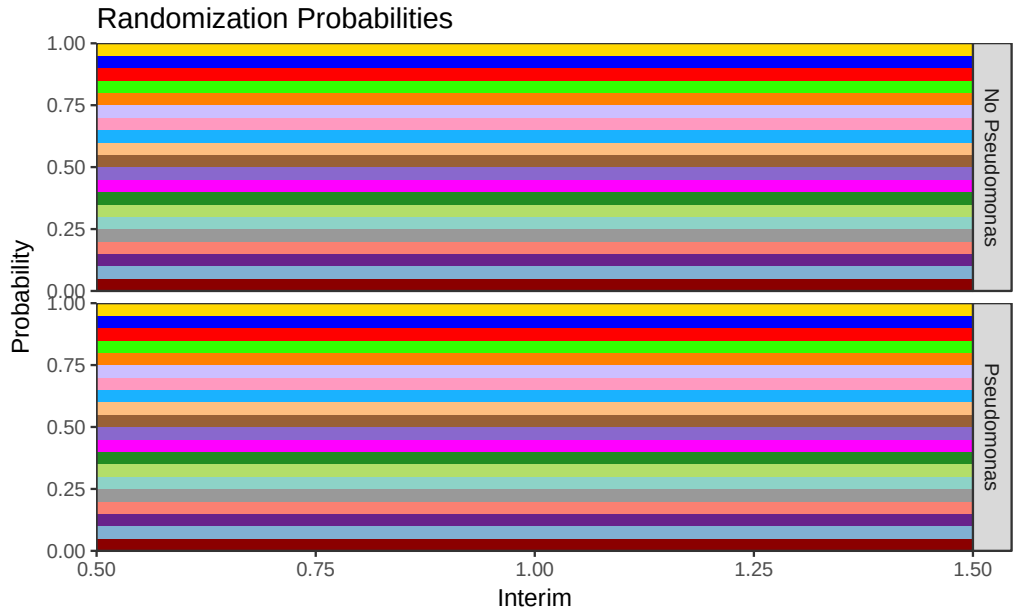
- Operating Characteristics (OCs)
  - Summaries of trial design over thousands of virtual trials
    - Power, Type I error, probability of arm dropping, average sample sizes, etc.
  - Compare competing designs & features
    - Vary input parameters/assumptions
- Example trials
  - Hypothetical trials (“movies”) with pictures/tables to illustrate what the design does with a single observed data set
    - You only get one trial!
    - See your trial in action before the real thing
    - Make sure the adaptive trial is doing what we want it to do (we don’t want surprises!)
- We iterate until we’re happy with the OCs and example trials
  - Process typically takes months

Example Trial: BEAT-CF Interim 1, N=250

Look #1: N = 250

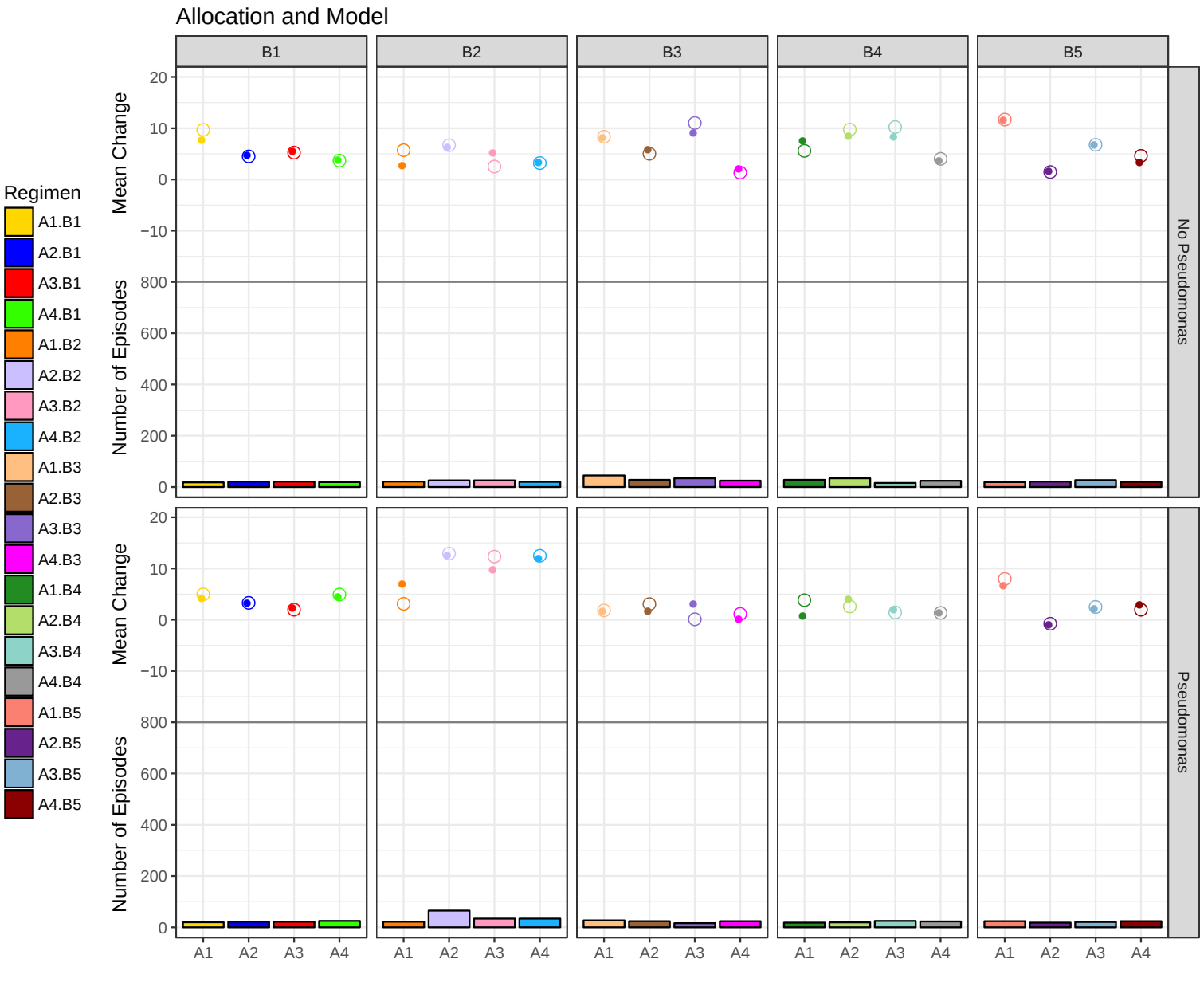


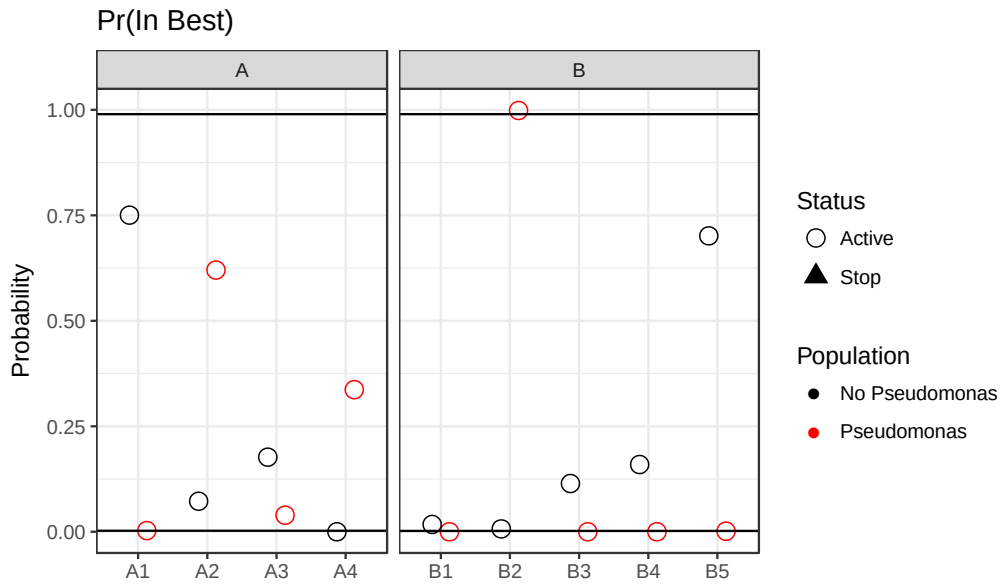


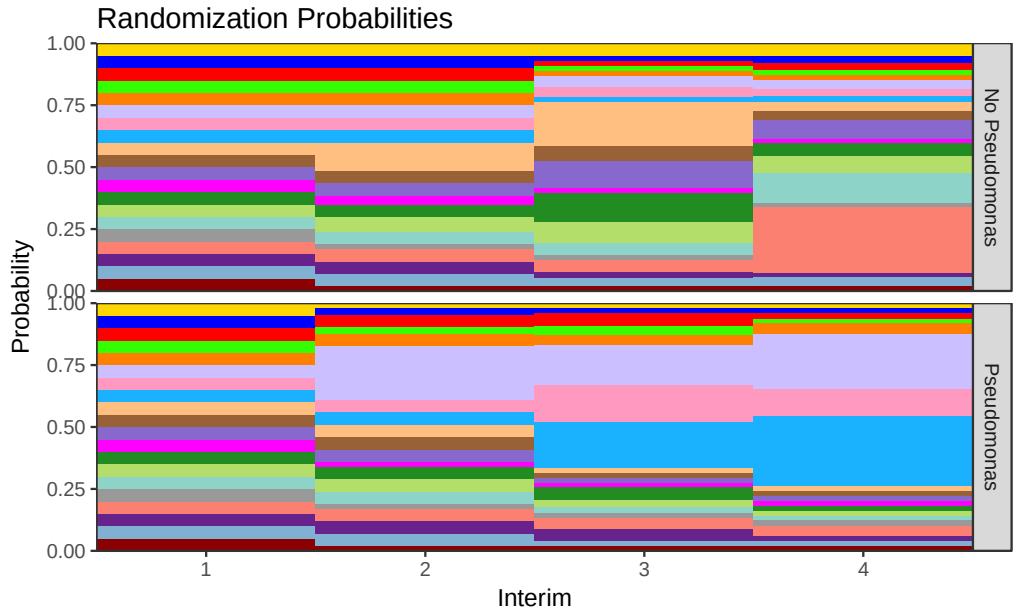


Example Trial: BEAT-CF Interim 4, N=1000

Look #4: N = 1000

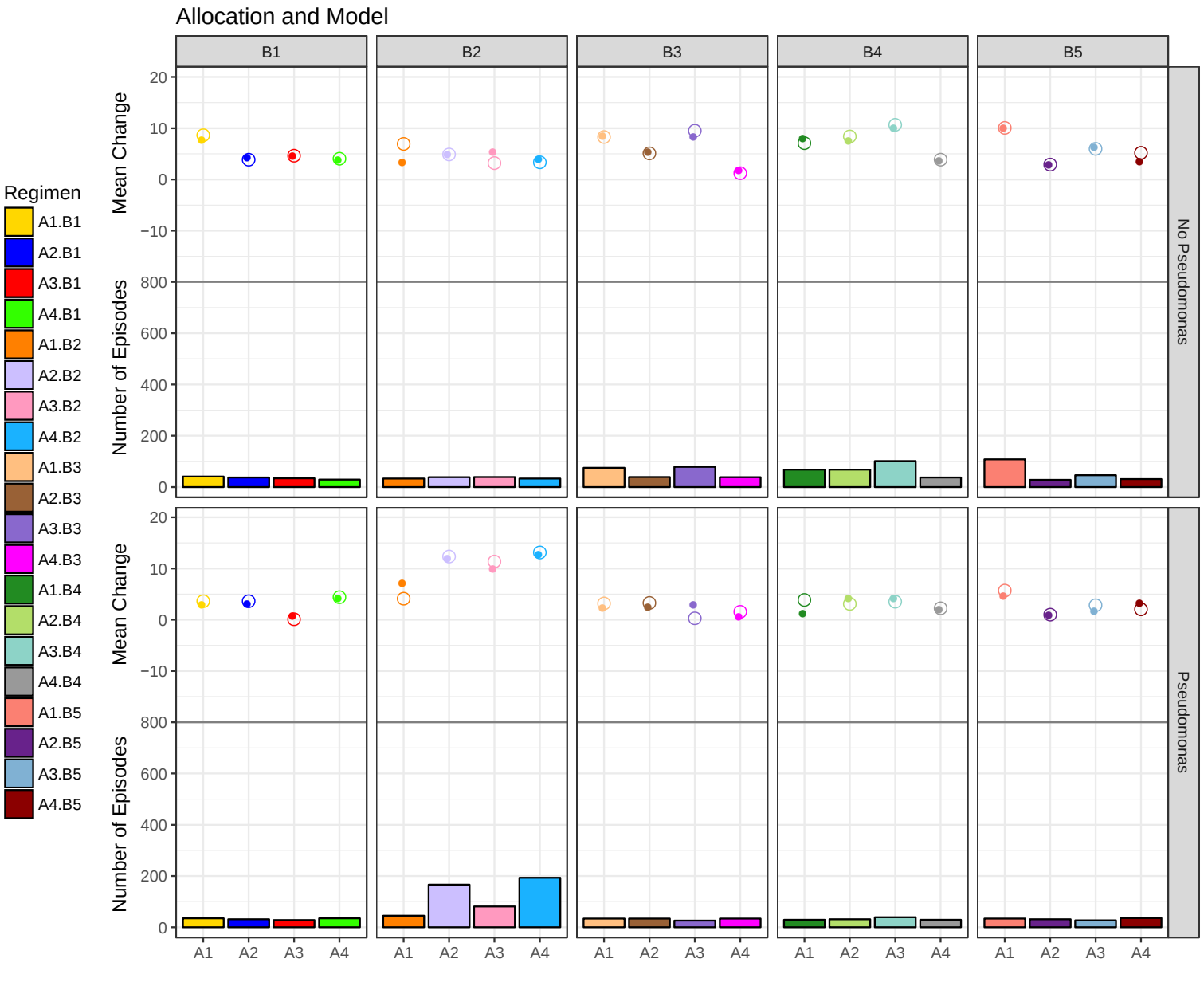


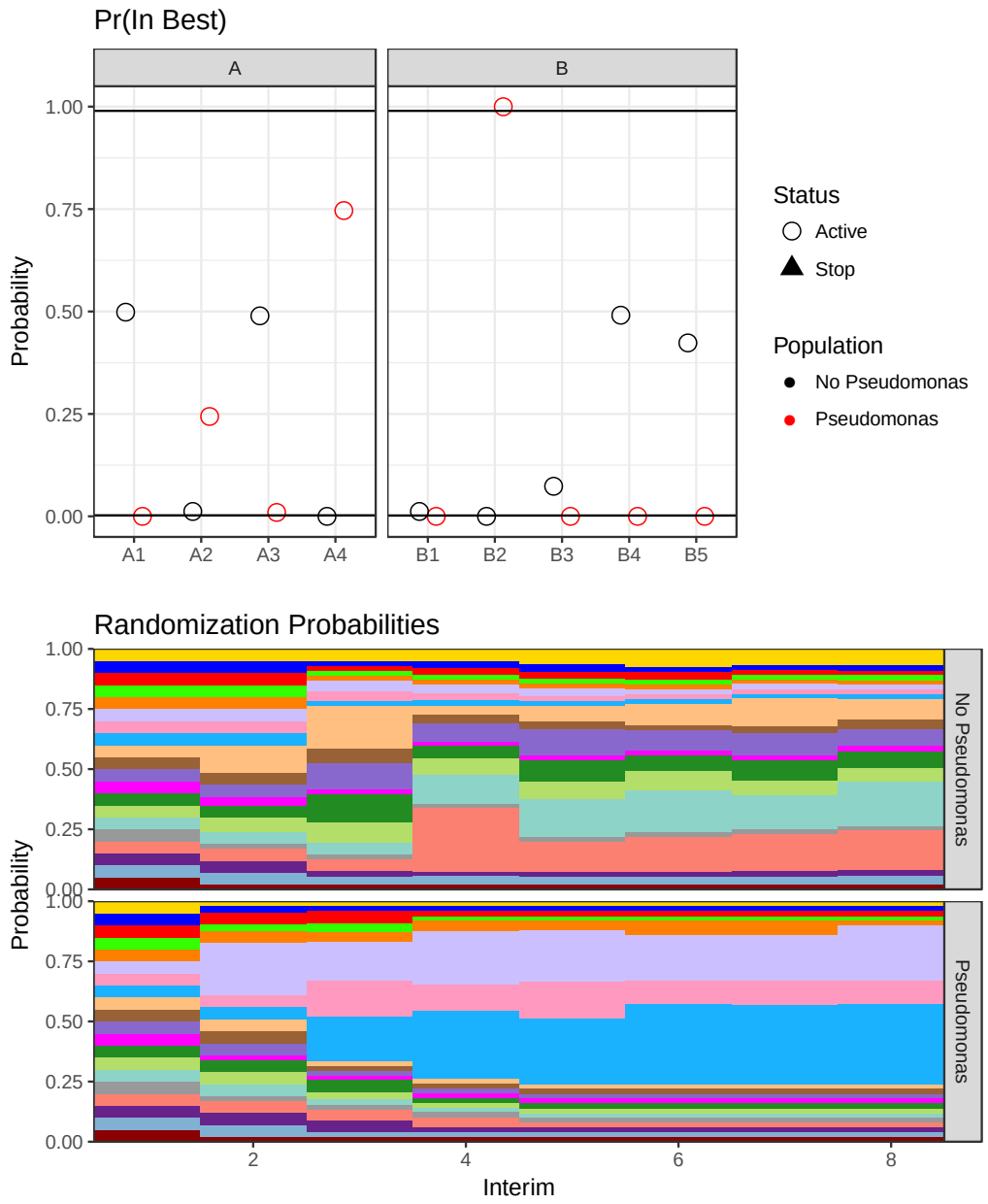




Example Trial: BEAT-CF Interim 8, N=2000

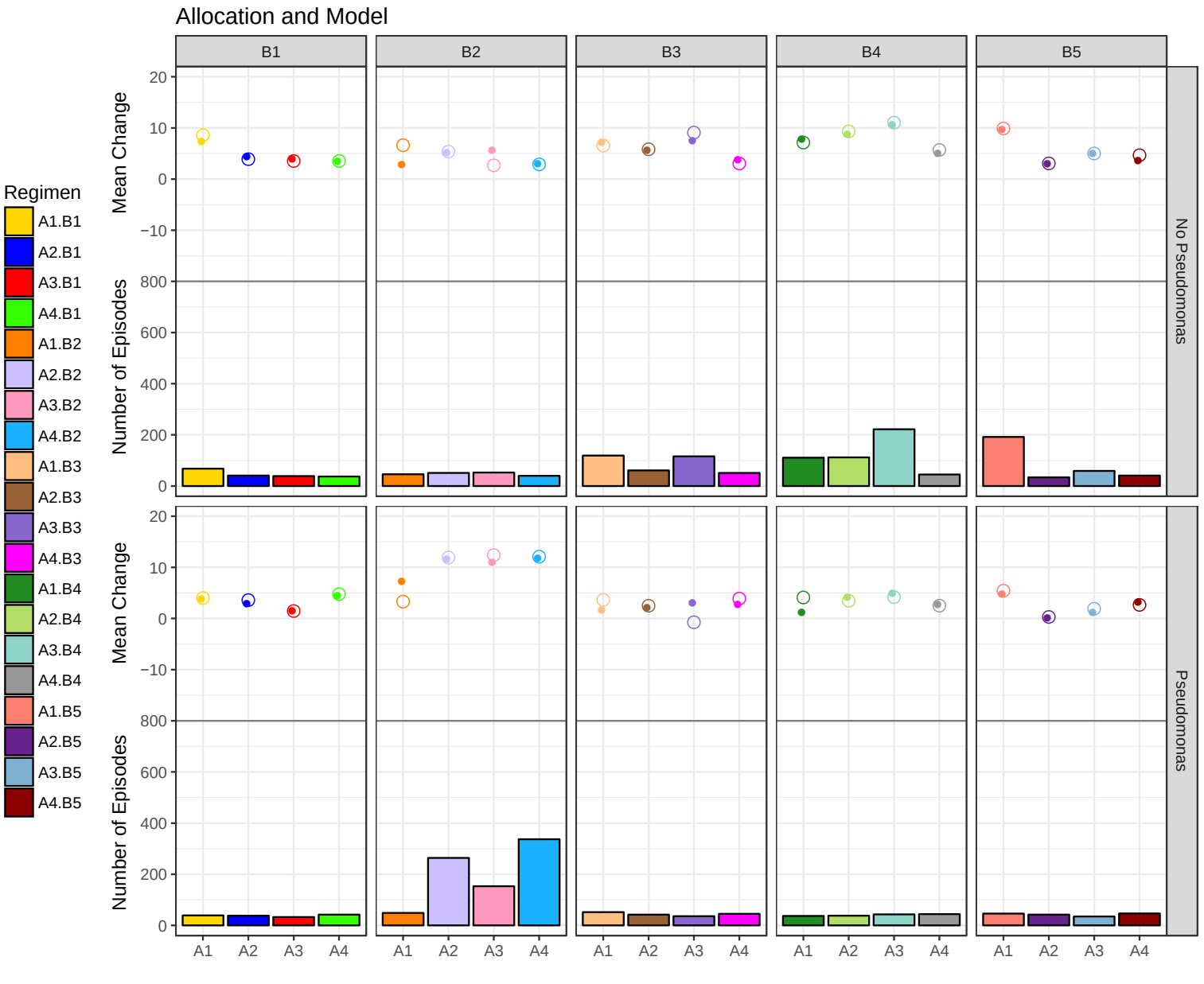
Look #8: N = 2000

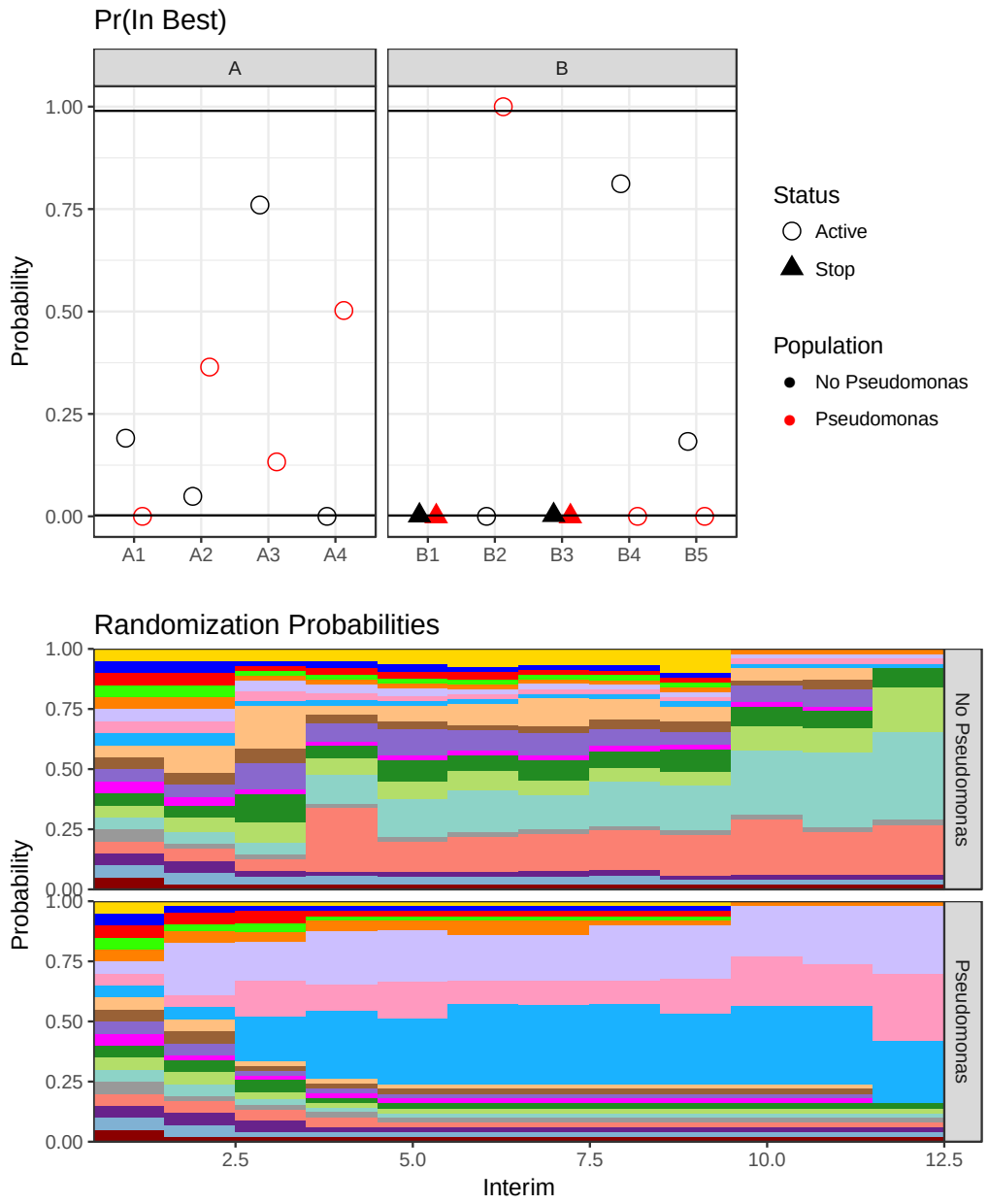




Example Trial: BEAT-CF Interim 12, N=3000

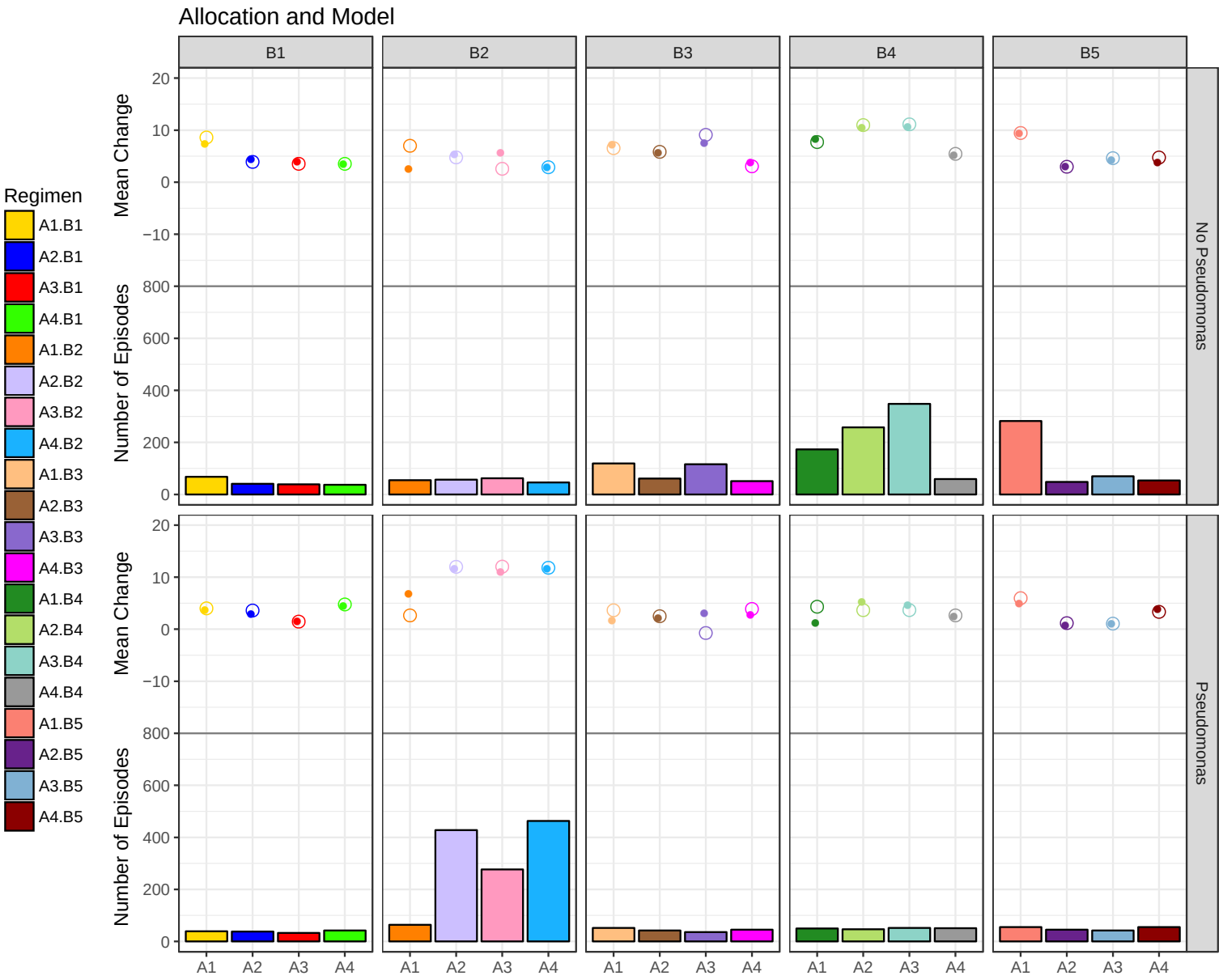
Look #12: N = 3000

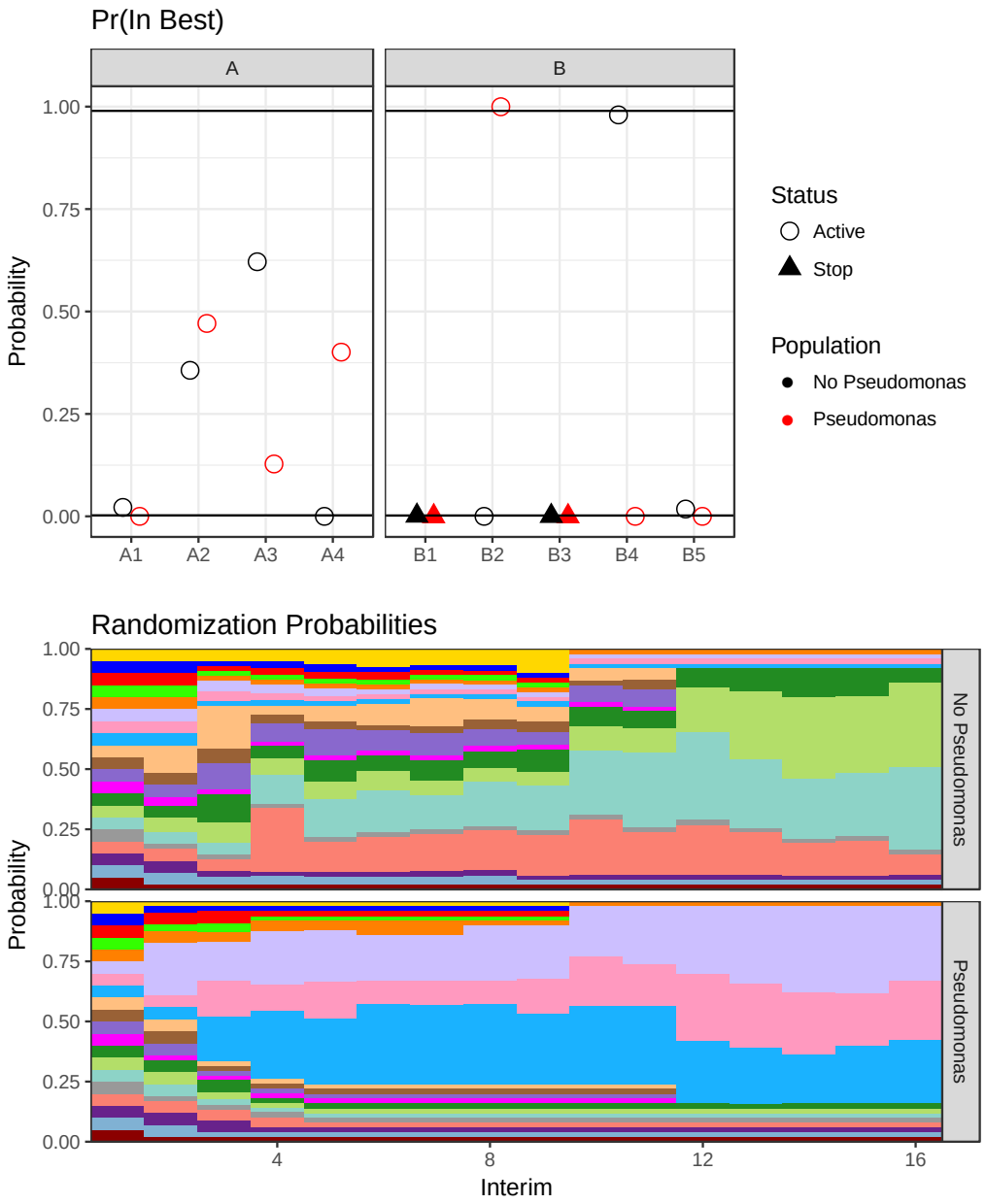




Example Trial: BEAT-CF Interim 16, N=4000

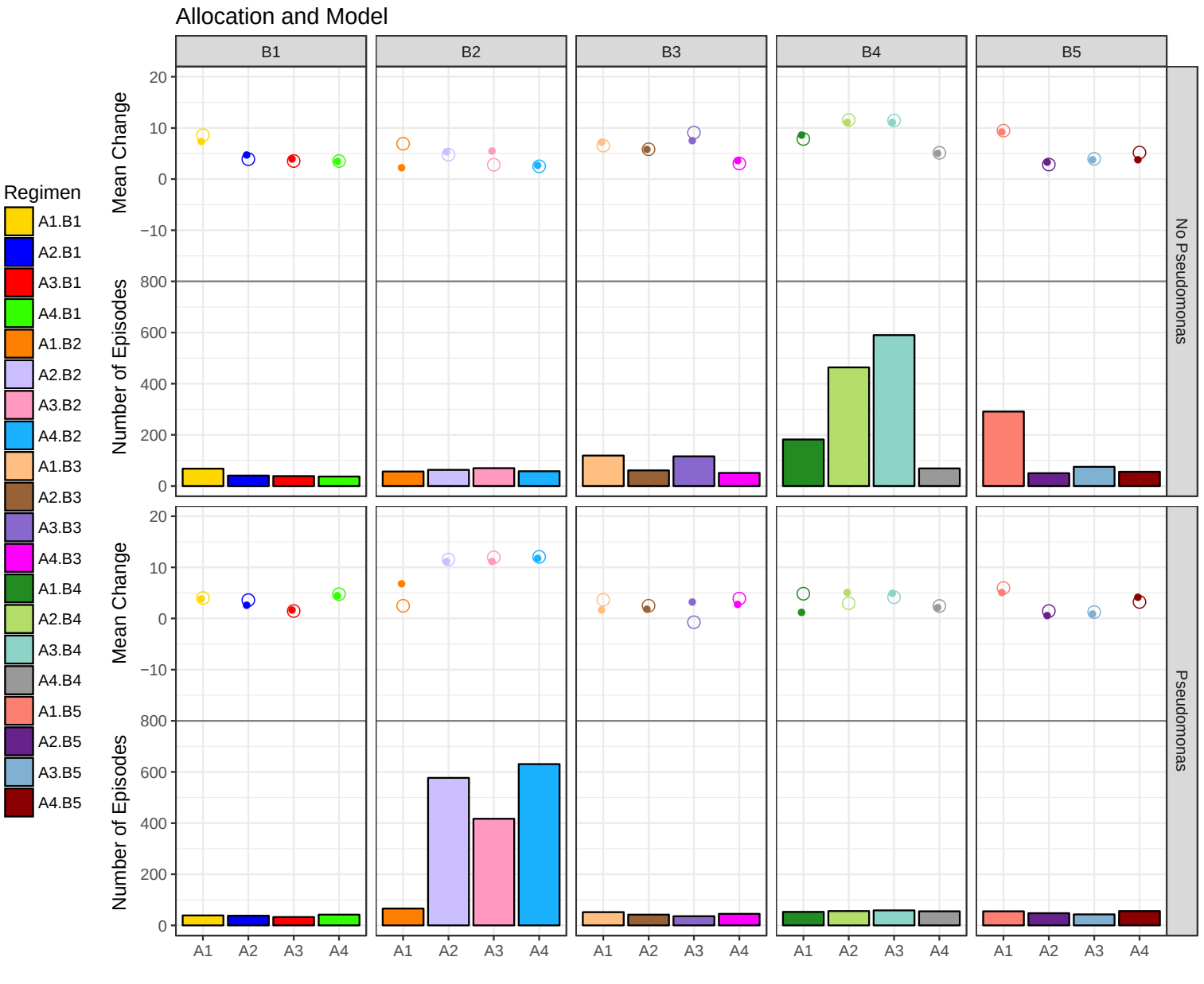
Look #16: N = 4000

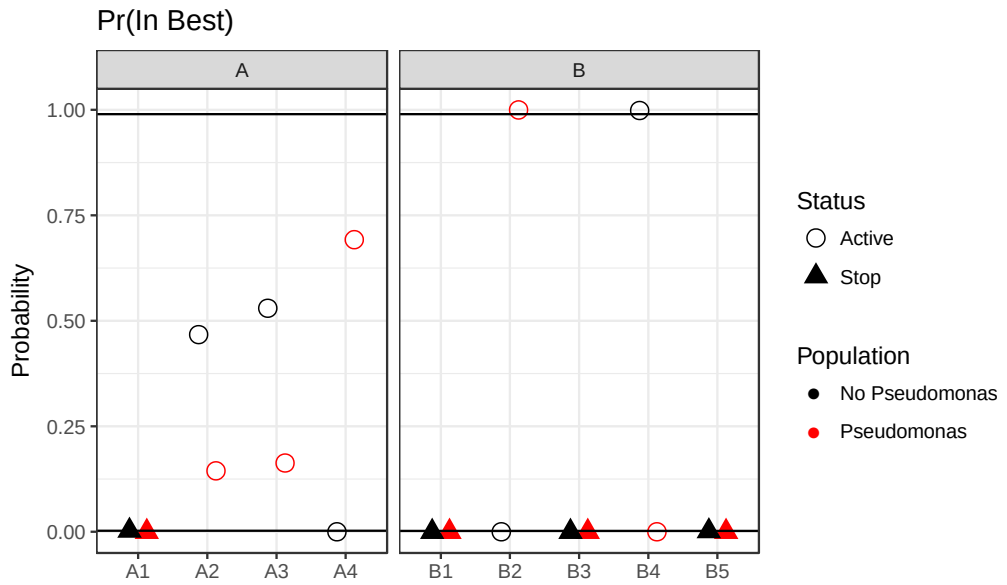




Example Trial: BEAT-CF Interim 20, N=5000

Look #20: N = 5000





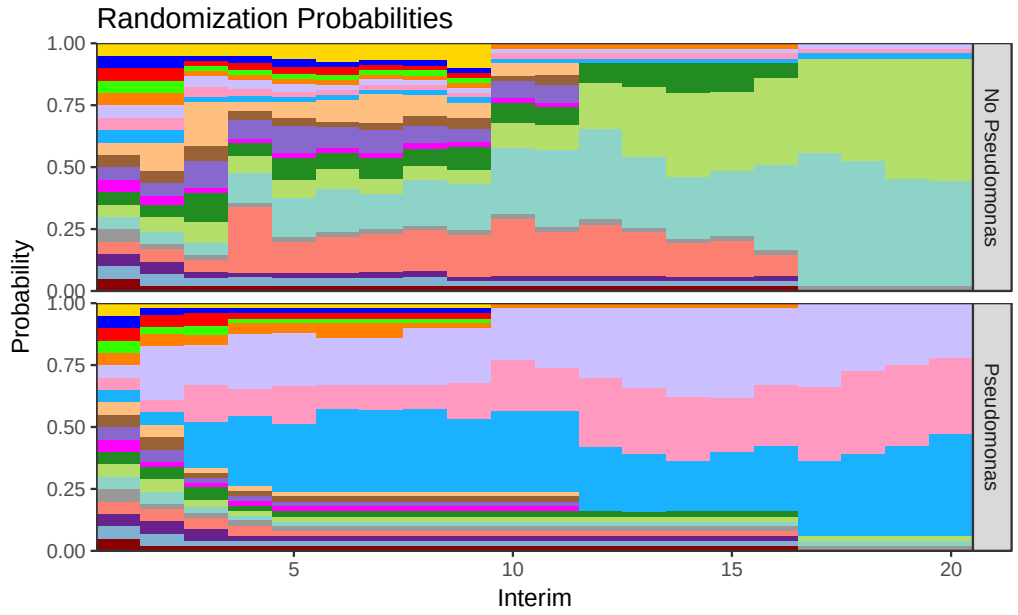
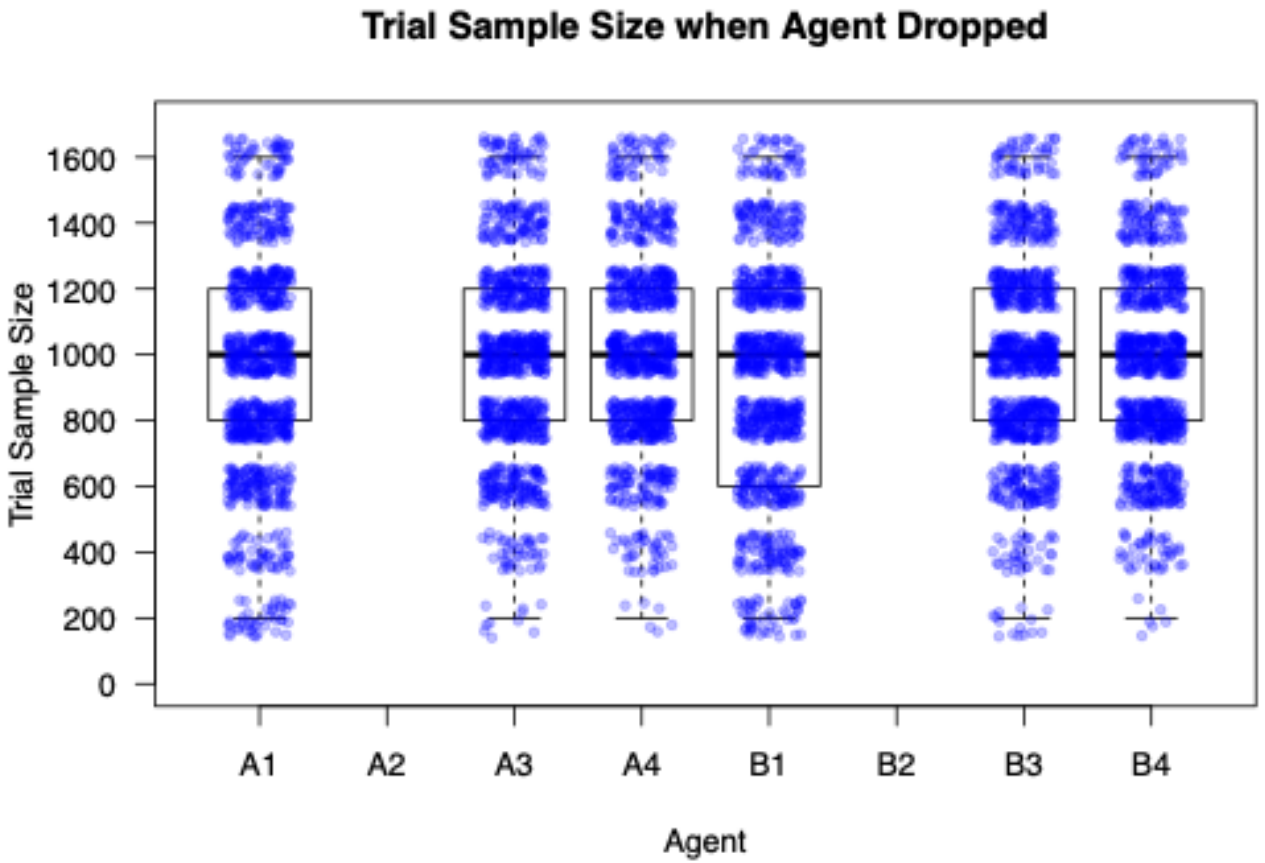


Table 64: Statistical Power by Agent and Subgroup

	Power				
	Low LF	High LF w/out Pseudomonas	High LF w/ Pseudomonas	Combined	Prob(DropTmt)
A1	0.000	0.000	0.000	0.000	0.944
A2	0.999	0.953	0.917	1.000	0.000
A3	0.000	0.000	0.000	0.000	0.944
A4	0.000	0.000	0.000	0.000	0.922
B1	0.000	0.000	0.000	0.000	0.945
B2	0.998	0.954	0.936	1.000	0.000
B3	0.000	0.000	0.000	0.000	0.934
B4	0.000	0.000	0.000	0.000	0.945



What Types of Adaptations?

- Depends on objectives, endpoints, analyses
- Arm dropping, early success, graduation to phase 3, response adaptive randomization, population enrichment, etc..
- Customized to each specific platform trial
  - Could be simple or complex
- Clinician's questions drive the adaptations
  - Need a statistician to help communicate what is possible

Teamwork

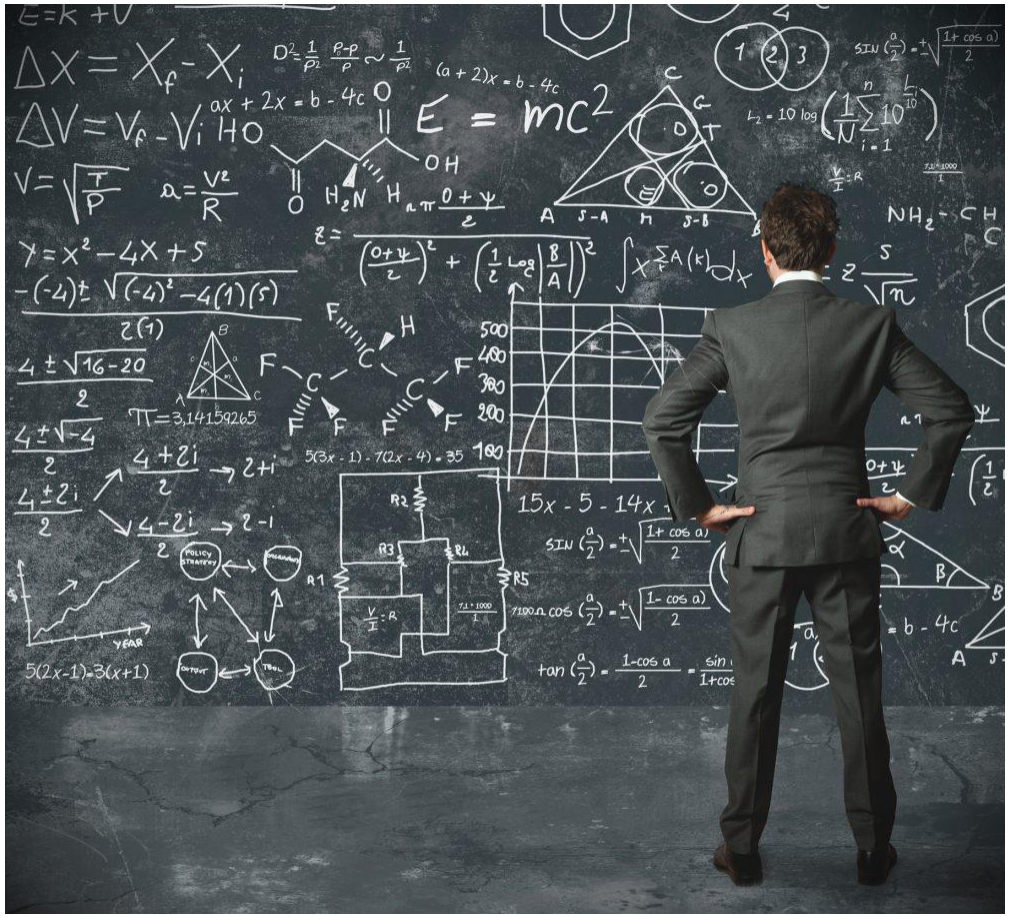
- Platform trial design requires a TEAM
  - Not a solo effort
  - Need clinical and statistical leaders
- Experts in diverse areas working towards a common goal
  - Communication is essential!

A Traditional Role of Statisticians

- A typical trial design
  - Clinicians develop research question
  - Clinicians develop protocol synopsis
  - Clinicians ask statistician for sample size calculation and short write-up of the primary analysis for the synopsis
  - Later, clinicians ask statistician to write full Statistical Analysis Plan
- Clinicians and statisticians work in silos!
  - Little collaboration and synergy
  - Statisticians viewed/used as “calculators”

Statisticians

- We tend to be introverts
- We like working by ourselves on our problems
- We tend to be pessimistic and doubting
- We tend to be very precise
- We worry about small issues and avoid the big issues
- We are poor speakers
- We speak “statistics”
- We are boring!



Statisticians

- We need speak the language of our collaborators
  - Clinician, CEO, clinical trialist, investor
- Are we leaders?
- Are we integrating ourselves into the team?
- Are we providing insight, innovation, to move the project, team, and company forward?
- Are we integral to the key decisions on the clinical trials, team, and drug development?
- Statisticians can’t design a platform trial in isolation
  - Clinical teams can’t design a platform trial without a statistical leader

A Modern Role for Statisticians

- Statisticians need to be leaders in platform trial design
  - Platform trials are collaborations between statistical scientists and clinical/research scientists
  - Statisticians: experts in the science of clinical trials
    - Bias, causation, blinding, unblinding, operational bias, variability, simulations, hypothesis testing, type I error, power, alpha-sharing, penalties, estimation, placebo effects, regression-to-the-mean, multiplicities, gatekeeping, p-values, …
- Synergist energy
  - Statistician needs to be the one to "bridge the gap"
  - Communication is essential
  - Focus on disease and patient treatment

Planning for Trial Operations

- Requires coordinated plan
  - Operations work occurs simultaneously with trial design
- A lot of different groups handling distinct tasks
  - Design, operations, numerous committees
- Trial maintenance
  - Always ongoing work
  - Trial design is never quite “finished”
- Fewer problems during trial implementation if we plan appropriately during the design stage

Intervention Timeline in PRINCIPLE


Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial


Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial


Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

Ivermectin

23 Jun 2021

Favipiravir

8 Apr 2021

Colchicine

4 Mar 2021 — 26 May 2021

Inhaled Budesonide

1 Dec 2020 — 31 March 2021

Doxycycline

24 Jul 2020 — 14 Dec 2020

Azithromycin

22 May 2020 — 30 Nov 2020

Hydroxychloroquine

2 Apr 2020 — 22 May 2020

Apr 2020 | Jun | Aug | Oct | Dec | Feb 2021 | Apr | Jun | Aug | ... | July 2022

Platform Infrastructure

- Design Committee (blinded)
  - Clinicians, statisticians, operations
  - Typical weekly meetings
  - Design, specific regimens, operations, regulatory interactions, etc.
- Regimen-specific design meetings
  - Weekly during design stage, then transition to operations
- Operations team
  - Weekly regimen-specific meetings (after design set)
  - Drug supply, blinding, logistics, etc.
  - Don’t typically involve the statisticians
- Other important groups (not comprehensive!)
  - DSMB
  - Regimen-specific steering committees
  - Therapy evaluation committee
  - Patient advisory committee

Statistical Groups

- Statistical expertise required
  - Design, disease, data management, implementation
- Sponsoring organization
  - Database management
  - Includes both blinded and unblinded statisticians
  - Perhaps subcontracting to CRO for safety reports, secondary analyses
- Independent Statistical Analysis Committee
  - Unblinded, small group of statisticians
  - Firewalled from design team members
- Blinded design team
  - Blinded to platform results until ready to be released to regimen partners

Clear Documentation

- Master Protocol
  - Regimen-specific appendices
- Master SAP
  - Regimen-specific SAP as Appendices
- Master Protocol Recommended Statistical Analysis & Design Report (MPRDR)
  - Recommended design for first few regimens
  - Appendix to the Master SAP
- Regimen-specific simulation appendix
  - Created for each regimen and included as an appendix to the regimen-specific SAP
  - Takes priority over MPRDR
- Table for conflict resolution
  - Hierarchy for Master Protocol, SAP, R-SAP, MPRDR, and regimen-specific simulation report
- Version control essential
  - Tracked changes

Data Sharing

- Releasing regimen results
  - Public announcements
  - Publications
- Not an issue with traditional trials
  - Completed trials
  - Data can be used to generate hypotheses for future research
- Challenge with sharing results in platform trials
  - Problematic for ongoing regimens if using shared control
  - Problematic for future regimens if using non-concurrent shared controls
- Align on what data/results can be shared, when, and to whom

Adding New Regimens

- Regimen-specific design meetings
  - Customize design for specific regimen
  - Sample size, analysis, any deviations from recommended design
  - Custom simulations included as appendix to the Regimen SAP
- Operations team meetings
  - Transition to weekly operations meetings
  - Drug supply, blinding, logistics, etc.
- FDA submissions (if applicable)
  - Each regimen specific appendix is submitted to IND as protocol amendment
  - FDA completes full review

Changes in SOC

- Changes in SOC can affect a platform trial
  - Affects regimens currently enrolling and future regimens
- Mitigation strategies
  - Consider in trial design how primary analysis can account for changes in SOC
  - Encourage completion of RCT for enrolling regimens without changes
  - Allow changes in the analysis model and/or stratification
  - Sensitivity analyses

Funding a Perpetual Platform Trial

- Funding
  - Need an organization willing to fund the planning and initial stages of a platform trial
  - Patient organization
  - Government grants
- Have plan for sustained funding
- For trials with industry partners
  - Can bring on industry partners after trial is designed
  - Getting the first partner can be difficult
  - Most companies don’t want to be the first (consider discounts)

Examples of Platform Trials

- Cancer
  - I-SPY2 in Breast Cancer (Grants, industry partners)
  - GBM AGILE in Glioblastoma multiforme (National Foundation for Cancer Research)
  - LUNG-MAP in Lung Cancer (NCI, SWOG, industry partners)
  - Precision Promise in Pancreatic Cancer (Pancreatic Cancer Action Network - PanCAN)
- Neurology
  - EPAD: European Prevention of Alzheimer's Dementia (IMI European grant)
  - DIAN: Dominantly Inherited Alzheimer's Network (Alzheimer's Association, National Institute of Aging)
  - P2P: Path to Prevention in Parkinson's **(Michael J. Fox Foundation)**
  - Healey ALS Platform Trial, Phase 2/3 with 7+ drugs (Healey & AMG Center for ALS)
- Respiratory
  - PrecISE in pediatric Asthma (NIH grant)
  - BEAT-CF in Cystic Fibrosis (Australian grant)
- Acute Ischemic Stroke: STEP (NIH-funded StrokeNet)

Examples of Platform Trials

- Infectious diseases
  - Ebola Platform design (Gates Foundation)
  - NIH Ebola design (NIH)
  - PREPARE: European Consortium for Disease Preparedness (EU grants)
    - Pandemic flu, Butler at al Lancet, Jan 2020
    - REMAP CAP (Community Acquired Pneumonia) ongoing, REMAPCAP.org
  - SNAP in Staphylococcus aureus (Australian grants)
- COVID-19
  - REMAP-COVID by International consortium critical care trial (European Union)
  - PRINCIPLE/PANORAMIC in UK, pre-hospital trial (UK NIHCR grants)
  - RECOVERY in UK (Bill Gates Foundation, NIHR, …)
  - ACTT by NIAID -- the Remdesivir trial
  - SOLIDARITY by WHO, 4 arms
  - ISPY-COVID: UCSF & WISDOM Network, Phase 2 (COVID R&D Consortium, Industry)
  - ACTIV by NIH

Summary

- Basics of a platform trial
- How to get started on trial design
  - Objectives
  - Skeleton designs
  - Cost, sample size
- Virtual trial design
  - Computer simulations as a design tool
  - Teamwork; role of statisticians
- Platform trial organization
  - Funding sources
- Focus on the disease and optimal treatment for patients!