Bayesian Adaptive Multi-Arm Platform Trials

Dr Julie Marsh

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Outline

Platform trial design

Stakeholders & expert elicitation

Clinical trial simulator

Next step: integrated eHealth platform trials

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VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

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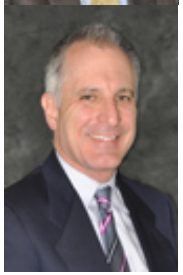

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The drug development enterprise is struggling. The development of new therapies is limited by high costs, slow progress, and a high failure rate, even in the late stages of development. Clinical trials are most commonly based on a "one population,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

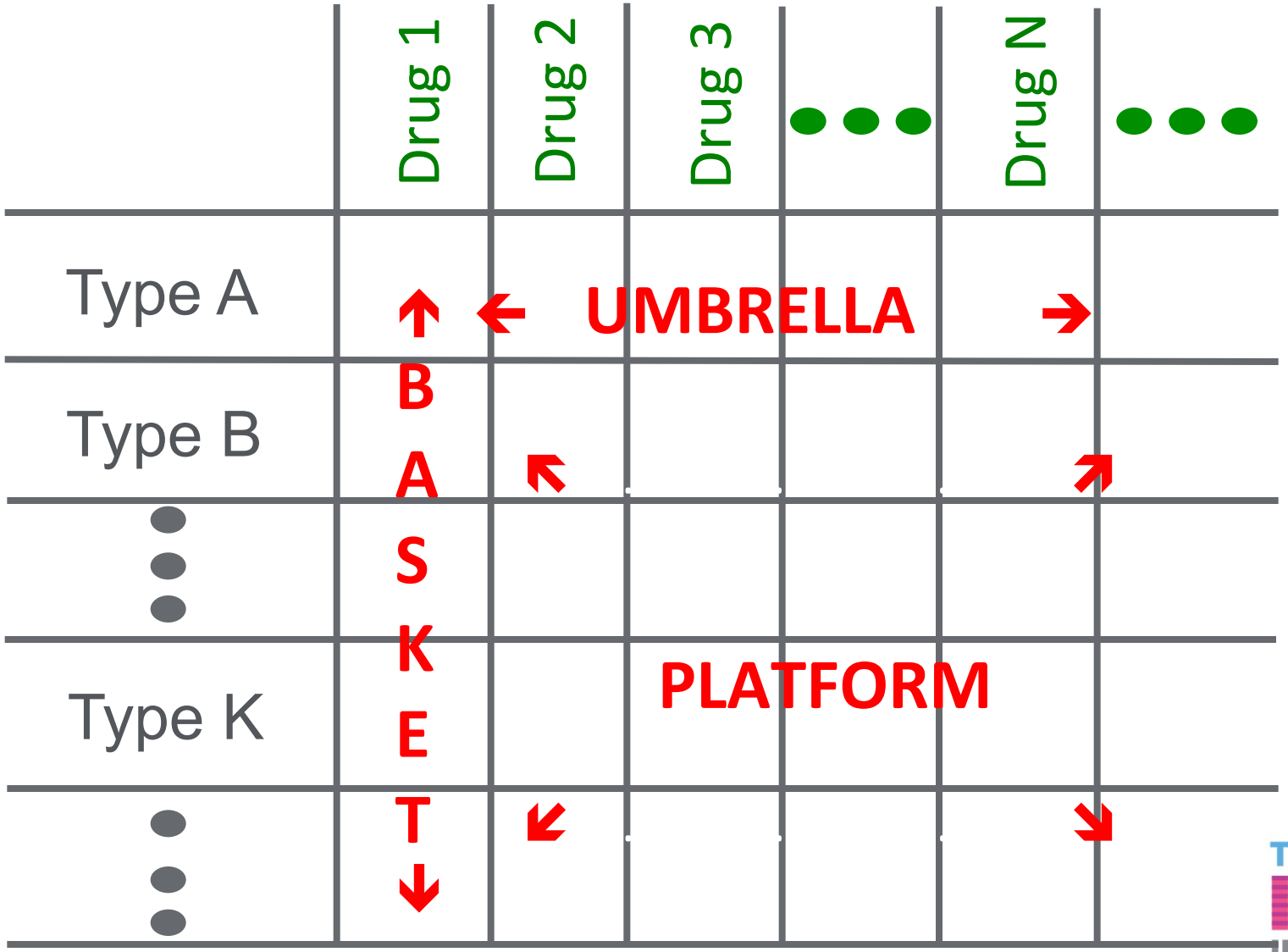
This approach has been largely unsuccessful for multiple diseases, including sepsis, dementia, and stroke. Despite promising preclinical and early human trials, there have been numerous negative phase 3 trials of treatments for Alzheimer disease[1] and more than 40 negative phase 3 trials of neuroprotectants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

Platform trial design



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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

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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

Platform trial design

Key features of a platform trial are:

- any number of treatment combinations
- treatments can be added or removed
- any number of subgroups
- no maximum sample size (perpetual)
- frequent sequential analyses
- predefined decision rules for adaptation
- treatment assignment controlled by a central statistical model & accruing data

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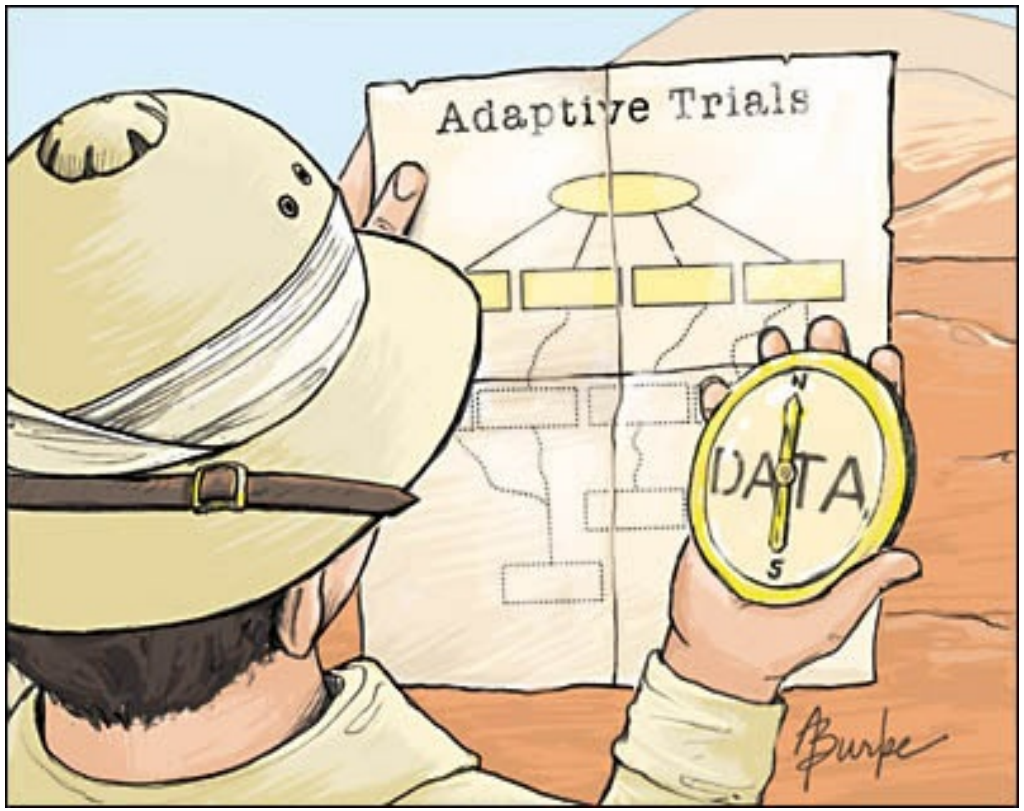
Platform trial design



Pre-specified flexibility documented in the master protocol.

JAMA 2006;296:1955-1957

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When to use a platform trial design

- Outcomes or biomarkers available rapidly relative to time required for entire trial
- Large uncertainty regarding relative efficacy, adverse event rates, variability, patient population in trial, etc.
- Multiple therapies and/or heterogeneity of treatment response
- New biomarkers and therapies becoming available
- Able to secure buy-in of stakeholders

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Stakeholders & expert elicitation

1. Identify the stakeholders and start listening. As a minimum this should include patient advocates, clinicians, nurses, statisticians and computer scientists.

   ✓ Partnership – these co-investigators will be driving the recruitment, treatment allocation, trial adherence, data collection & repeat sequential analyses.

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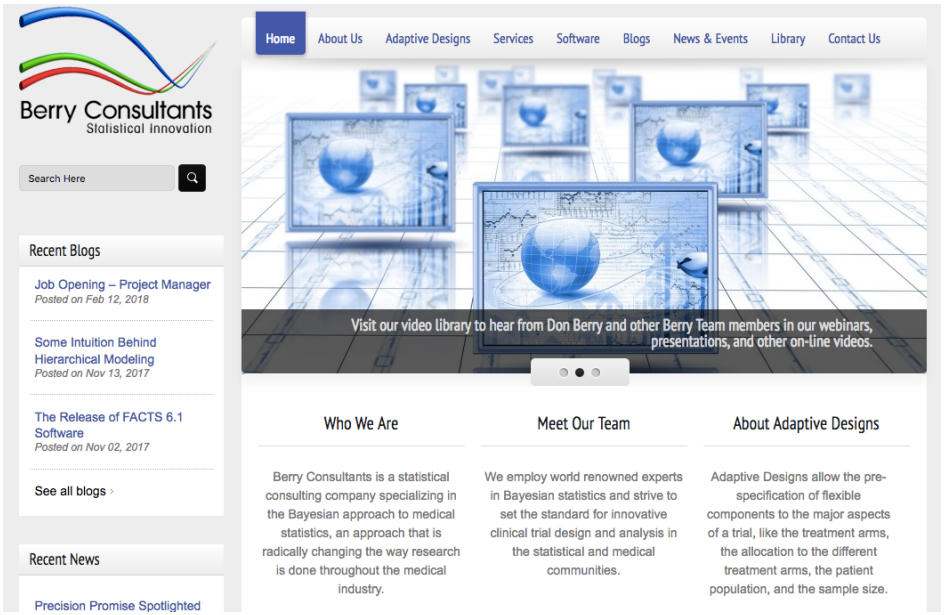
Stakeholders & expert elicitation

2. Consider getting help from a group with platform trial experience.



Community Acquired Pneumonia (PREPARE REMAP-CAP)
Cystic fibrosis (BEAT CF)
Hepatitis C (PLATINUM C)
Influenza (PREPARE ALICE)
Breast Cancer (I-Spy2)
Brain Cancer (GBM-AGILE)
Pancreatic Cancer
Antibiotics
Alzheimer's (EPAD, DIAN)
Lung Cancer (LUNG-MAP)
Ebola
Several rare diseases… and others in the pipeline.

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Stakeholders & expert elicitation

3. Map out the casual network for the disease and agree the research questions.

   Consider using a structured elicitation process (such as a modified Delphi procedure:Investigate-Discuss-Estimate-Aggregate) to identify the eligible population and trial outcomes. This improves the accuracy and transparency of the resulting judgements and defines the domains & subgroups.

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Stakeholders & expert elicitation

4. Define the underlying distributions for:
   - control and treatment response;
   - accrual, drop-out and missing data rates;

   Identify plausible trial outcome scenarios.

   Evidence may be available from historical data (such as previous trials), published research or hospital audit data. Or it may be necessary to implement another structured elicitation process with disease area experts.

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Stakeholders & expert elicitation

4. Define the underlying distributions for:
   - control and treatment response;
   - accrual, drop-out and missing data rates;

Ide

Beware: Expert judgements can be prone to contextual and recall biases.

Evidence may be available from historical data (such as previous trials), published research or hospital audit data. Or it may be necessary to implement another structured elicitation process with disease area experts.

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Stakeholders & expert elicitation

5. Ideally get help from an experienced computer science team on ways to efficiently identify patients, allocate treatments and collect data.

   Efficient platform trials build in patient privacy when integrating:

   - disease-specific or healthcare-based registries;
   - clinician and/or healthcare systems;
   - patient and/or carer feedback;
   - laboratory or ‘omic data.

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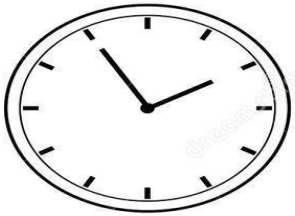
Clinical Trial Simulator

Over 2 years later, you are **almost** ready for a grant application. However, the range of sample sizes, decisions rules for trial success and futility and the timing and number of interim analyses all need to be determined by trial simulation.



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Clinical Trial Simulator

- Simulations are used to see the trial in action before we start recruitment into the trial
- Iterative process with feedback from study investigators
  - Add more domains or subgroups?
  - Allow new therapies to enter the ongoing trial?
  - More frequent analyses?
  - Calibrate aggressiveness of adaptive randomization
  - Perpetual?

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Clinical Trial Simulator

Factors to consider when designing trial simulator:

- Accrual rate
- Distribution for the control response
- Distribution for prior (often weakly informative)
- Number/timing of sequential analyses
- Thresholds for trial success & futility
- Minimum number of patients with endpoint before declaration of early success/failure

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Clinical Trial Simulator

Example: BEAT Cystic Fibrosis

- Poor consistency in management of pulmonary exacerbations across centers
- Uncertainty in backbone antibiotic, adjunct antibiotic, airway clearance methods/regimens, muco-active therapies, anti-inflammatory (glucocorticosteroids), etc.
- Heterogeneity in patient response (age, recent hospitalization, *Pseudomonas* colonization, genetic biomarkers)
- Research Question:

  What is the optimal treatment for this patient?

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Clinical Trial Simulator Example

Domain A:

Primary antibiotics

1. Ceftriaxone
2. Ceftazadime
3. Tazocin
4. Cefepime

Domain B:

Adjunct antibiotics

1. IV Tobramycin
2. IV Amikacin,
3. Inhaled Tobramycin
4. Inhaled Colistin
5. None

Patient Subgroups:

Pseudomonas in last 12 months

1. No
2. Yes

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Clinical Trial Simulator Example

Take a best guess on the trial simulator parameters

- an accrual rate of 5 patients per week
- sequential analyses every 250-100 patients
- weakly informative prior
- success thresholds: between $p(\vartheta_d>0)>0.9999$ for early analyses & $p(\vartheta_d>\vartheta)>0.975$ for final analysis
- futility thresholds: between $p(\vartheta_d>0)<0.0001$ for early analyses & $p(\vartheta_d>0)<0.2$ for final analysis
- response adaptive randomization after 15 episodes in a given cell

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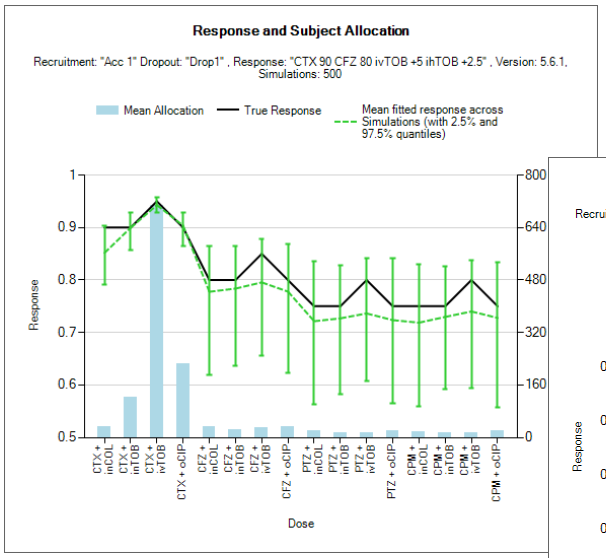
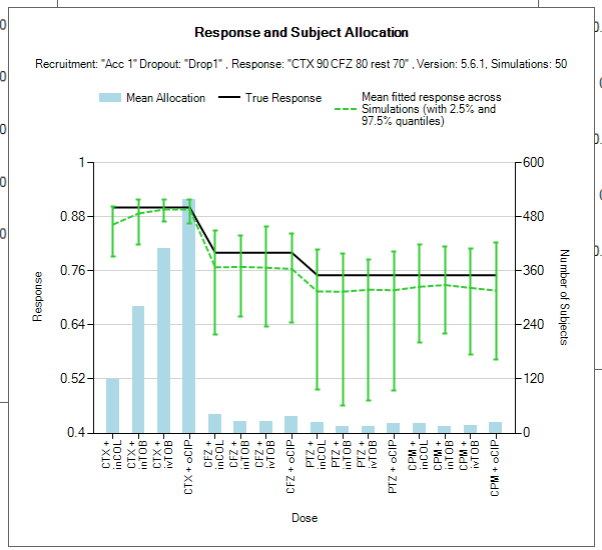
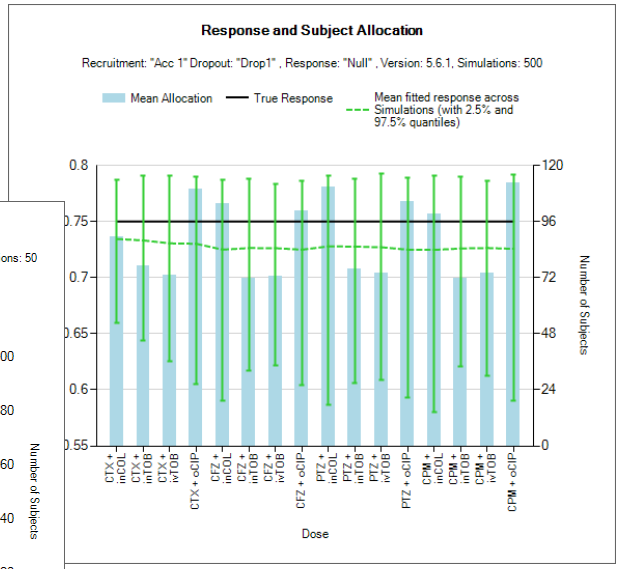
Clinical Trial Simulator Example

- Plausible trial scenarios (including null model)







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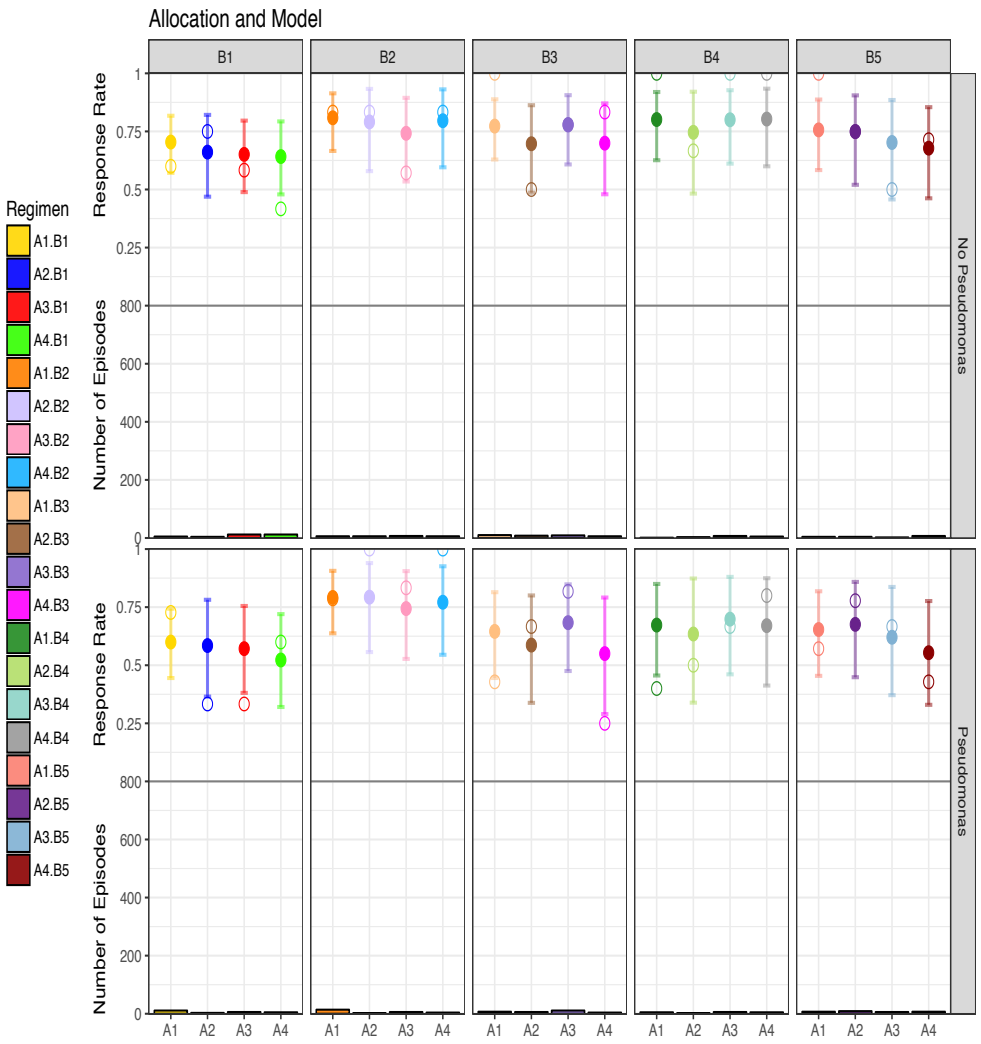
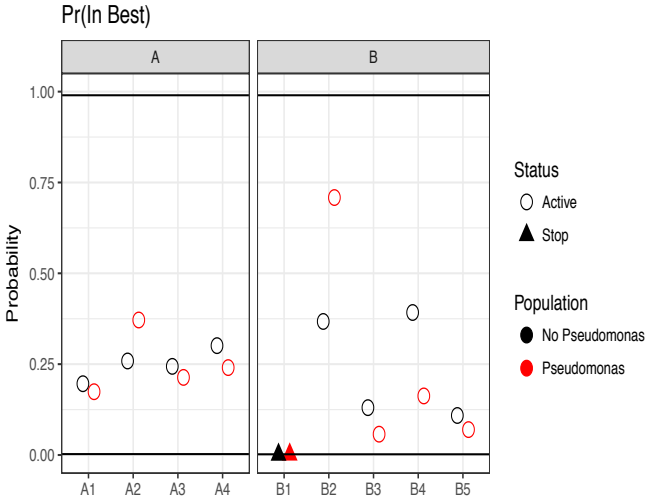
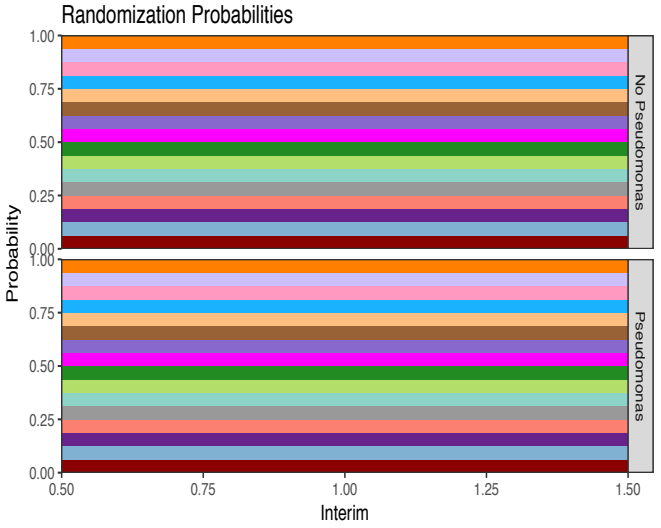
Interim 1, N=250

Look #1: N = 250

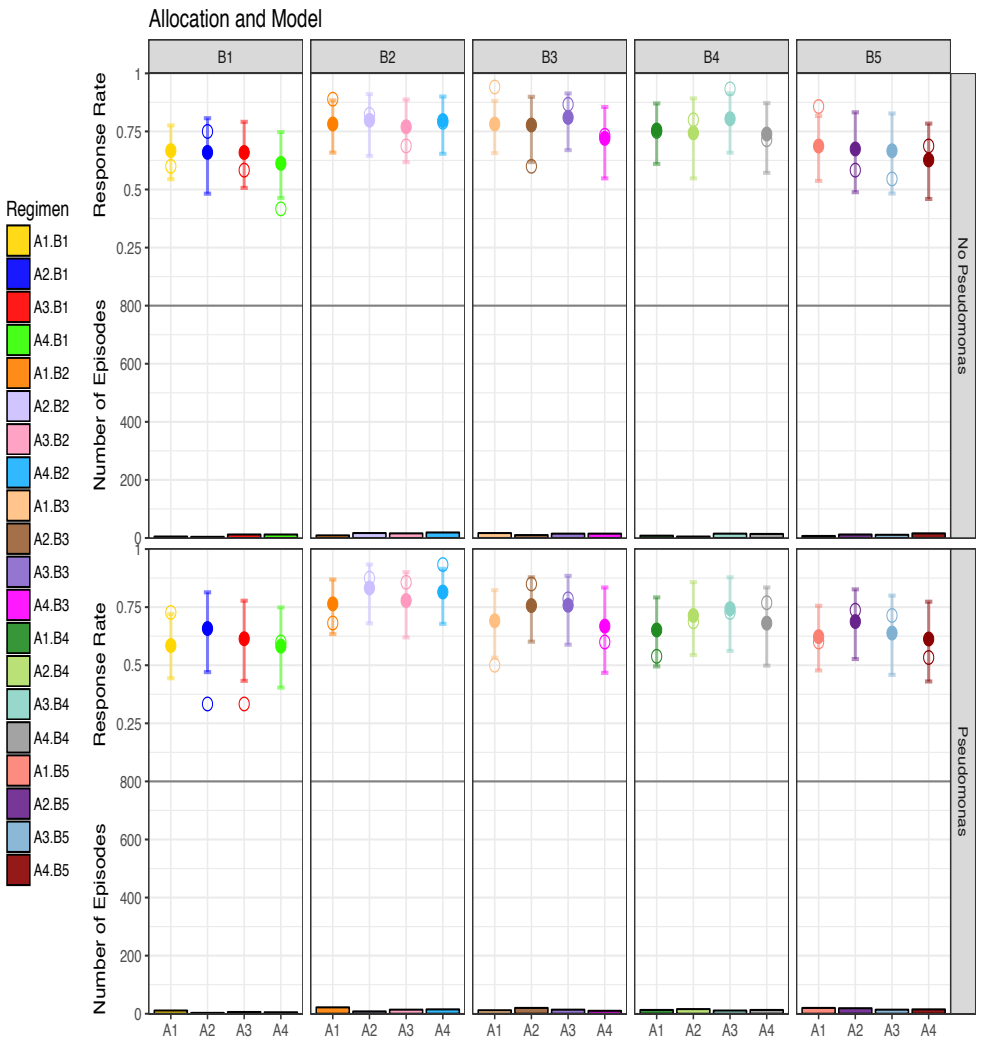


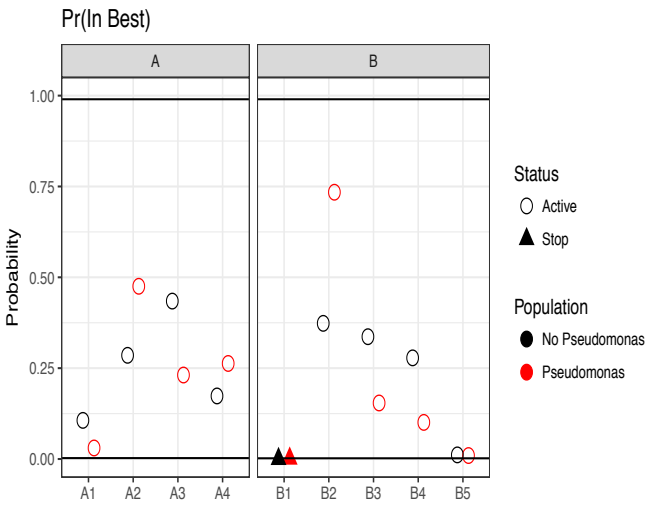


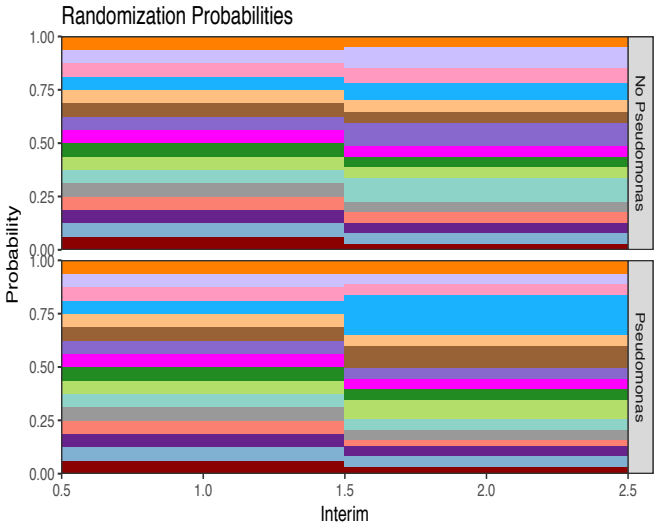


Interim 2, N=500

Look #2: N = 500

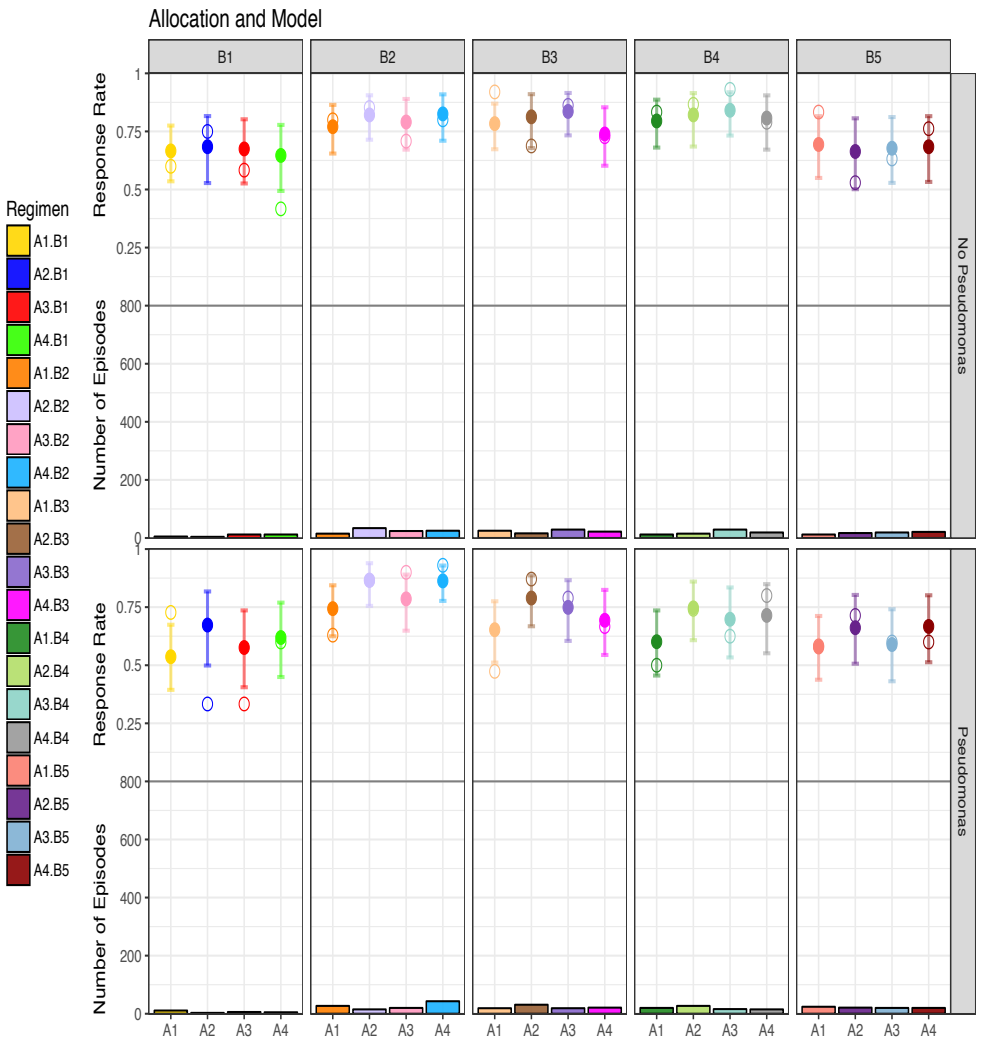


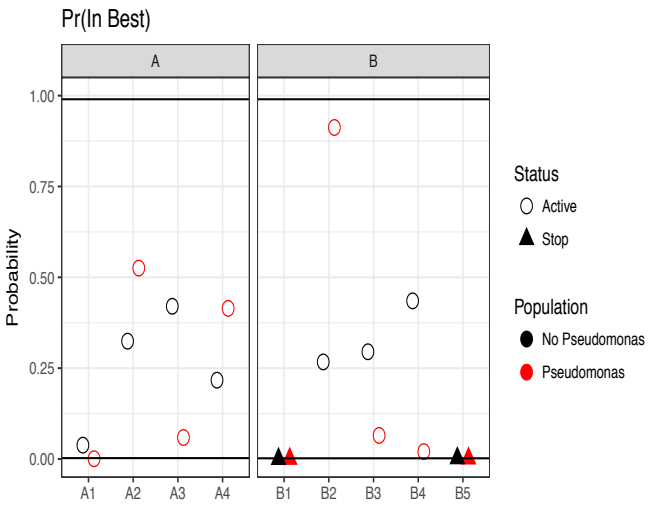


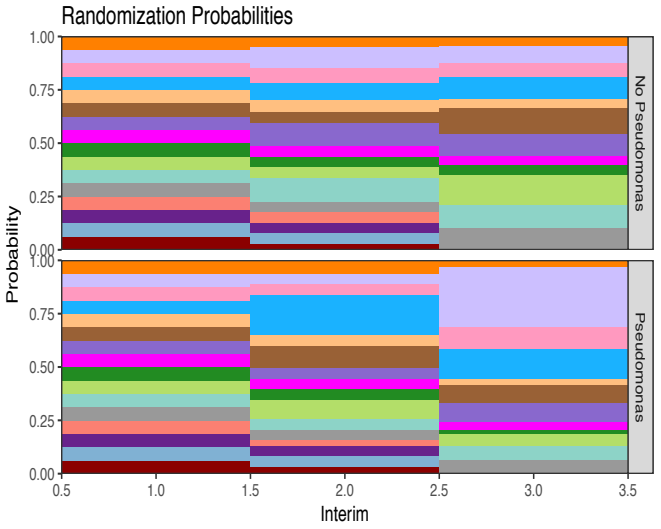


Interim 3, N=750

Look #3: N = 750

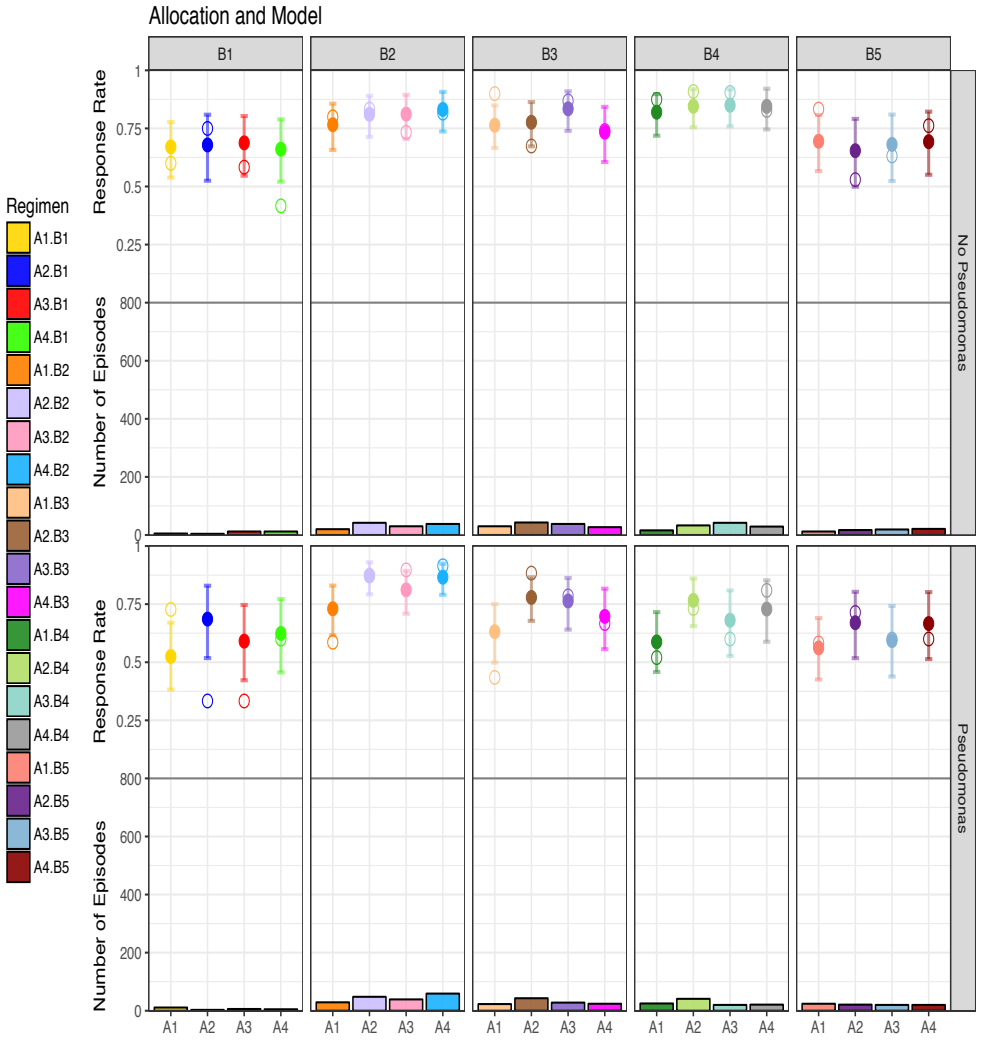


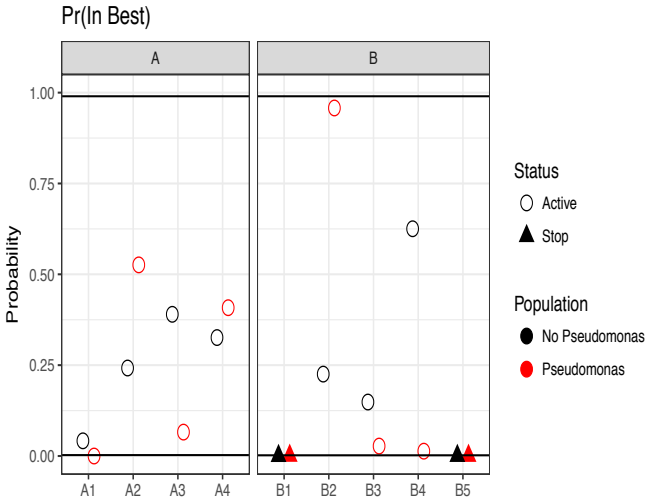


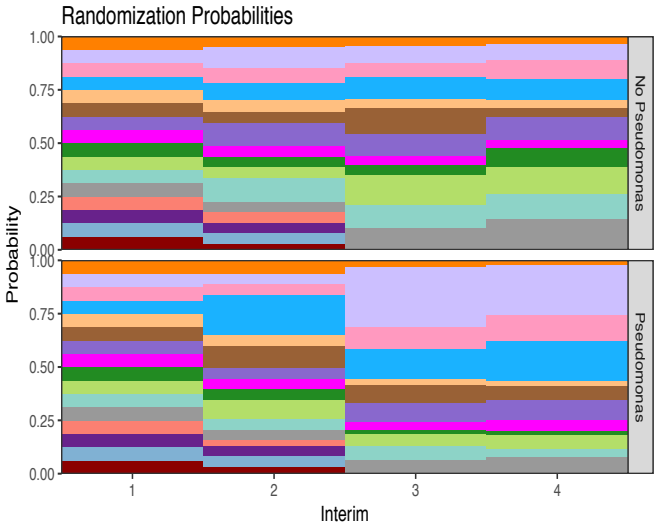


Interim 4, N=1000

Look #4: N = 1000

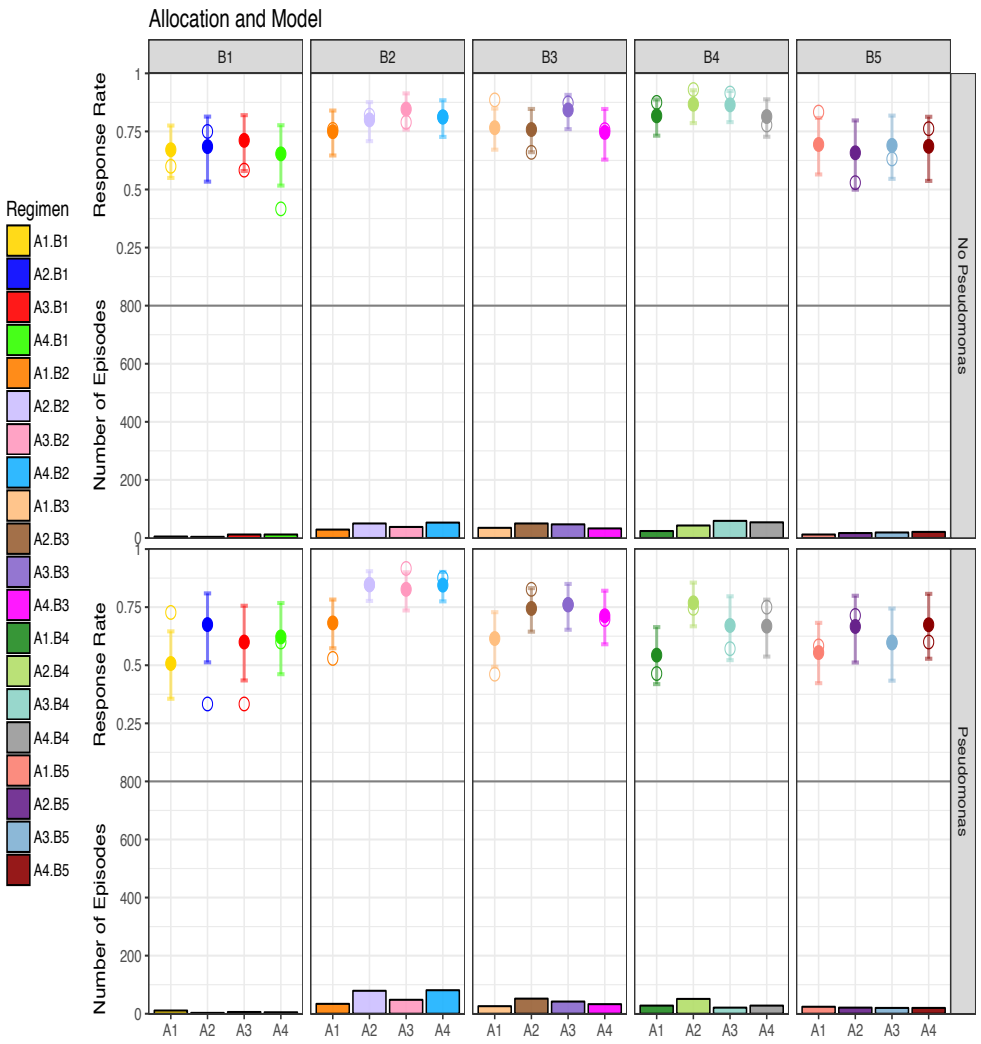


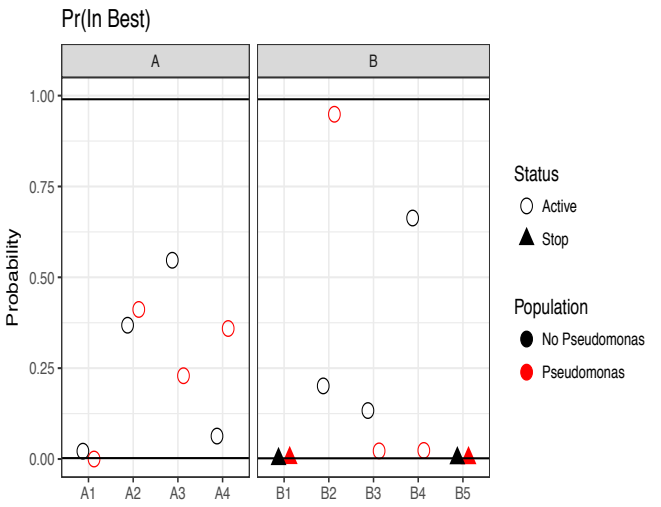


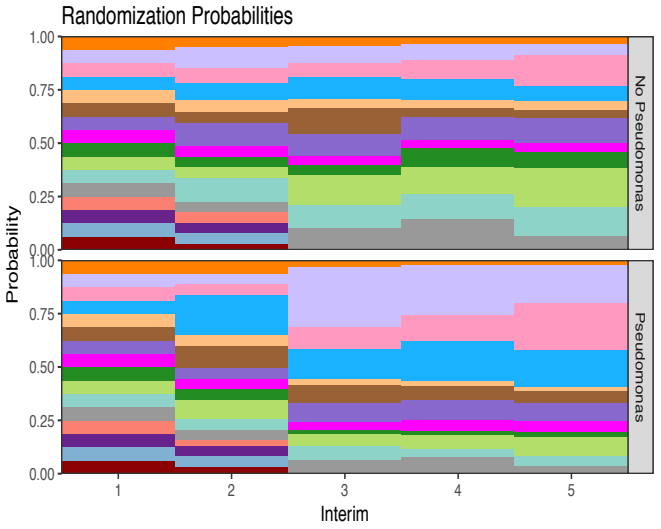


Interim 5, N=1250

Look #5: N = 1250

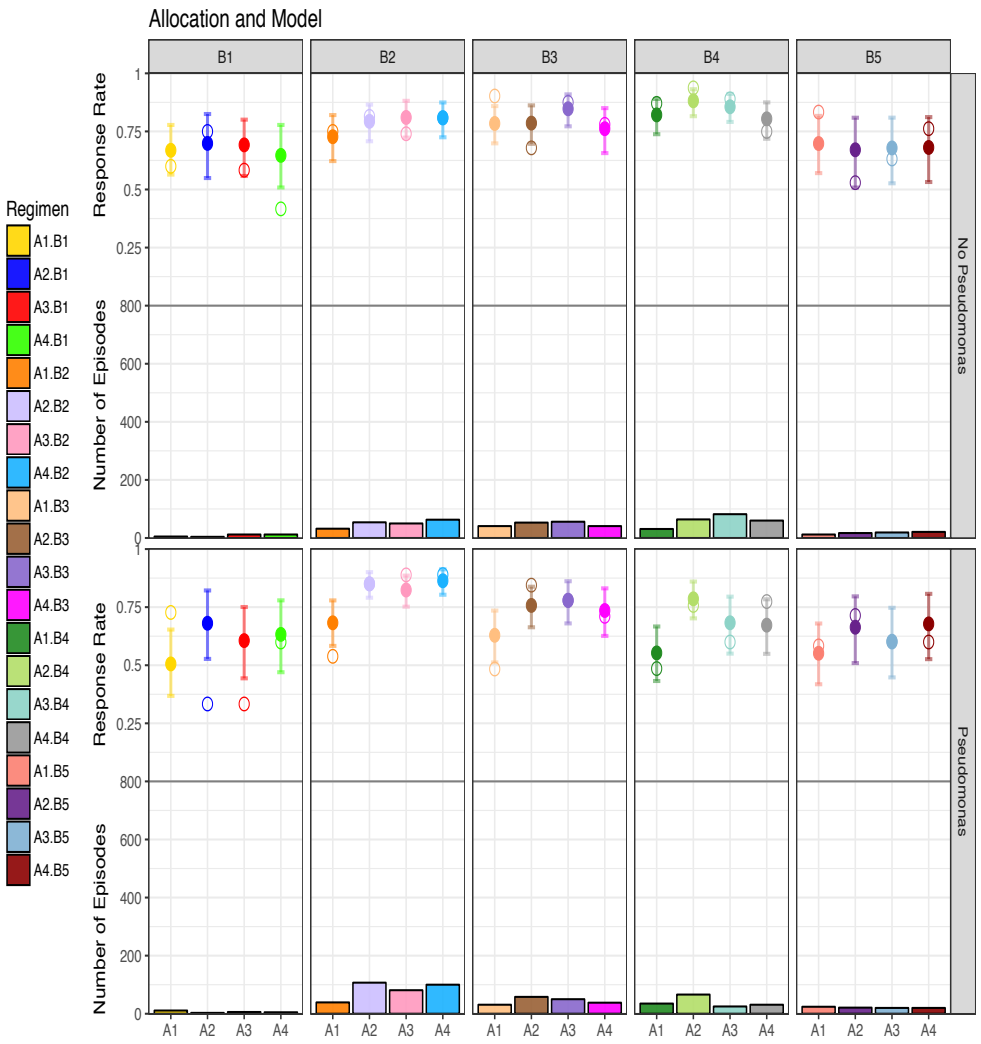


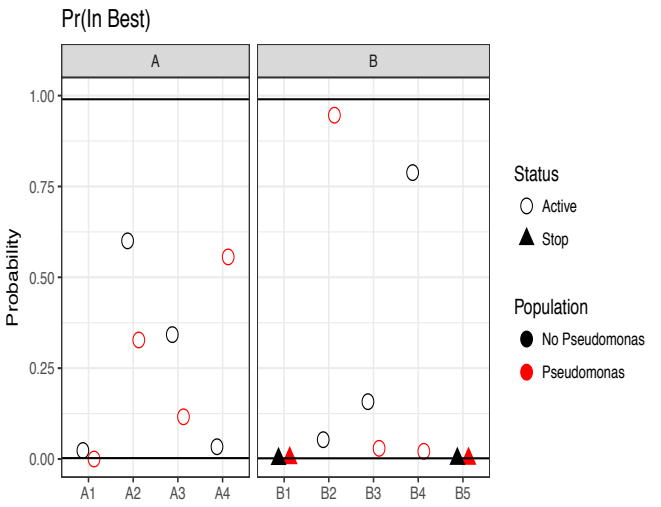


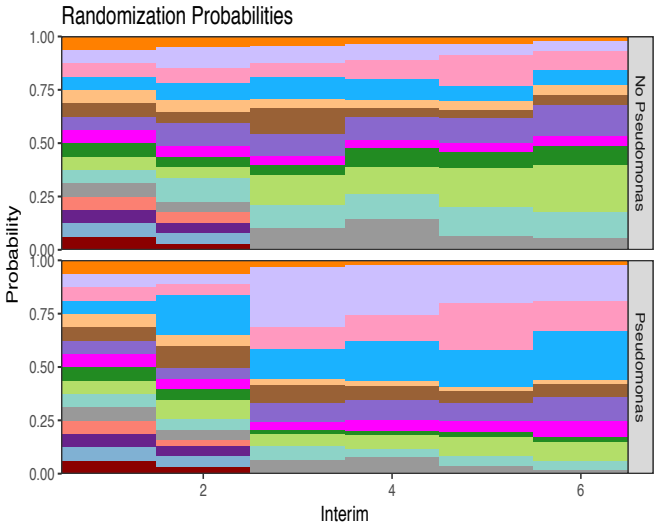


Interim 6, N=1500

Look #6: N = 1500

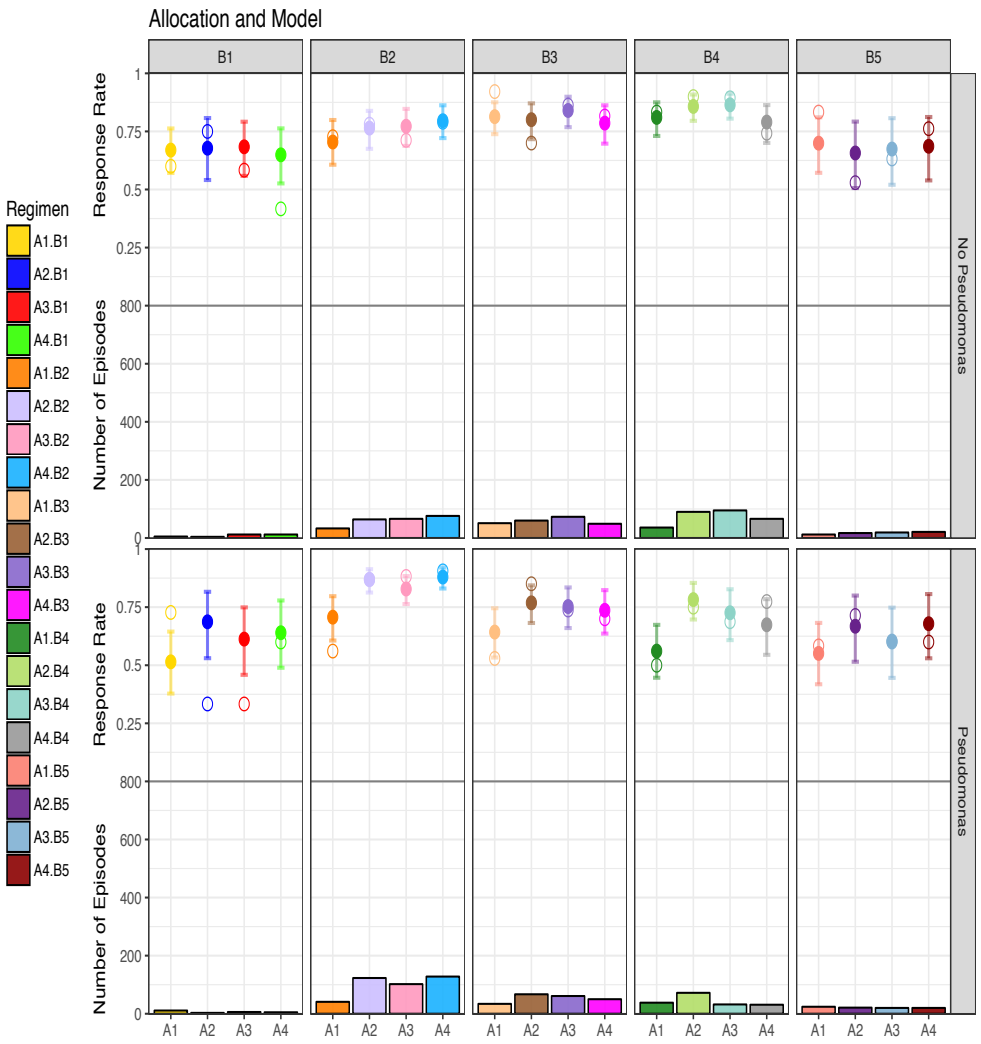


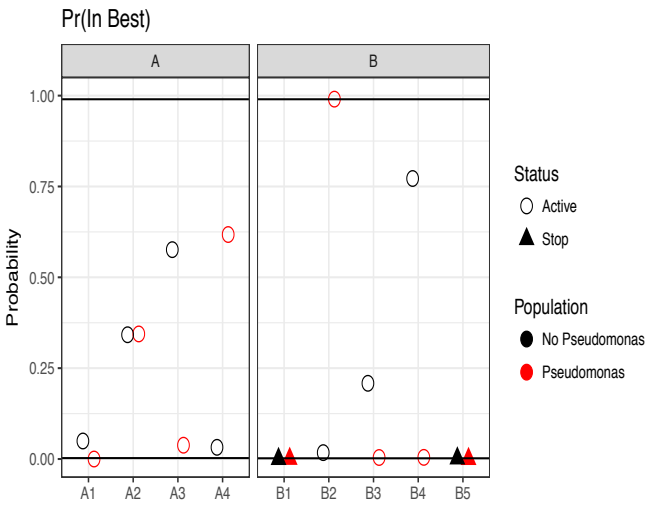


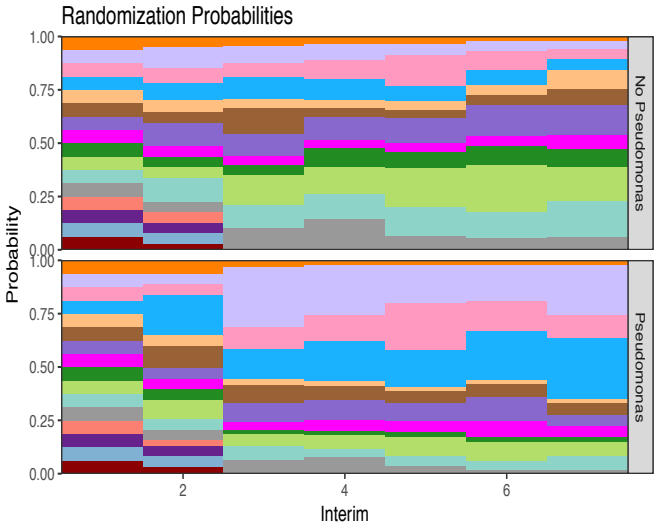


Interim 7, N=1750

Look #7: N = 1750

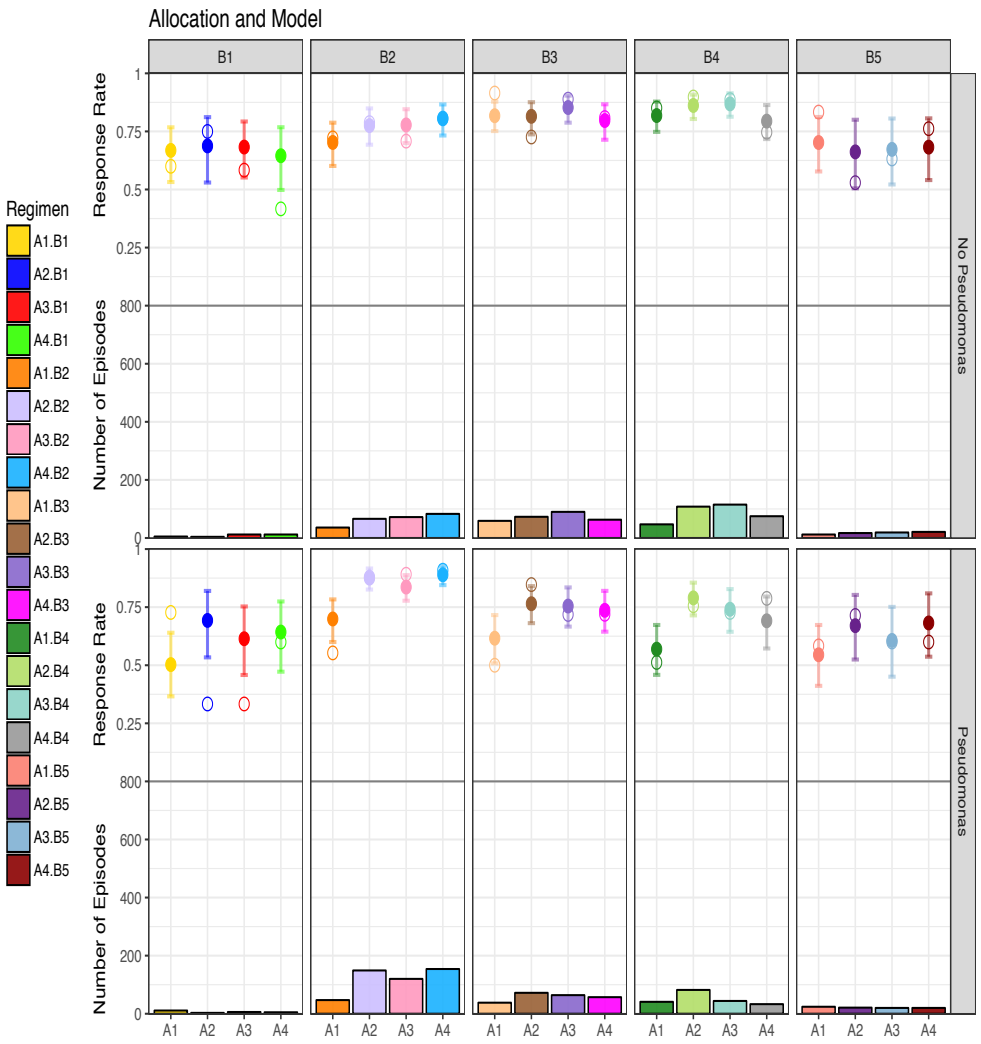


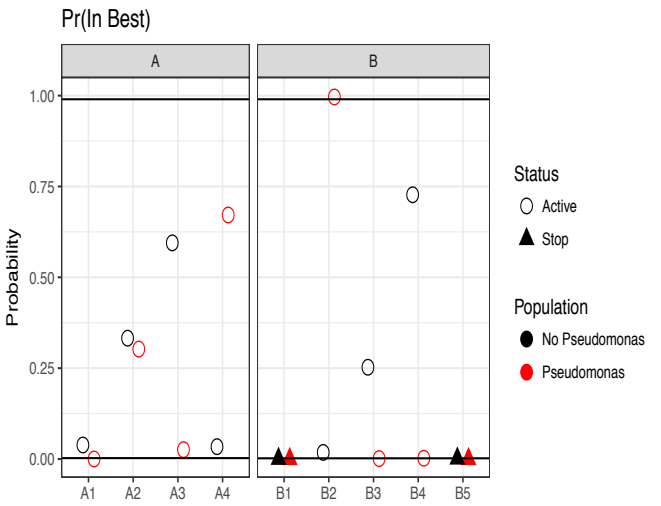


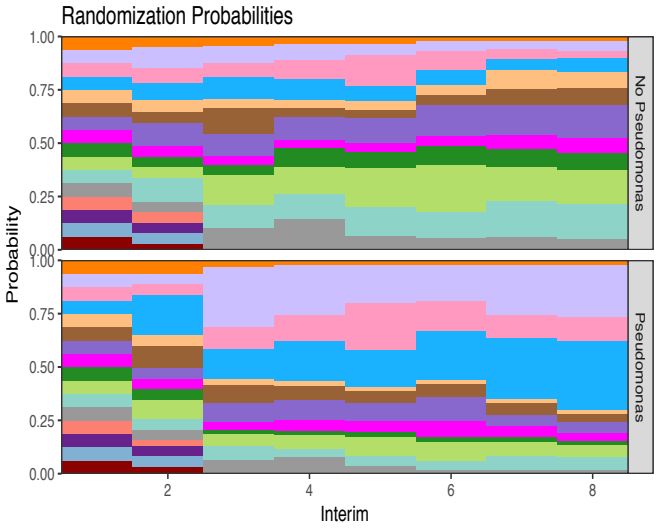


Interim 8, N=2000

Look #8: N = 2000

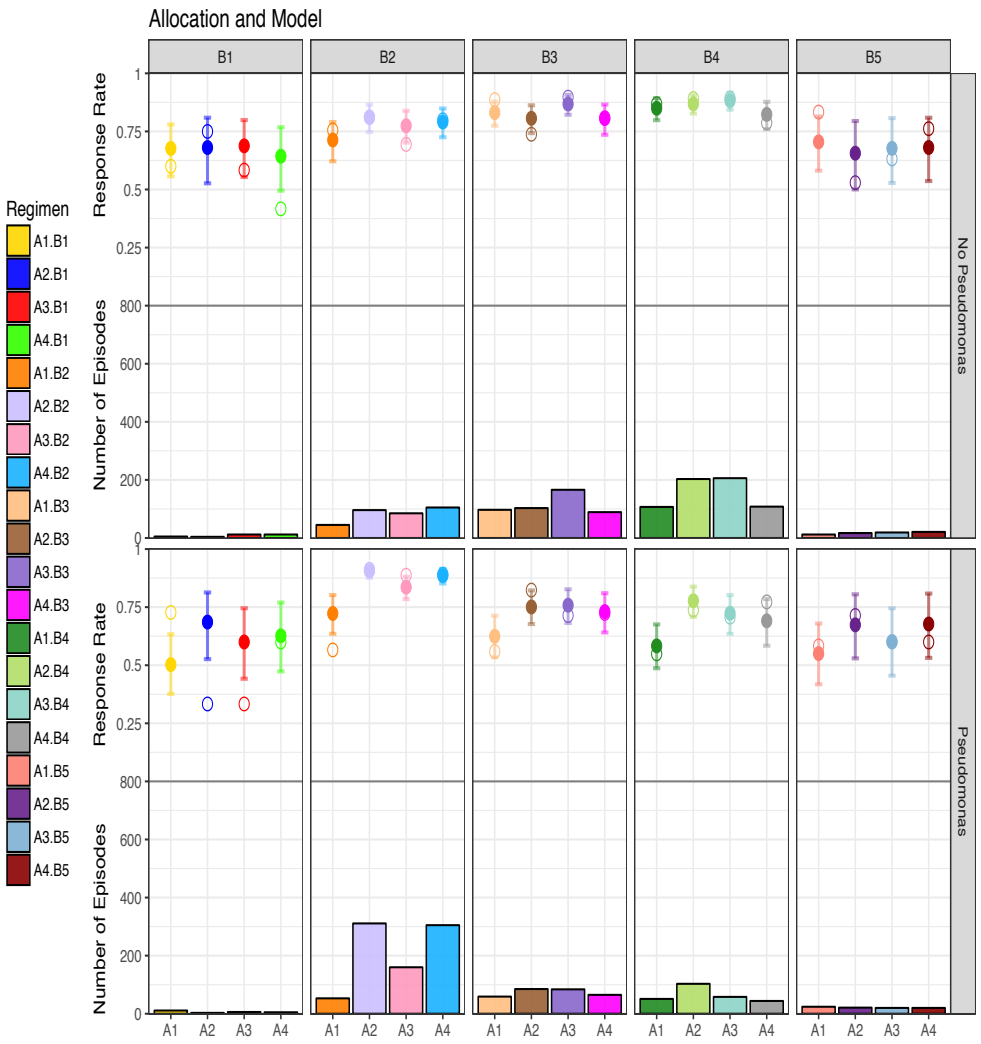


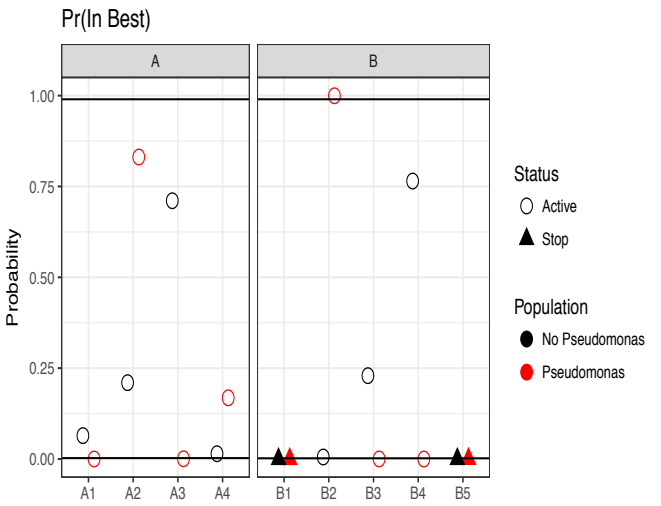


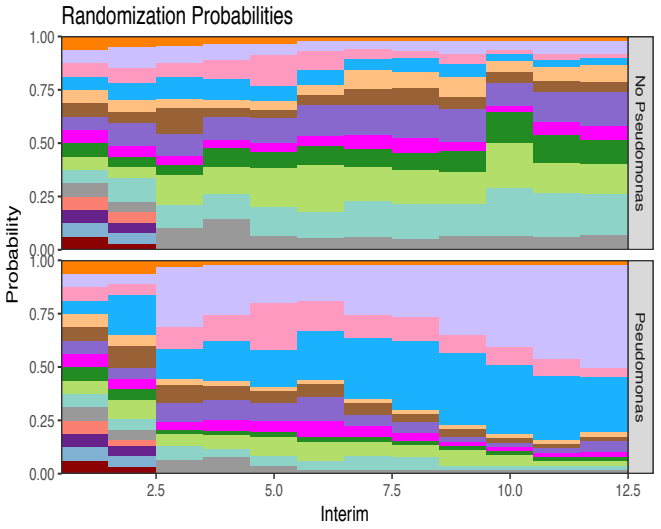


Interim 12, N=3000

Look #12: N = 3000

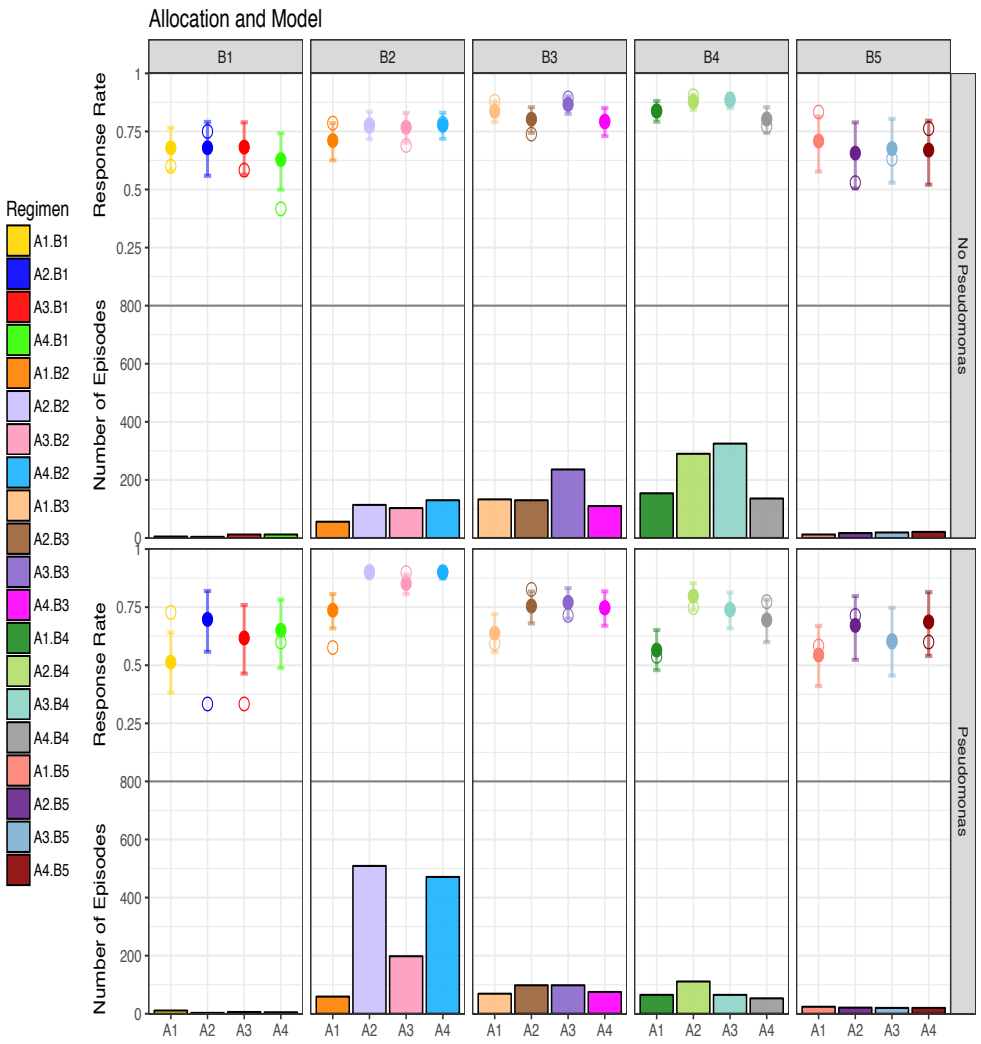


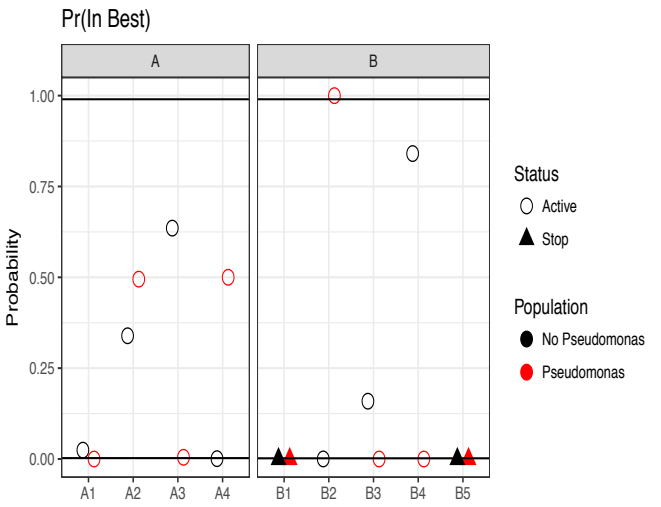


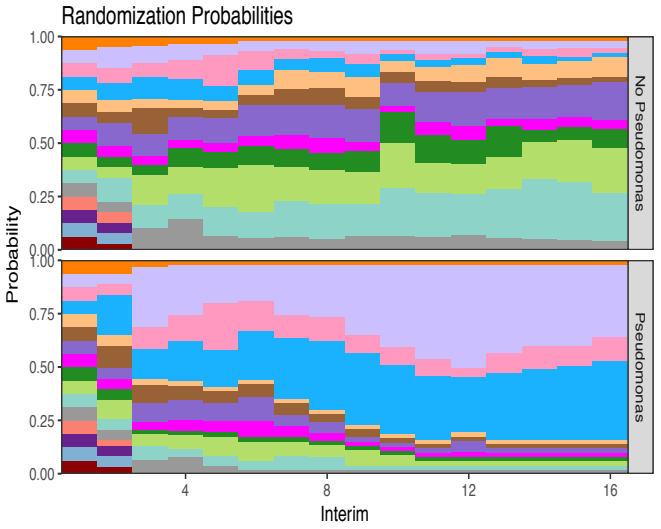


Interim 16, N=4000

Look #16: N = 4000

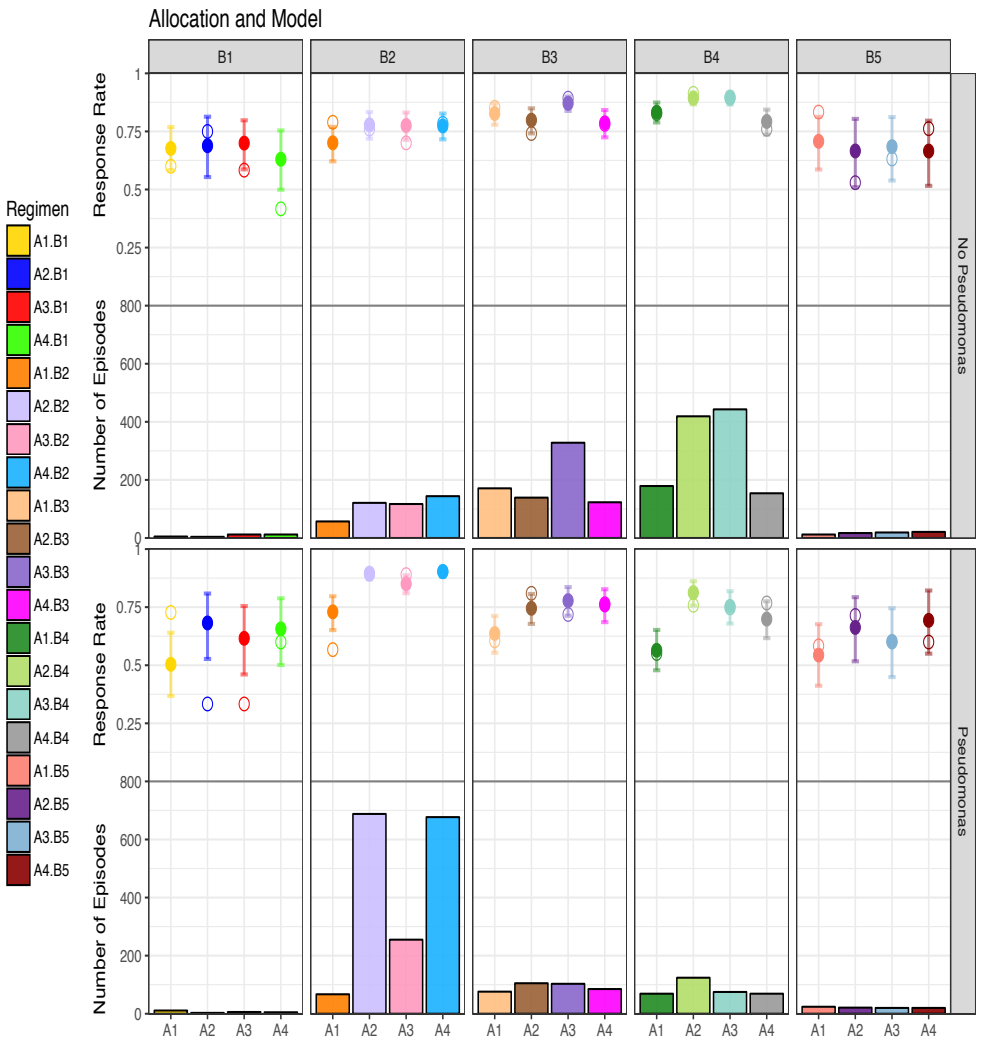


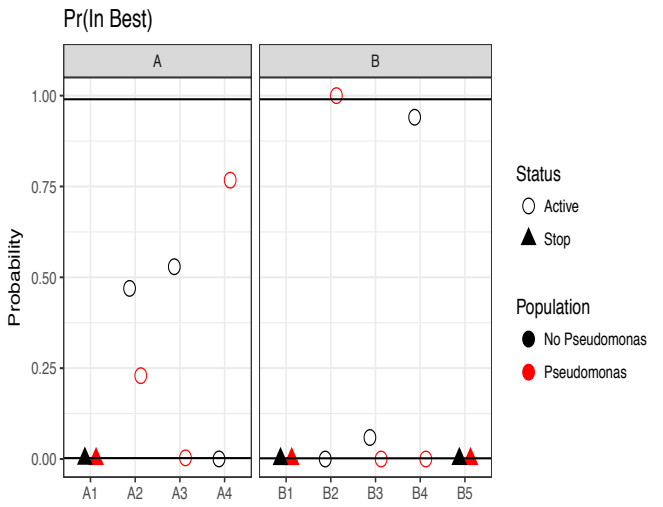


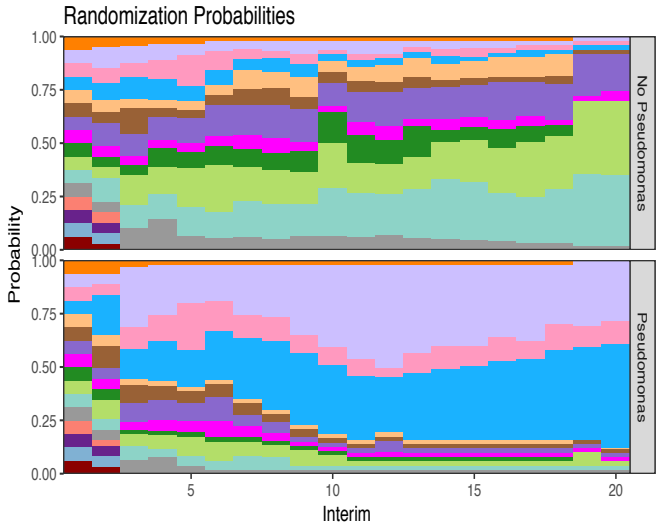


Interim 20, N=5000

Look #20: N = 5000







Clinical Trial Simulator

We need to run many simulations, often around 10,000 for the null model and around 5,000 for other scenarios. These can be summarised to determine the trial operating characteristics.

- False positive (Type 1) error rate
- Power (1-Type II error rate)
- Average sample size for each scenario

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Clinical Trial Simulator

But this is just one scenario – now simulate all possible scenarios.

And factor in all those other parameters:

- Accrual rate
- Distribution for the control response
- Distribution for prior (often weakly informative)
- Number of interims
- Thresholds for trial success & futility
- Minimum number of patients with endpoint before declaration of early success/failure

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Clinical Trial Simulator

It is easy to see how the trial simulations are such a core component in platform trials.

The FDA chaired a seminar on 20 March 2018 to discuss innovative designs, predominantly complex adaptive designs, in drug development. What came across clearly was the need to pre-specific everything in the trial simulations and in the protocol.

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Next step: integrated eHealth platform trials

Integrated eHealth records & clinical trials

BioMed Research International
Volume 2015 (2015), Article ID 707891, 8 pages
http://dx.doi.org/10.1155/2015/707891

AIMS

(1) assist in the assessment of trial feasibility,

(2) aid patient recruitment,

(3) allow automated preloading of clinical information from a patient's EHR to a trial data collection form, and

(4) use EHR information in the reporting of Serious Adverse Events (SAE) during a trial.

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Next step: integrated eHealth platform trials

BioMed Research International

Abstract

Background. The conduct of clinical trials is increasingly challenging due to greater complexity and governance requirements as well as difficulties with recruitment and retention. Electronic Health Records for Clinical Research (EHR4CR) aims at improving the conduct of trials by using existing routinely collected data, but little is known … working practices. … tion of the proje… uctured interview… HR4CR platform. … onduct of clinica… could enhance … mation governan… that it could red… cy, and informati…

"… belief that it could reduce workloads and improve the conduct and quality of trials. However, data security, privacy and information governance issues need to be carefully managed in the development of the platform."

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