Platform Trials for Evaluating Multimodal Therapies for Brain Disorders

Roger J. Lewis, MD, PhD
Department of Emergency Medicine
Harbor-UCLA Medical Center
David Geffen School of Medicine at UCLA
Los Angeles Biomedical Research Institute
Berry Consultants, LLC

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- Berry Consultants, LLC
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  - Octapharma

Background

- Multimodal ≡ combination treatments
- Treatment options may be grouped by “modes,” e.g., drugs, behavioral
- Goal is to efficiently and accurately detect and quantify synergy of treatments, i.e., interactions
- Major challenges
  - Subgroups and heterogeneity of treatment effect
  - Confounding by patient, clinical, and disease characteristics
  - Inadequately informative endpoints

Thesis

- Evaluating multimodal therapies in brain disorders is a complex problem that will be excruciatingly slow, costly, and inefficient unless we adopt innovative strategies to tackle this complexity

Motivation for Adaptive Trials

- Once patients begin to be enrolled in a clinical trial and their outcomes become known, information accumulates that reduces uncertainty regarding optimal treatments
- Adaptive clinical trials are designed to take advantage of this accumulating information, by allowing modification to key trial parameters in response to accumulating information and according to predefined rules, to gain efficiency or achieve other goals (e.g, effective treatment)

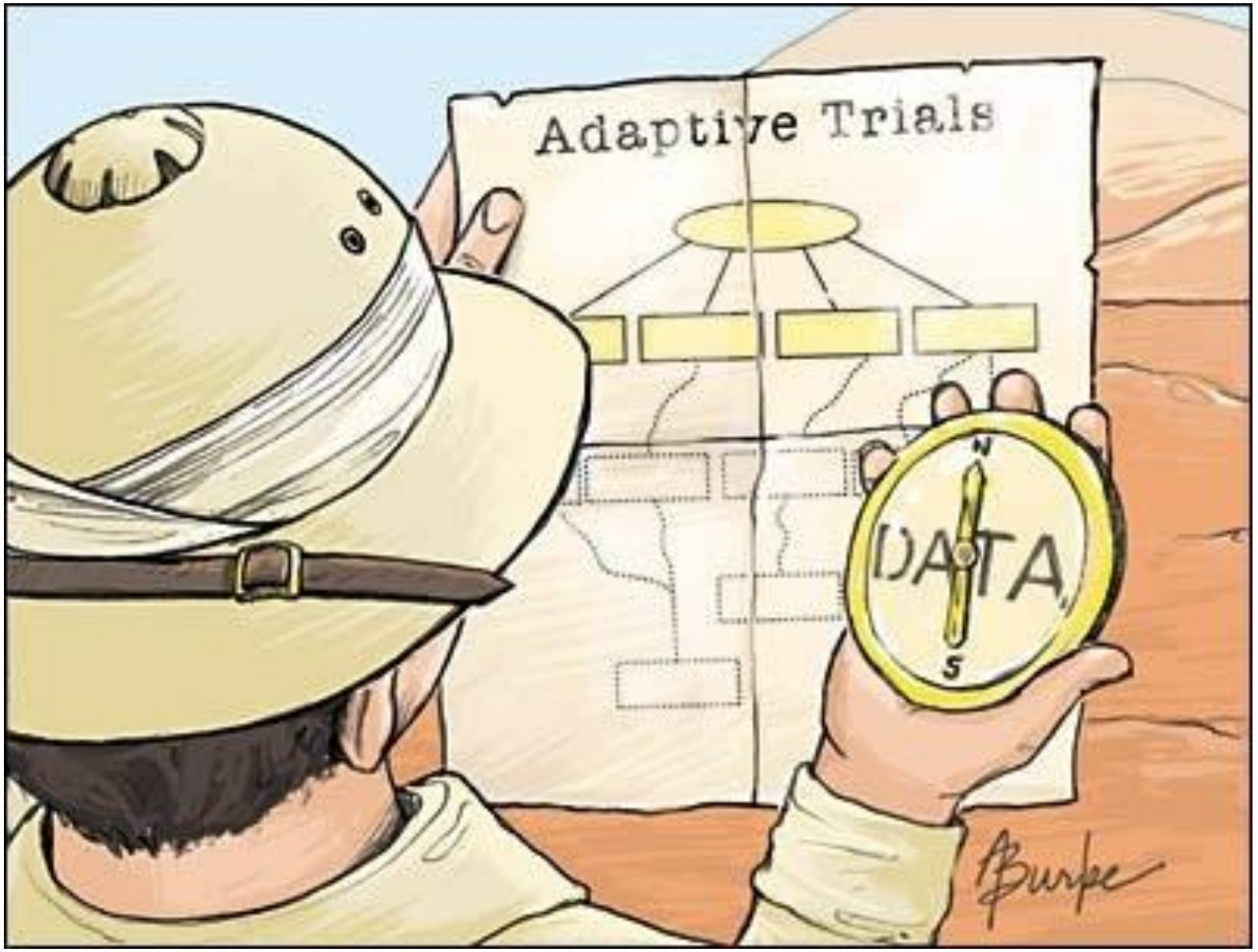
Adaptive Clinical Trials

A Partial Remedy for the Therapeutic Misconception?

William J. Meurer, MD, MS
Roger J. Lewis, MD, PhD
Donald A. Berry, PhD

THERE IS A COMMON "THERAPEUTIC MISCONCEPTION" among patients considering participation in clinical trials.[1] Some trial participants and family members believe that the goal of a clinical trial is to improve their outcomes—a misperception often reinforced by media advertising of clinical research.[2] Clinical trials have primarily scientific aims and rarely attempt to collectively improve the outcomes of their participants. The overarching goal of most clinical trials is to evaluate the effect of a treatment on disease outcomes.[3] Comparisons are usually

Although knowledge regarding the relative effectiveness of the treatments involved accumulates over the course of a clinical trial, beginning with a state of equipoise and having high confidence near the end, fixed assignment ensures that this information is ignored. The result is that a fixed proportion of patients will receive potentially inferior therapy—whichever therapy that turns out to be—assuming there are differences in efficacy of the treatments in the trial. The primary scientific goal of a clinical trial should not be compromised, but interim information available in a trial could be used to improve the outcomes of trial participants, especially those who enroll later in the trial. Using accumulating information can increase the probability, but not guarantee, that future trial participants are assigned to the study group with a better expected outcome



JAMA 2006;296:1955-1957.

Response-adaptive Randomization

- **Response-adaptive randomization** to improve important trial characteristics
- May be used to address one or more of:
  - To improve subject outcomes by preferentially randomizing patients to the better performing arm
  - To improve the efficiency of estimation by preferentially assigning patients to treatments in a manner that increases statistical efficiency
  - To improve the efficiency in addressing multiple hypotheses by randomizing patients in a way that emphasizes sequential goals
  - Includes arm dropping

Platform Trial

- An experimental infrastructure to evaluate multiple treatments, often for a group of diseases, and intended to function continually and be productive beyond the evaluation of any individual treatment
  - Designed around effective treatment of the disease rather than a single treatment
  - Dynamic list of available treatments, assigned with response-adaptive randomization
  - Preferred treatments may depend on health system, patient, or disease-level characteristics

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 combinations of treatments, in heterogeneous patient

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 between a traditional clinical trial and a platform trial

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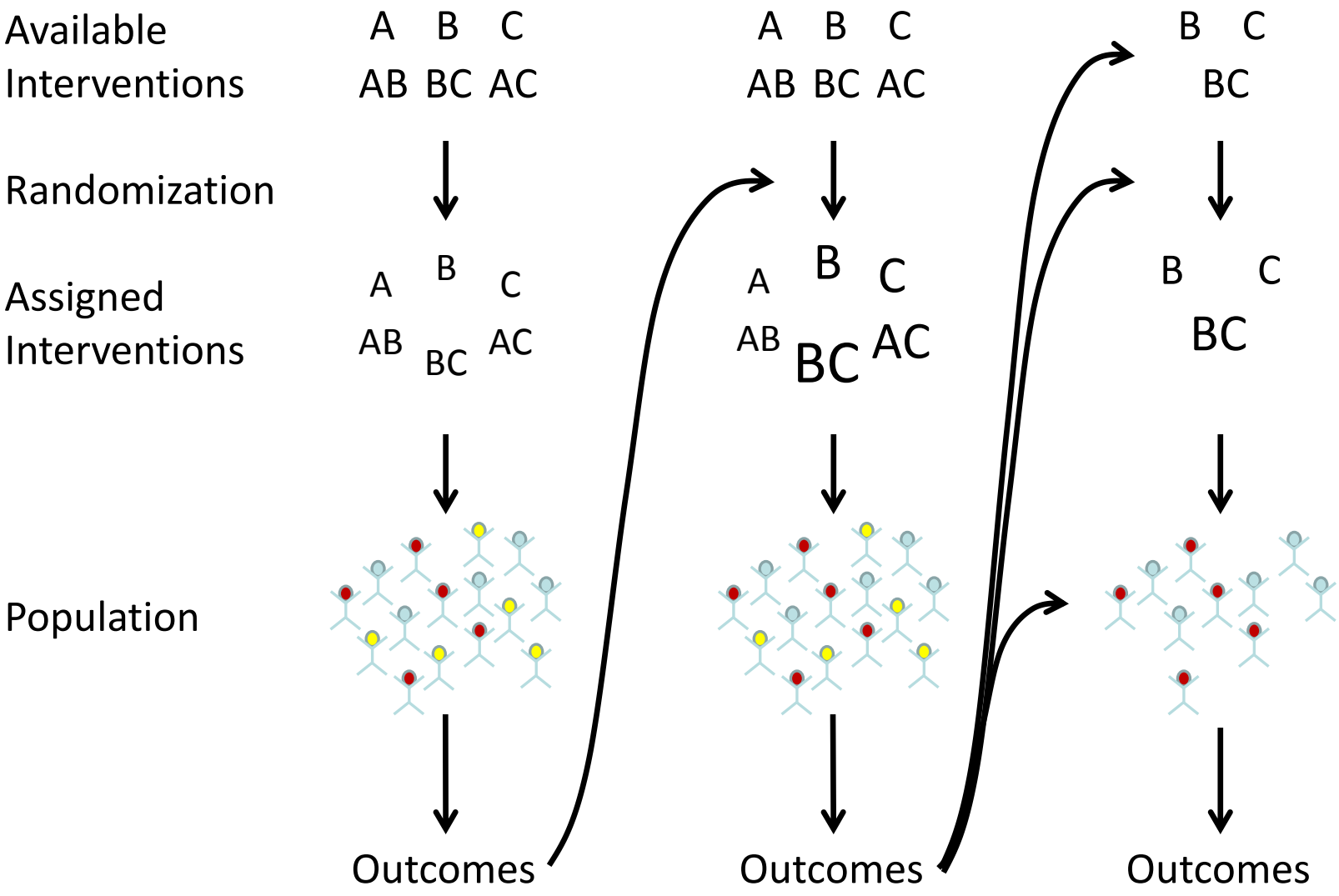
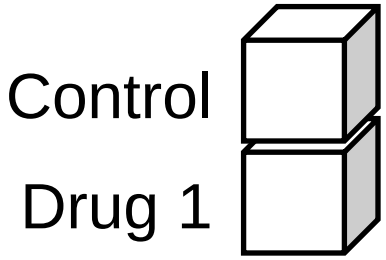
Evolution of a Platform Trial over Time



Building a Platform Trial



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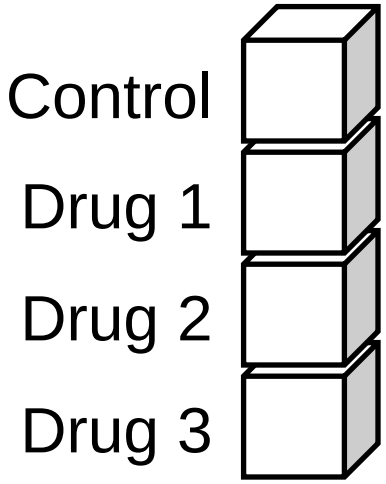

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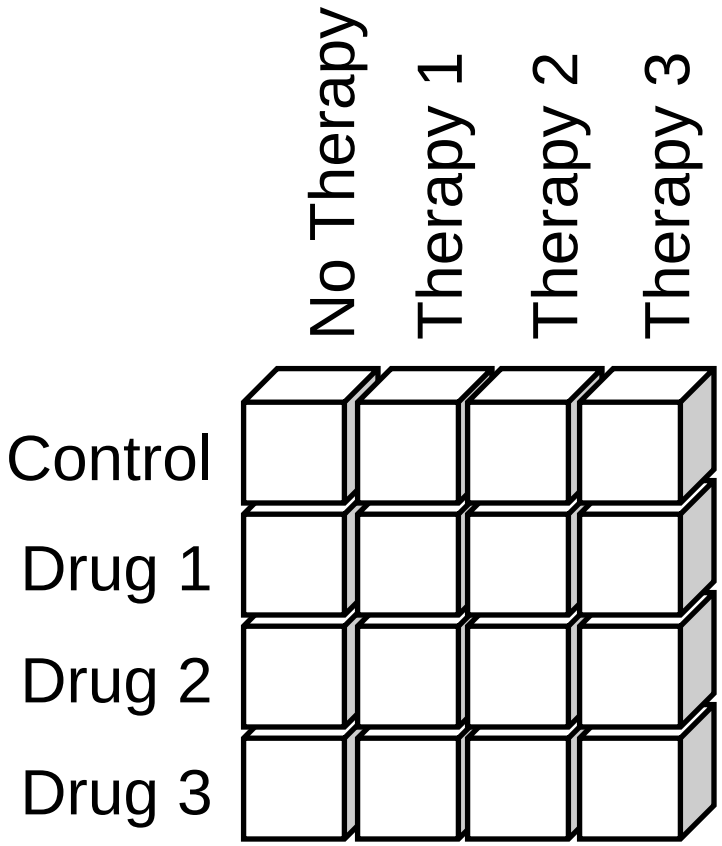
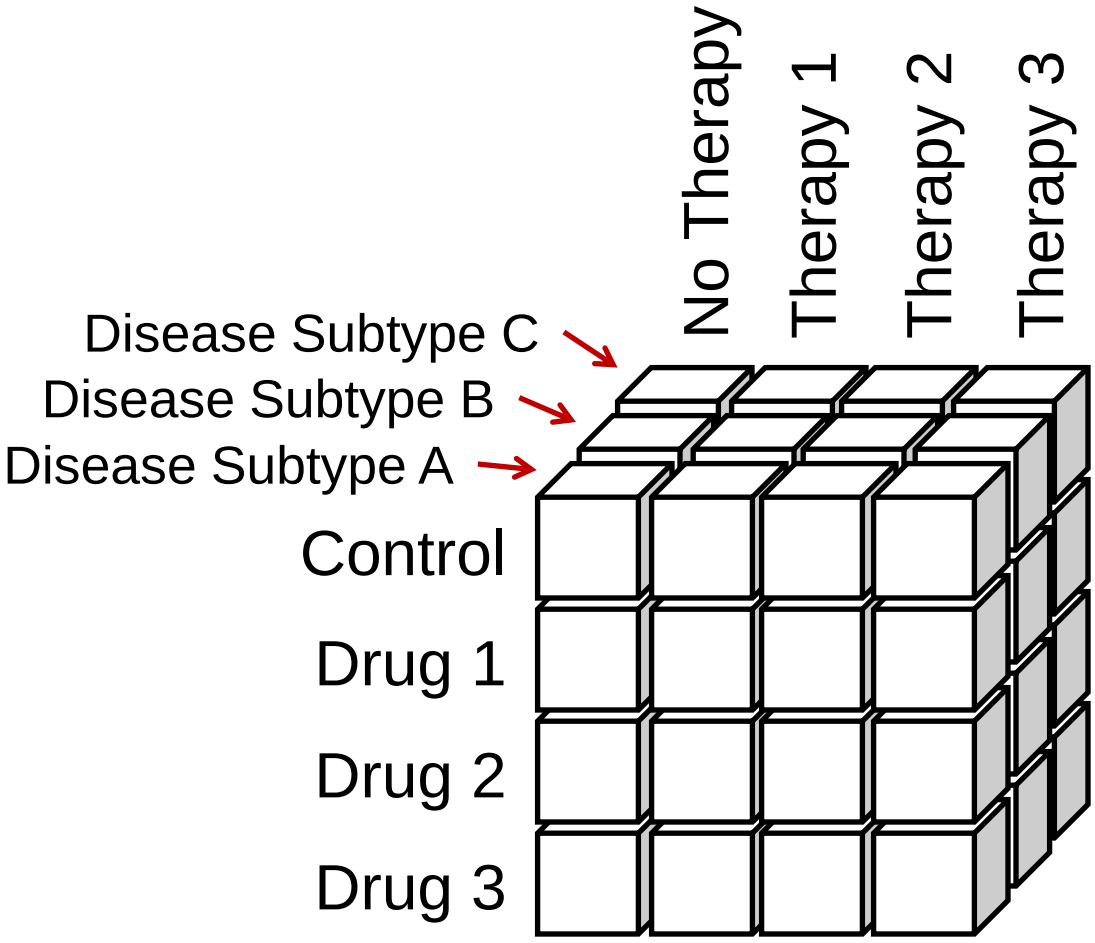


Building a Platform Trial



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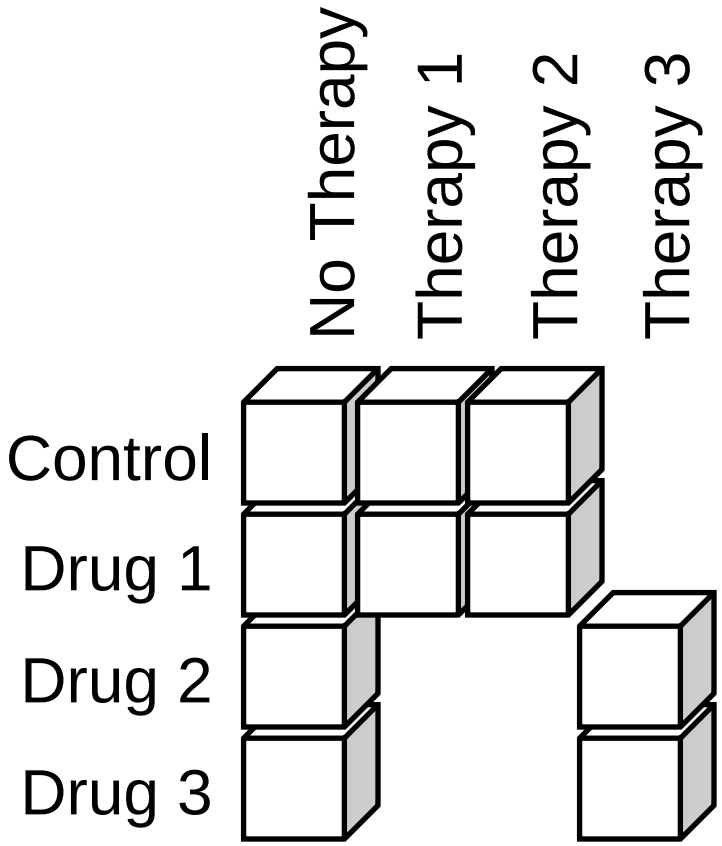
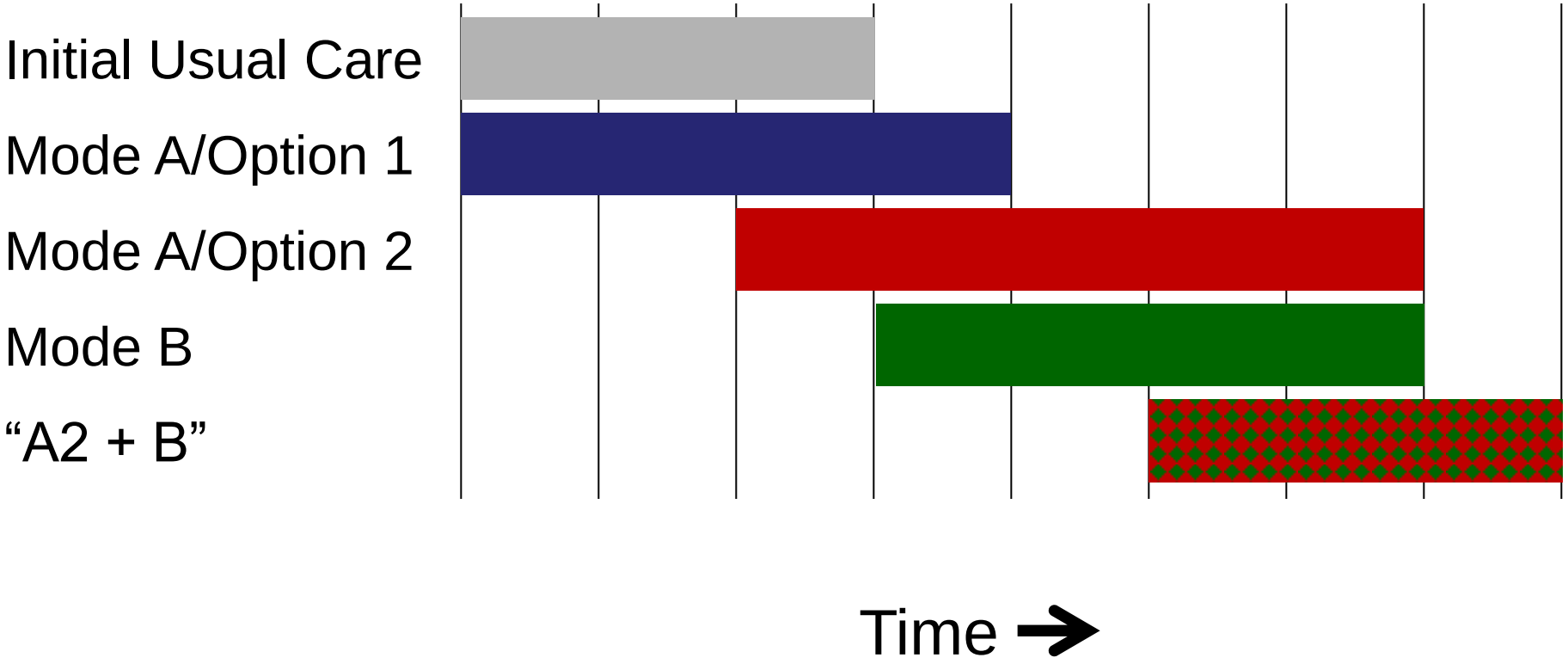


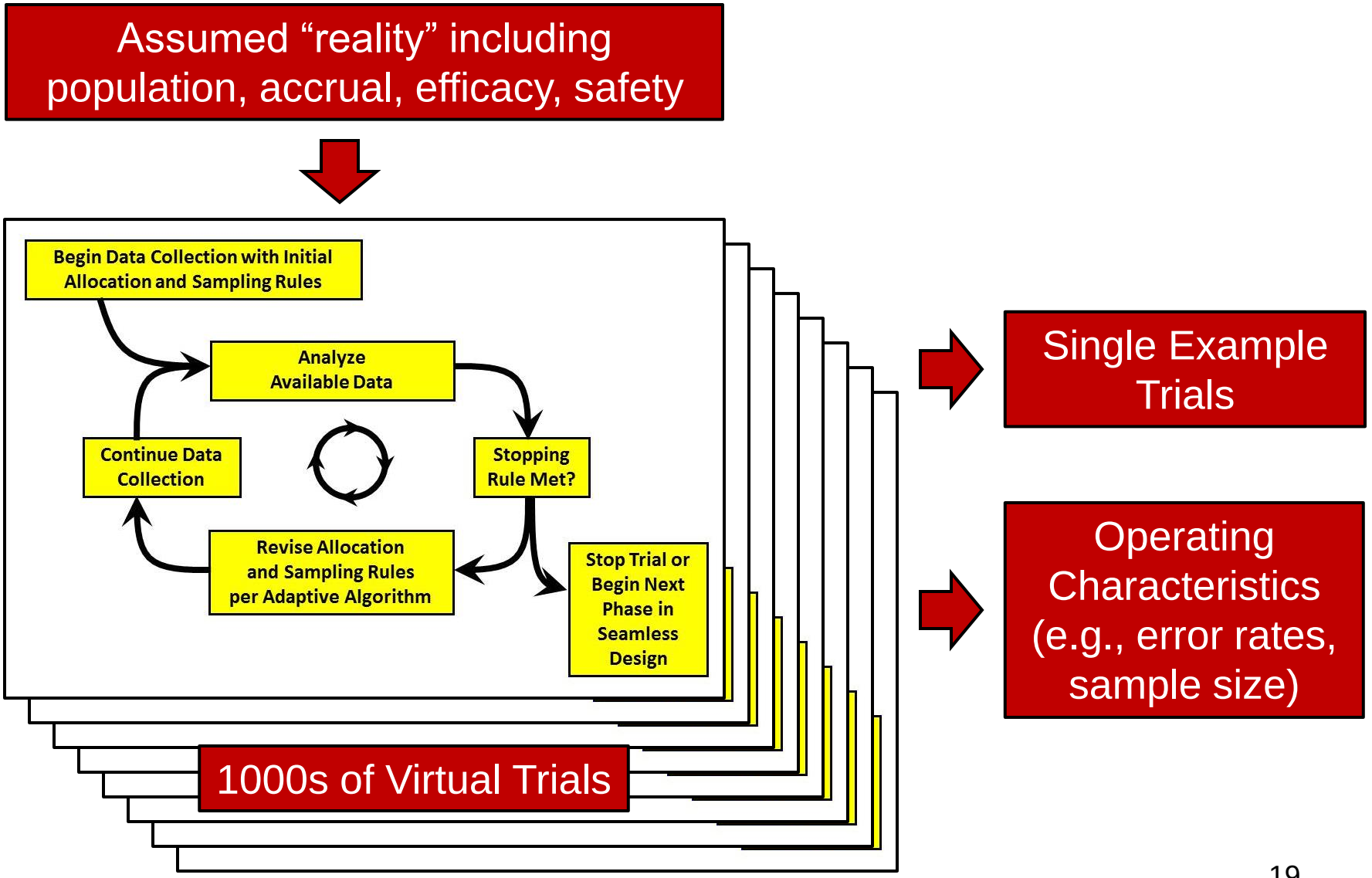
Platform Trial



Potential Statistical Efficiencies

- Adaptations
  - Response adaptive randomization
  - Enrichment
- Statistical Innovations
  - Treatment heterogeneity models (“borrowing”)
  - Hierarchical Models
  - Maximally informative endpoints

Trial Simulation



Welcome to EPAD

Collaborative research to better understand the early stages of Alzheimer's disease and prevent dementia before symptoms occur.

The EPAD project is part of a global effort in the fight against Alzheimer's disease and is a major European initiative to create a novel environment for testing numerous interventions targeted at the prevention of Alzheimer's dementia.

Watch Dr. Simon Lovestone explaining the IMI-EPAD project. >

Latest News

EPAD and EMIF partners voice concern for future of dementia research if Britain leaves EU

2016-06-14

EPAD
European Prevention of Alzheimer's Dementia Consortium

- In December 2013 Innovative Medicines Initiative (IMI) put out a call (53M) for building a platform trial for the prevention of Alzheimer's
- Public/Private Initiative
- Longitudinal Cohort Study -> Randomized adaptive platform trial
- Multiple agents in phase II setting
  - Meet biomarker target
  - Meet cognitive POC
    - Stratified by subgroups
  - Disease modeling

EPAD
European Prevention of Alzheimer's Dementia Consortium

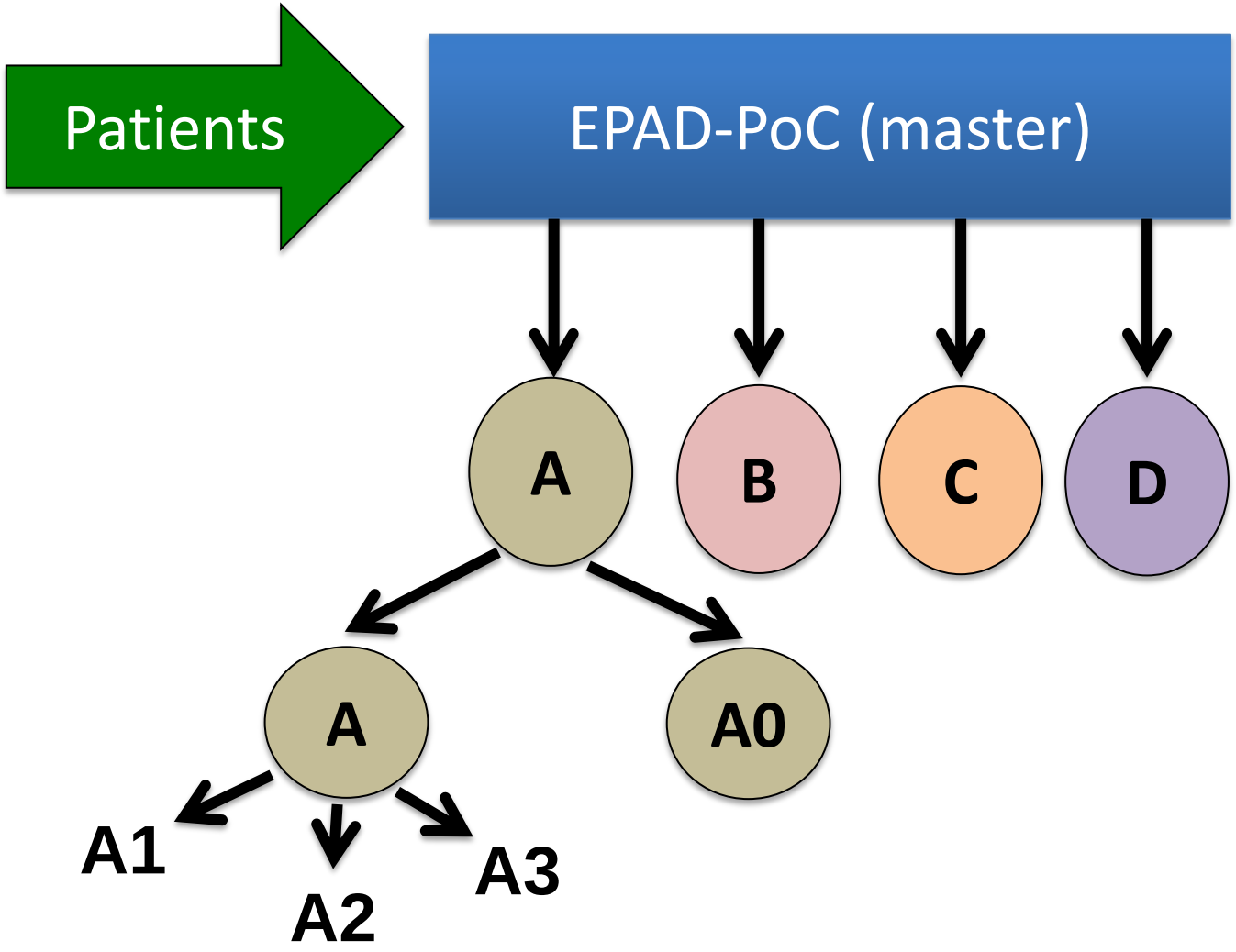
PoC Statistical Concepts: A double-blind, randomized, placebo-controlled, adaptive platform, Proof-of-Concept clinical trial of multiple interventions for the secondary prevention of Alzheimer's Dementia in subjects from Preclinical to Prodromal stages of Alzheimer's Disease

Scott Berry

Barcelona Global Assembly

May 2016

Randomization



NBDA
National Biomarker Development Alliance

"collaboratively creating the standards for evidence-based end-to-end biomarker development to advance precision medicine"

GBM AGILE

About GBM AGILE and the National Biomarker Development Alliance (NBDA)

GBM AGILE is being developed through the National Biomarker Development Alliance (NBDA), a non-profit organization created as part of the Research Collaboratory at Arizona State University (ASU). The NBDA's mission is to collaboratively create standards-based end-to-end systems solutions for biomarker discovery, development and delivery to advance precision medicine. The NBDA operates through trans-disciplinary and trans-sector networks to develop new research networks and consortia that focus on "demonstration projects" that advance all aspects of biomarker research and applications – especially developing smarter and more efficient clinical trials. Although NBDA is generally disease agnostic, rare diseases like GBM are a focus for the Alliance since in most cases few if any biomarkers exist and most clinical trials fail. The NBDA is also engaged in advancing biomarkers through the FDA Biomarker Qualification Program and has several initiatives underway, including biomarkers that will be used in the GBM AGILE trial. Overall, the NBDA is dedicated to moving high quality, effective biomarkers through all phases of discovery, development and validation more rapidly and efficiently to ensure that the promise of precision (molecularly based) medicine will be available to all patients.

"A Story of Convergence, Commitment, Collaboration, and Compassion"

Glioblastoma Multiforme – GBM is the most common and aggressive form of adult malignant brain cancer. An enigmatic and deadly disease, GBM will be diagnosed in over 12,000 Americans this year and in tens of thousands more around the globe. Five-year survival for GBM is less than 5 percent (median survival is one year), and worse, these dismal statistics have not changed for decades. Although GBM is often referred to as a rare disease, its human and economic cost is staggering.

Help Support GBM AGILE

Individual Donations
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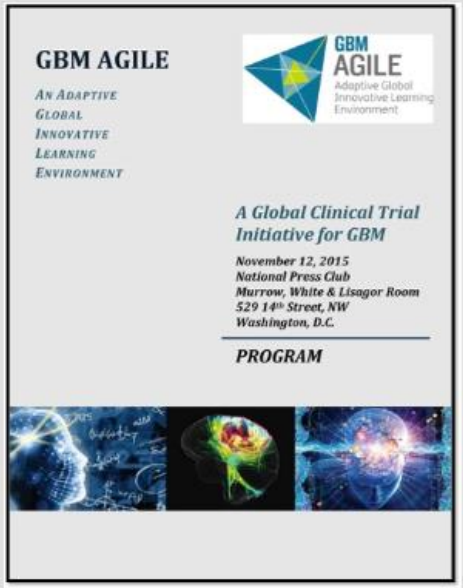
GBM Press Event Links

GBM AGILE
Adaptive Global Innovative Learning Environment

Launch Video
Press Release
Press Event Program
GBM AGILE Executive Committee
GBM AGILE Overall Trial Structure



GBM-AGILE

- “Using a Bayesian, statistically driven design and incorporating biomarkers to divide GBM into subclasses, GBM AGILE will more rapidly and efficiently test single agents and combinations of drugs, biologics, etc. Beyond increasing the numbers of agents tested and the speed of the screening process, effective therapies can progress quickly and more cost-effectively to “graduate” from GBM AGILE – and move on to a confirmatory phase 3 registration trial.”

Conclusions

- Platform trial designs can be used to efficiently "explore" the effects of multiple treatments and combination or "multimodal" therapies
- This may allow us to practically or more quickly demonstrate the benefits of multimodal therapies for brain disorders
- Important efforts are already underway in other medical domains (e.g., oncology, critical care, infectious diseases) and in the treatment of Alzheimer's dementia and glioblastoma multiforme