Adaptive Clinical Trial Designs for Remote Damage Control Resuscitation (RDCR)

Roger J. Lewis, MD, PhD
Professor and Chair
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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Motivation for Adaptive Trials

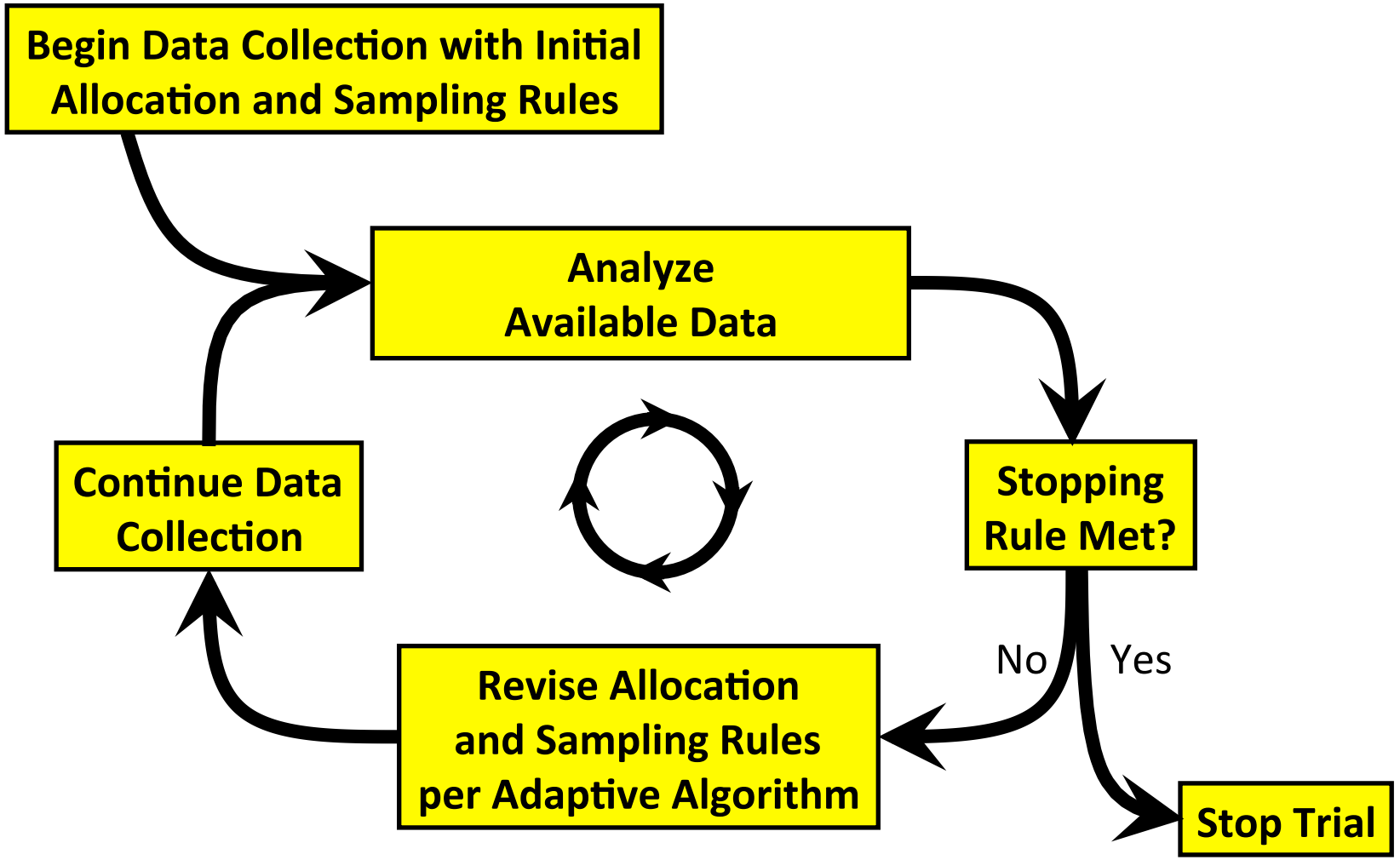
- When designing a trial there is substantial uncertainty (e.g., how best to treat subjects, what is the best measure of benefit, event rates, optimal dose, best duration, target population)
- This creates uncertainty in the optimal trial design
- Traditionally, all key trial parameters are defined and held constant during execution
- This can lead to increased risk of negative or failed trials, even if a treatment is inherently effective

Key Advantage of an Adaptive Trial

- Once patients are enrolled and their outcomes known, information accumulates that reduces this uncertainty
- 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 prespecified rules
- This can, in some circumstances, increase the probability of getting the right answer at the end of the trial

JAMA 2006;296:1955-1957.

The Adaptive Process



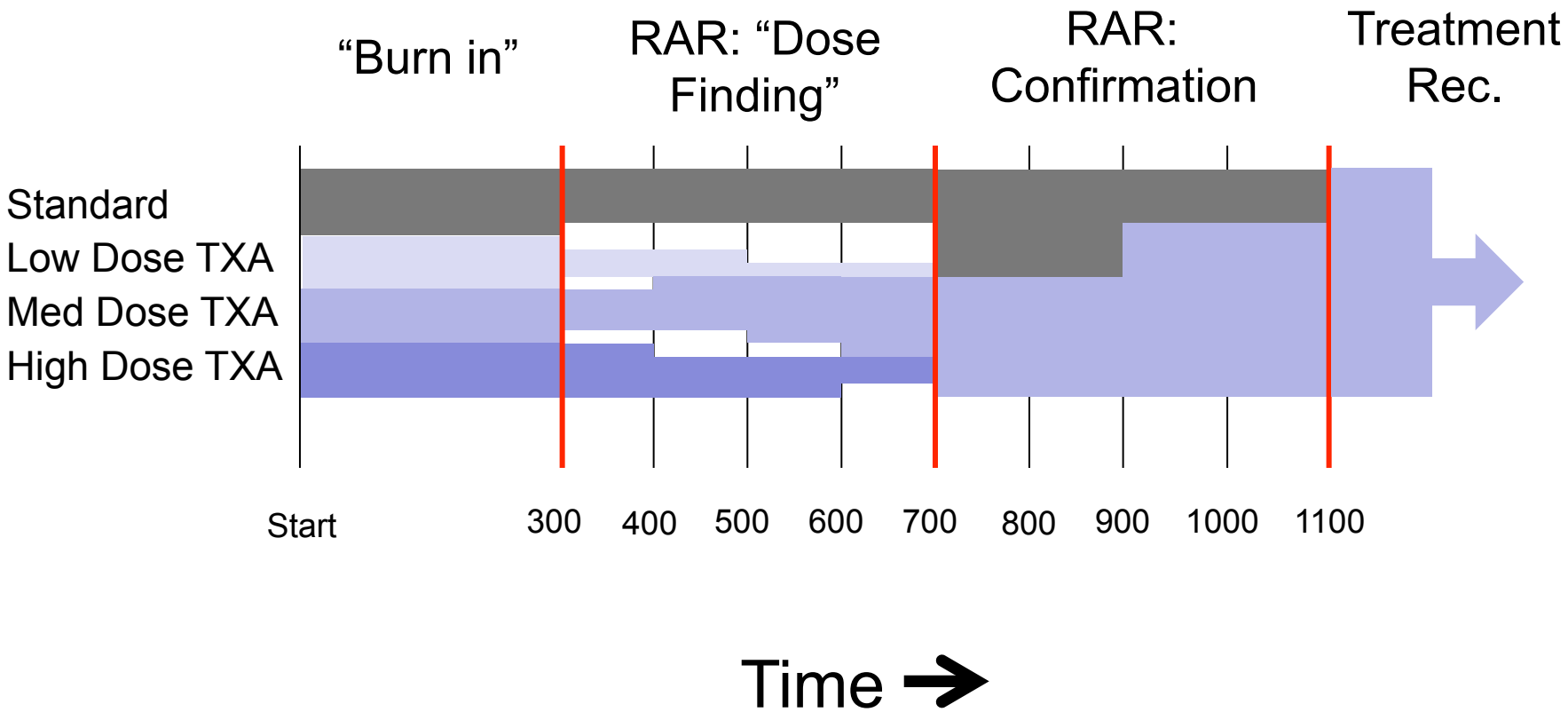
Adaptive Strategies

- Frequent interim analyses
- Explicit longitudinal modeling of the relationship between proximate and primary outcomes
- Hierarchical modelling (sharing/borrowing of information)
- Response-adaptive randomization
  - Includes adding or dropping of arms
- Explicit decision rules based on Bayesian predictive probabilities at each interim analysis
- Dose-response modeling
- Enrichment designs

Response-adaptive Randomization

- Response-adaptive randomization may be used:
  - To improve subject outcomes by preferentially randomizing patients to the better performing arm
  - To improve the efficiency of estimation by preferentially assigning patients to doses 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

Learning Strategy: Example



Adaptive Clinical Trials

A Partial Remedy for the Therapeutic Misconception?

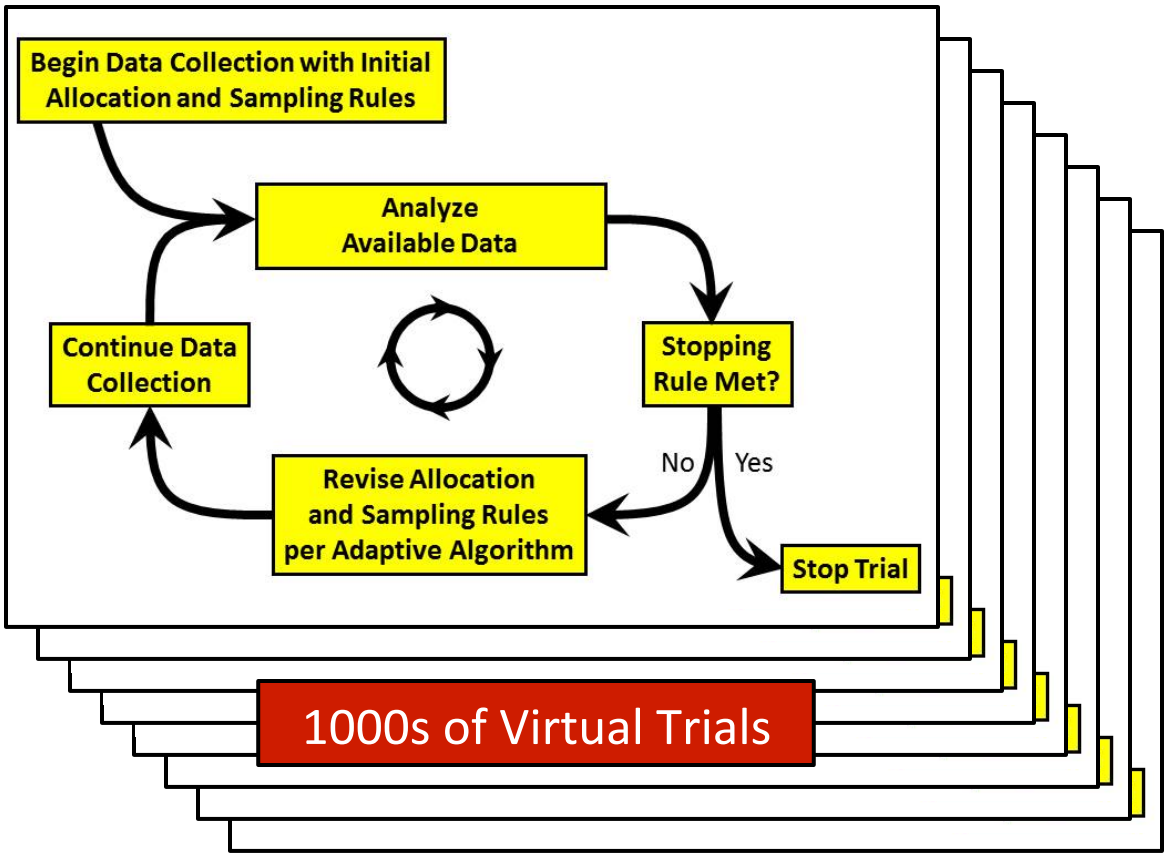
William J. Meurer, MD, MS
Roger J. Lewis, MD, PhD
Donald A. Berry, PhD

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

Trial Simulation

Assumed "reality" including population, accrual, efficacy, safety



Single Example Trials

Operating Characteristics (e.g., error rates, sample size)

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 a group of related diseases and treatments (e.g., traumatic injury patterns)
  - Dynamic list of available treatments, potentially assigned with response-adaptive randomization
  - Preferred treatments may depend on health system, patient, or disease-level characteristics

Terminology

- Master Protocol versus Platform Trial
- Other Terms
  - Umbrella trial
  - Basket trial
  - Perpetual trial
- Randomized, embedded, multifactorial, adaptive platform (REMAP) trial*

* Derek Angus

Guiding Principles

- All clinical trial approaches can yield the wrong answer
- Goal is to design a trial that minimizes that risk by assessing
  - Likelihood of the risk (e.g., type II error & low power, discordant treatment effects, drift in treatment effect over time)
  - Severity of the risk (e.g., bias versus an incorrect conclusion)
  - Ability of different approaches to mitigate risk
  - Ability to implement the trial as designed

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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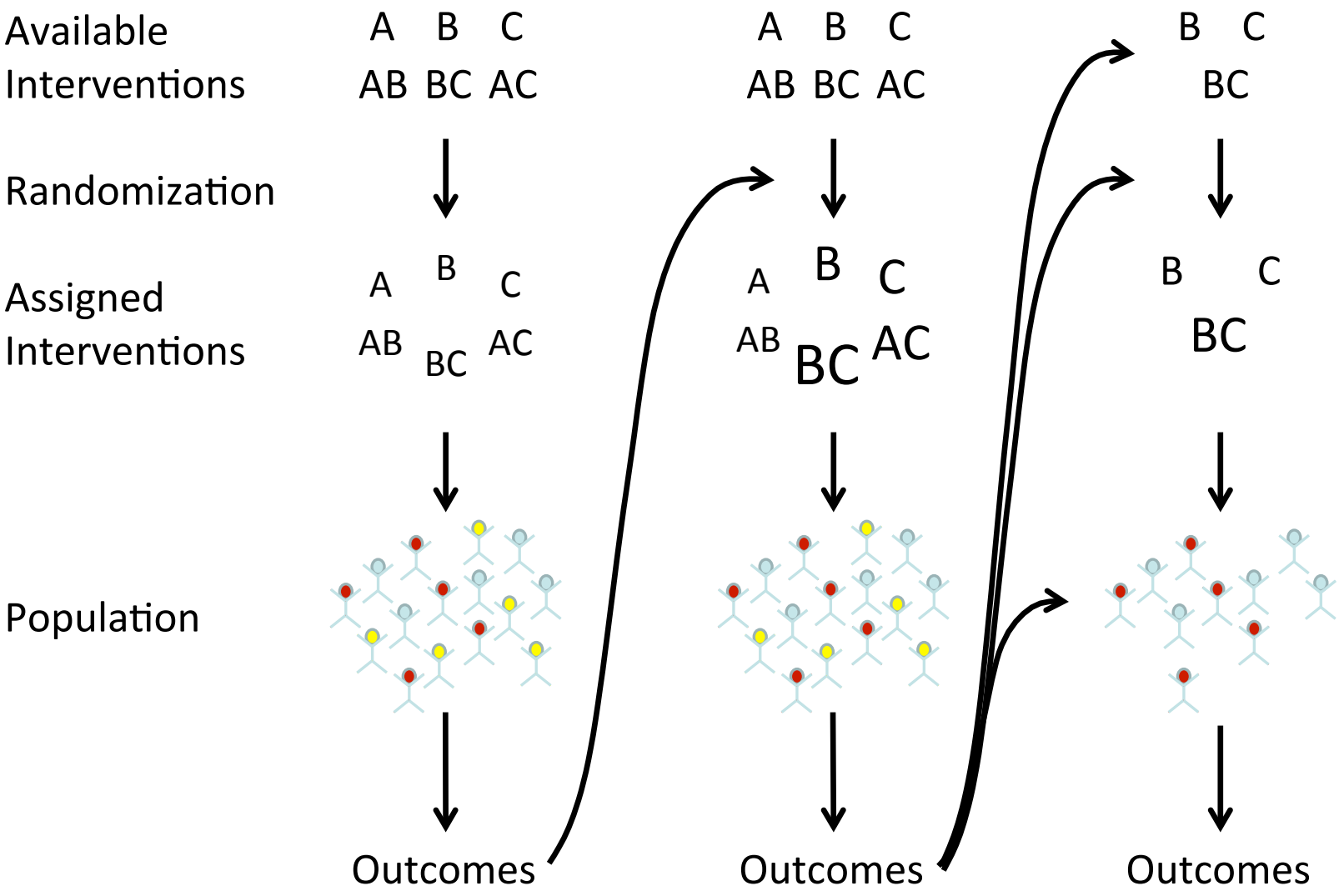
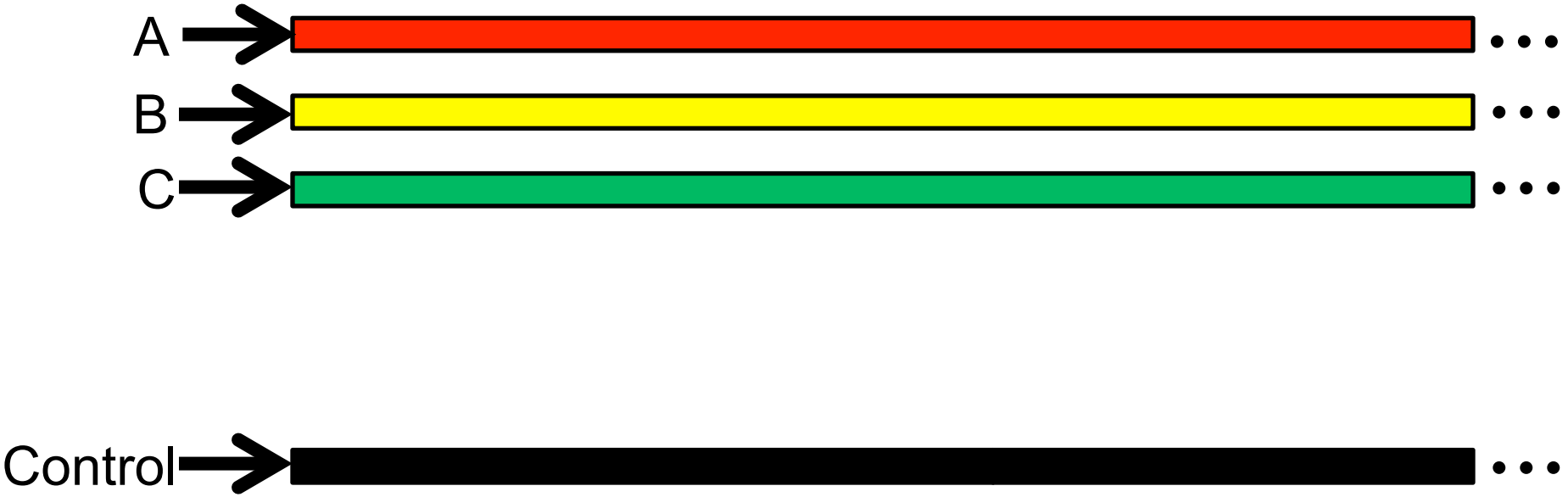
Evolution of a Platform Trial over Time



Potential Features of a Platform Trial



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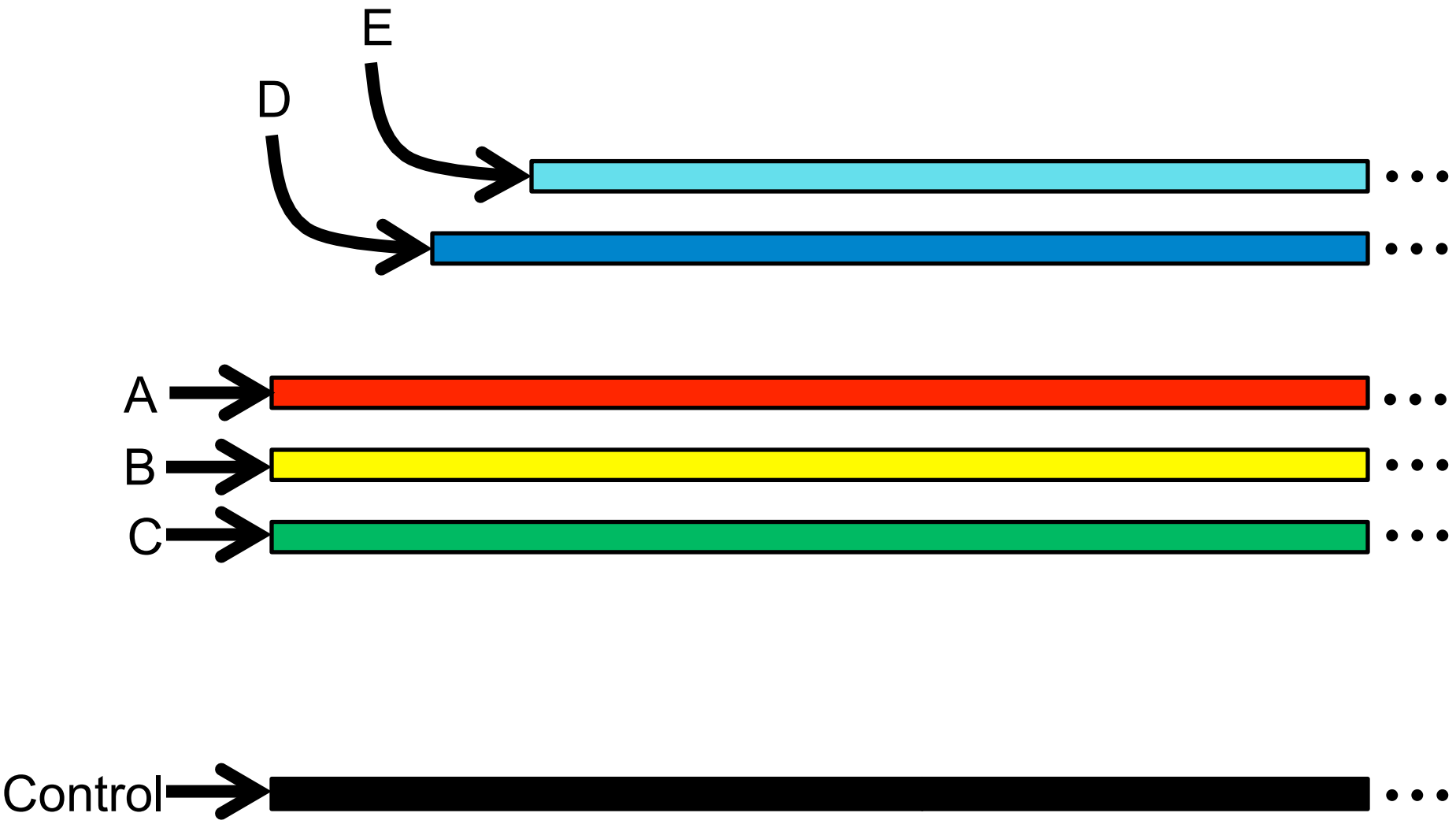

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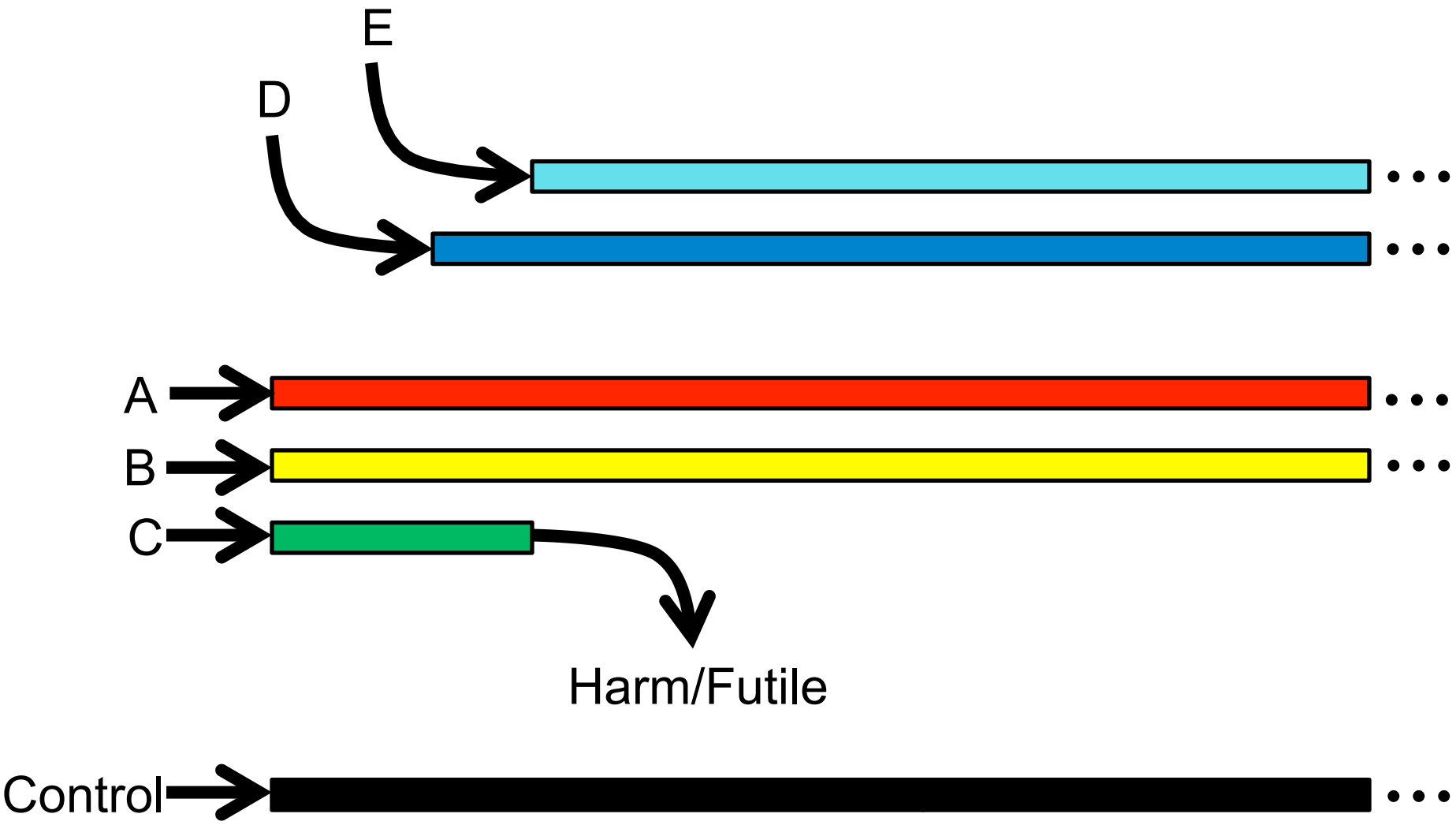

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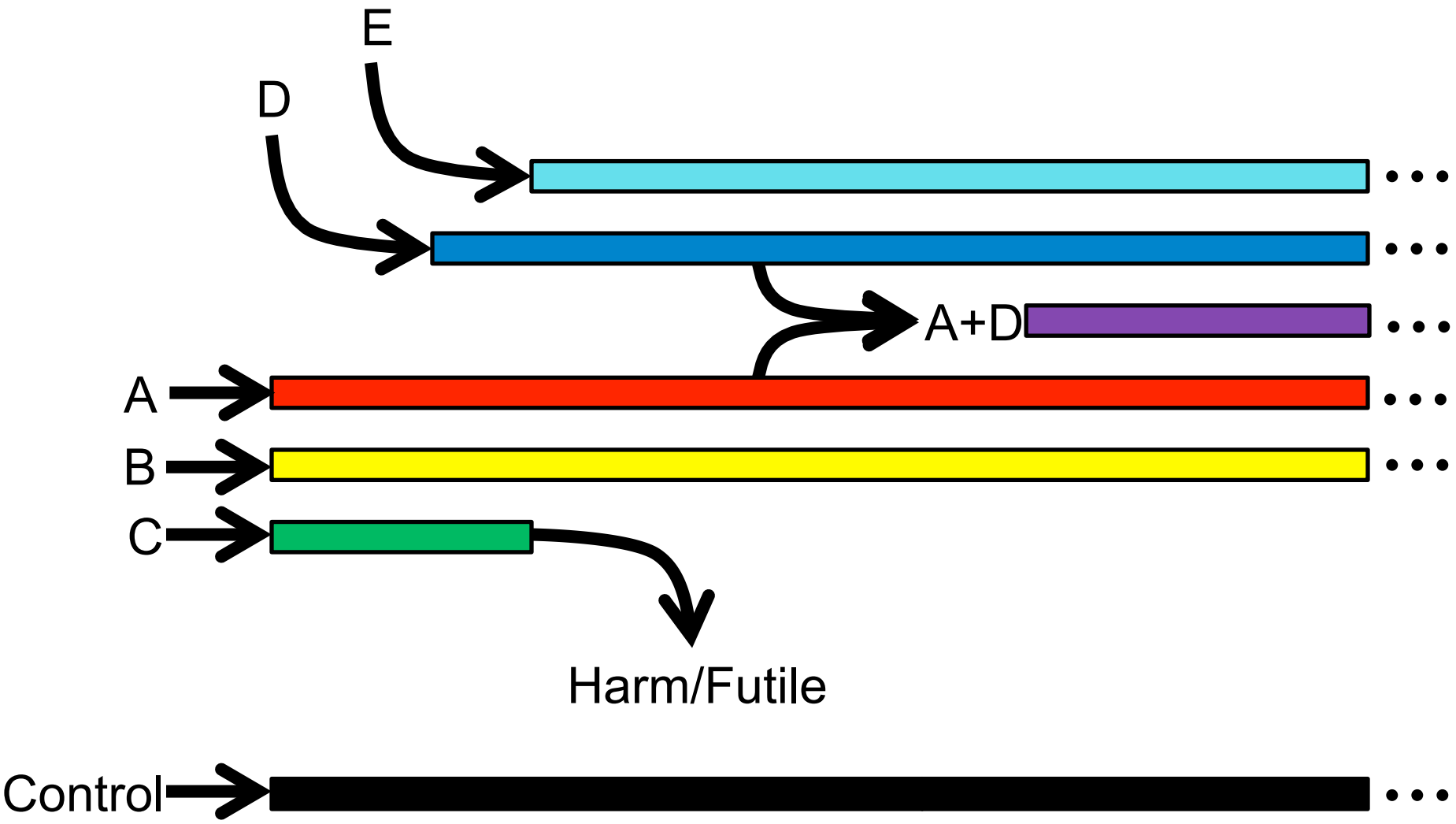

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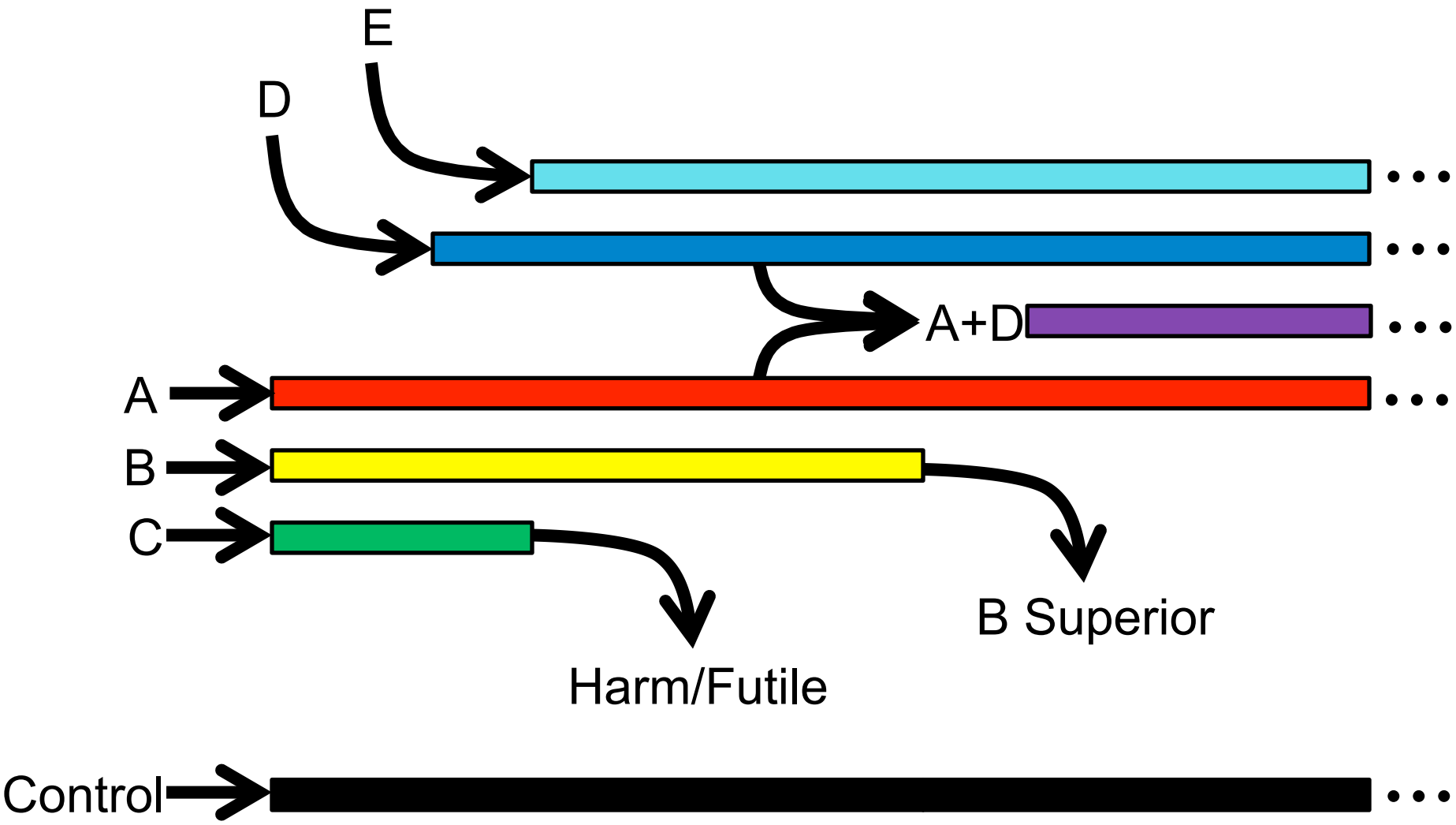

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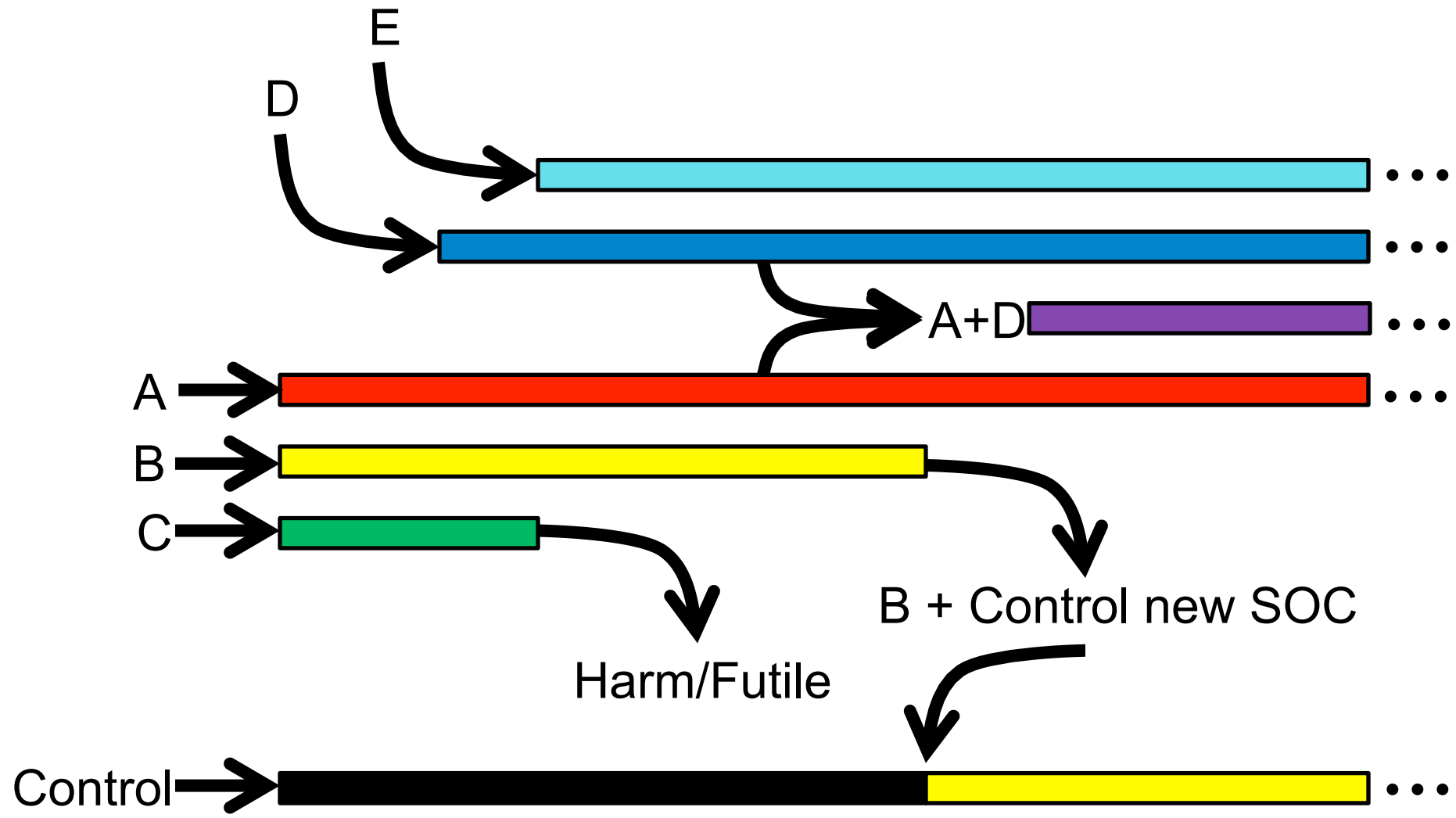


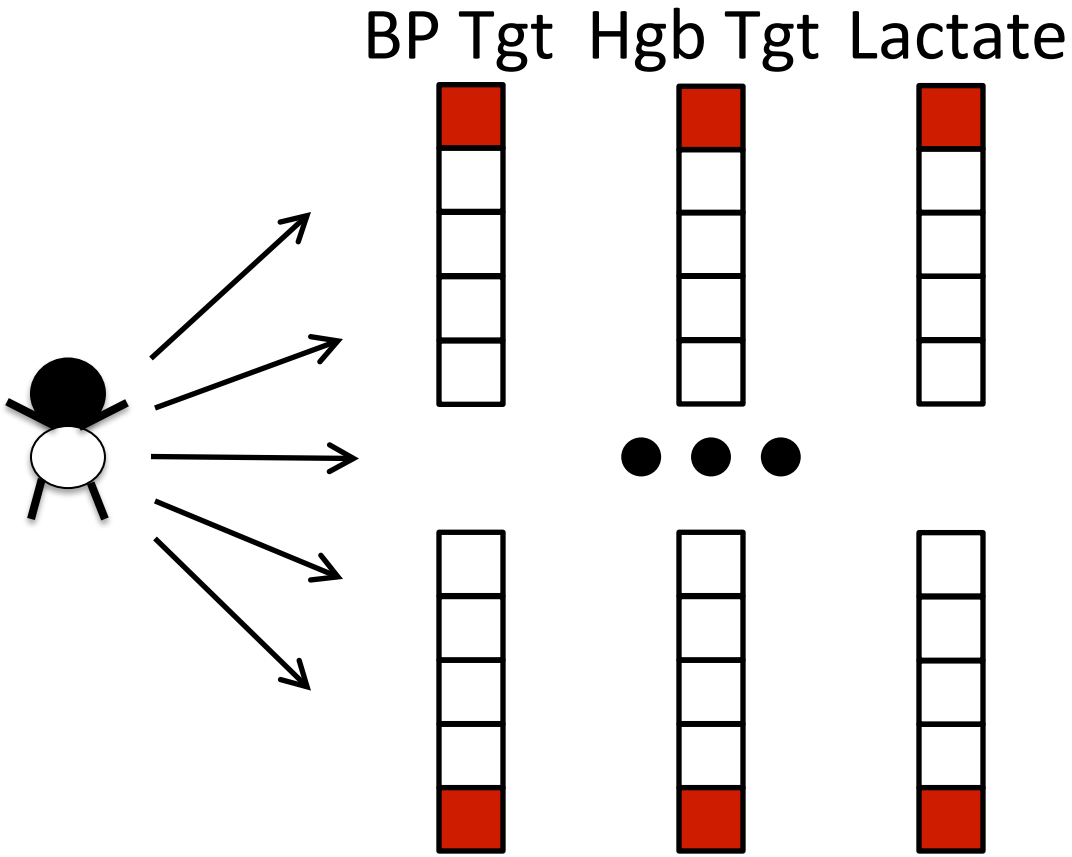
Key Question and Challenges

- Can we study strategies for remote damage control resuscitation (RDCR) in a single trial and integrate information in an efficient way?
- Multiplicities
  - Injury severity and patterns
  - Location of treatment (field, EMS, ED, OR, ICU)
  - Blood product, plasma, and related treatments
  - Other damage control strategies (e.g., low tidal volume ventilation, immunological strategies)

Opportunities

- Outcomes are known relatively quickly relative to the length of the trial
- Modern imaging allows accurate characterization of many injury patterns

Adaptive Trial Schematic



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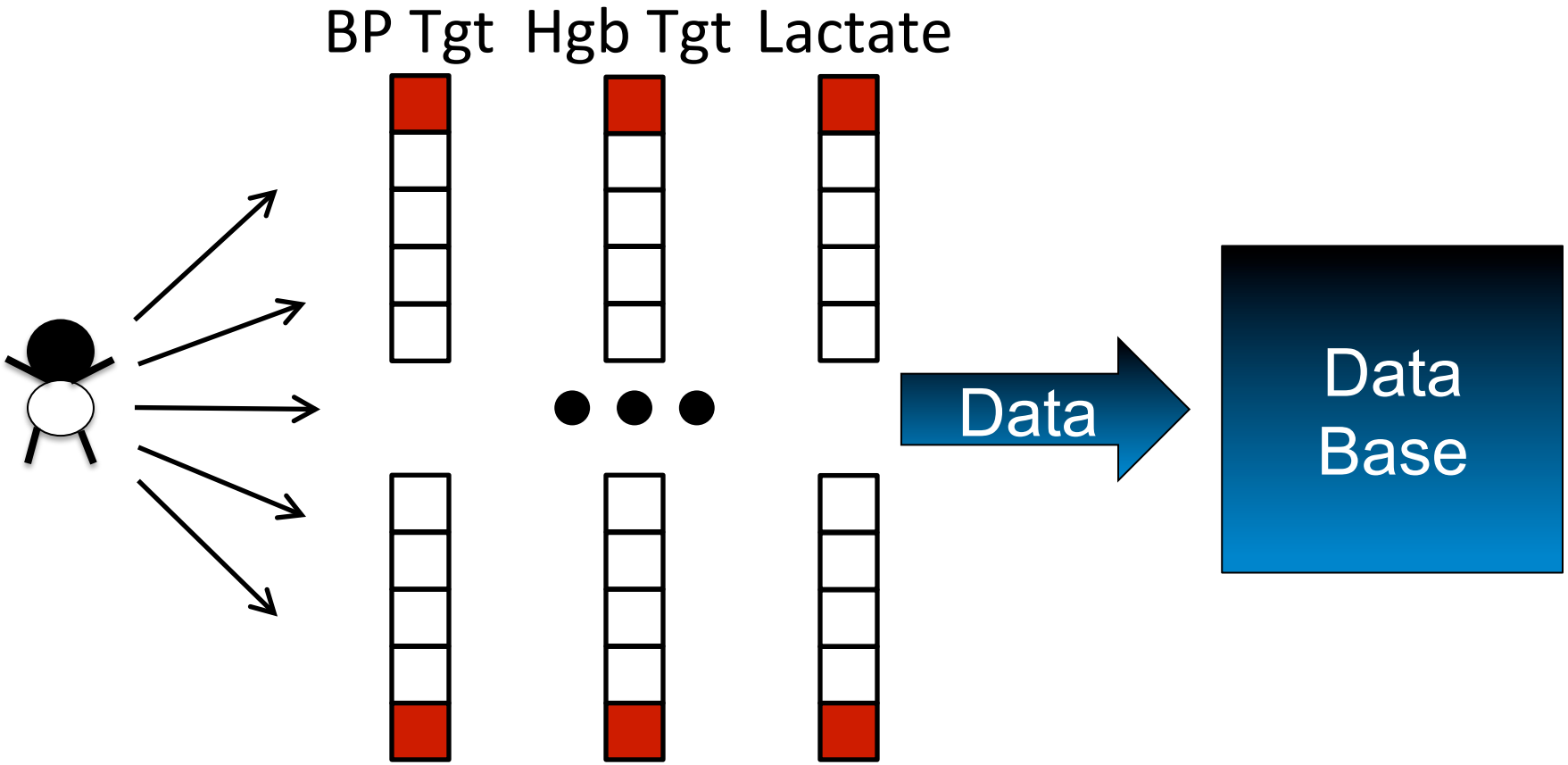

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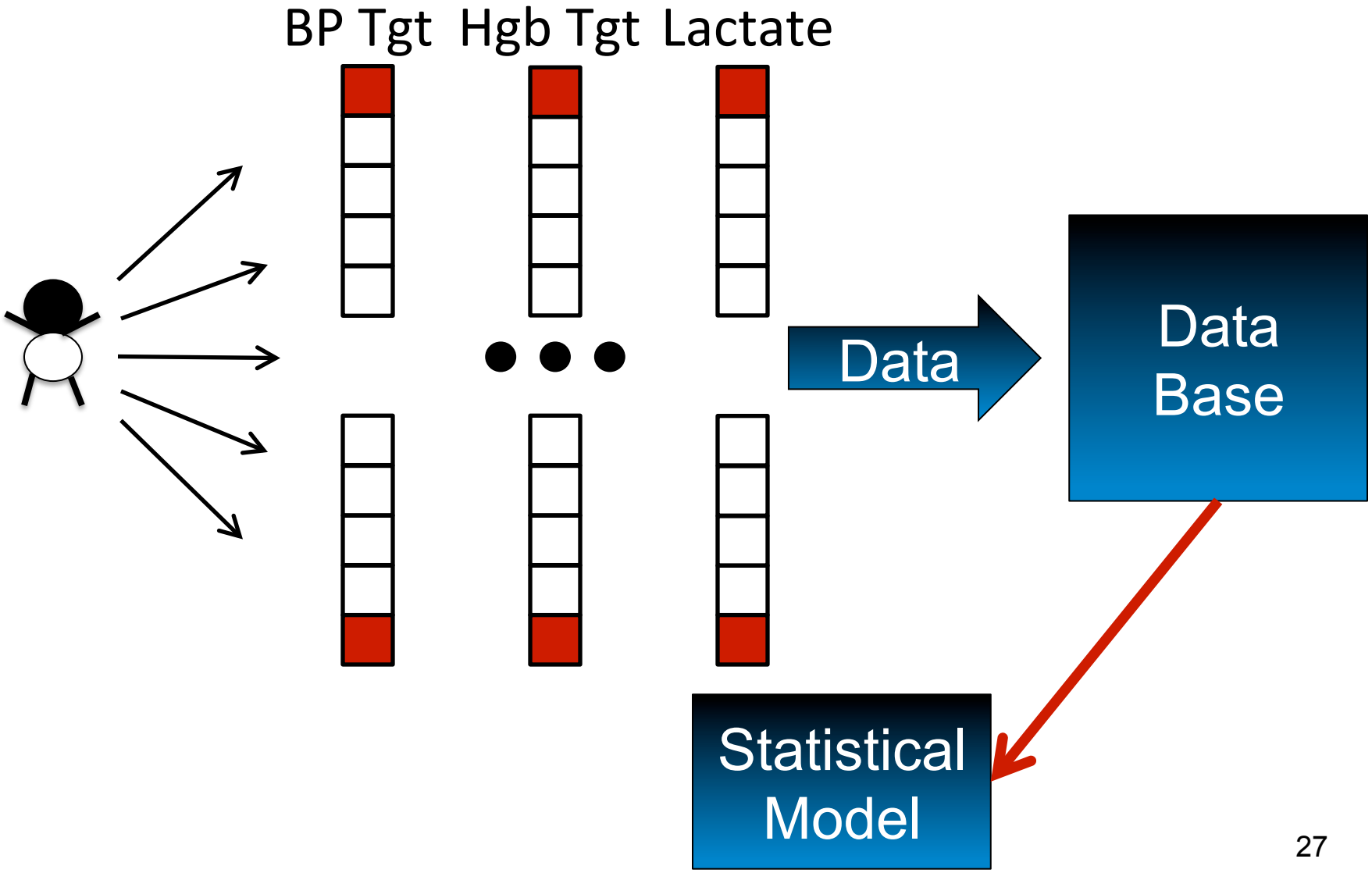
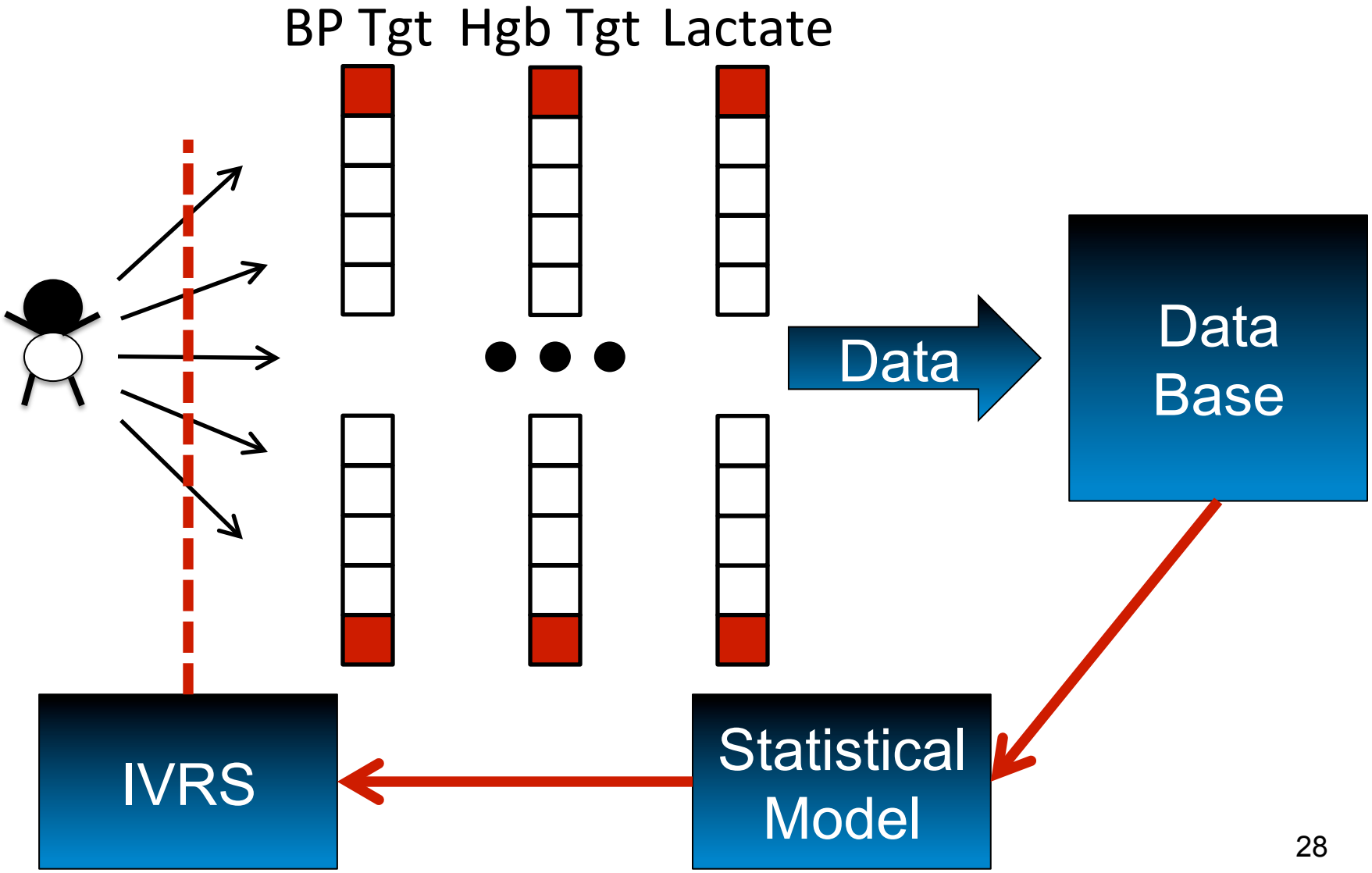
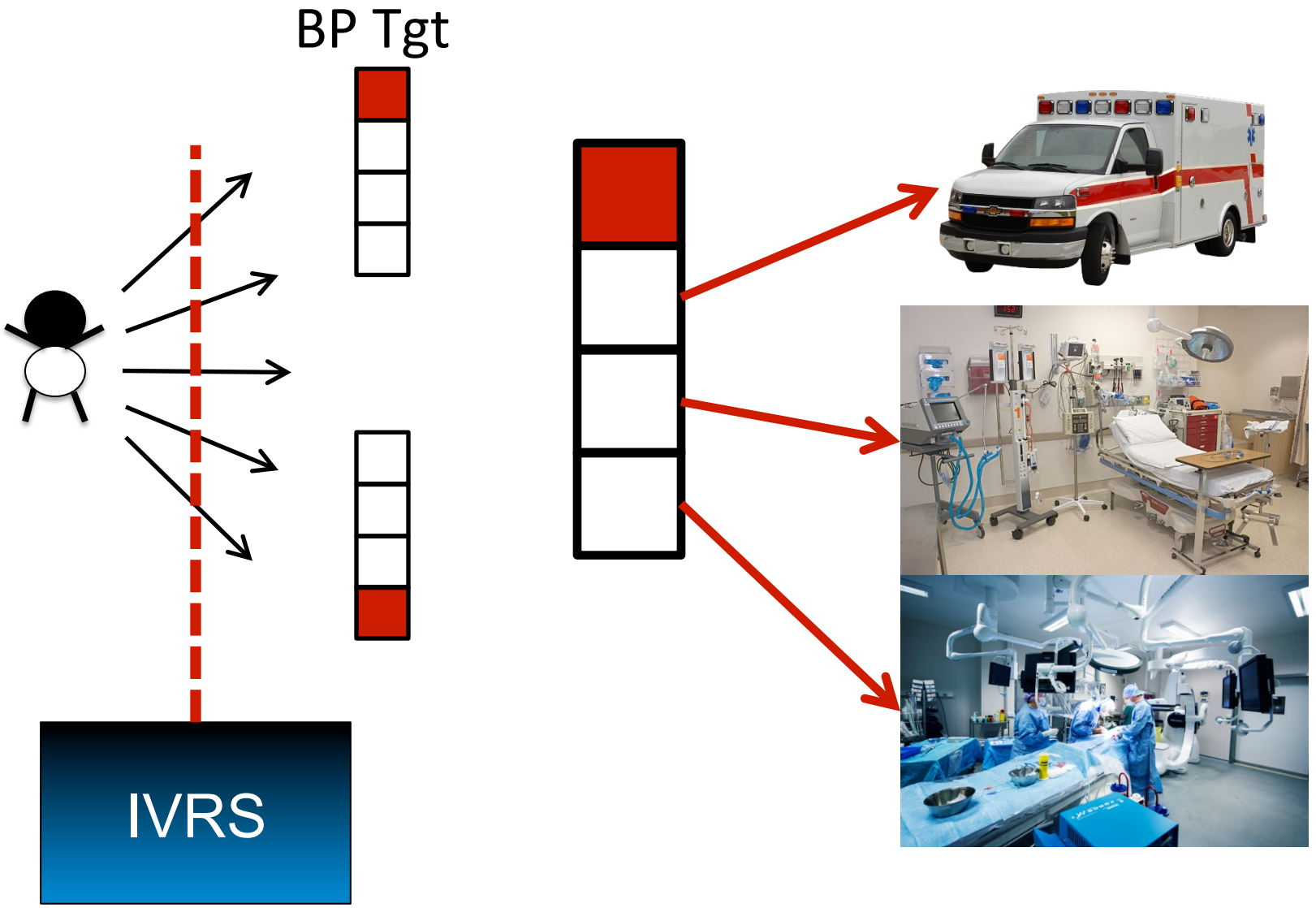


Adaptive Trial Schematic



Addressing Location of Intervention



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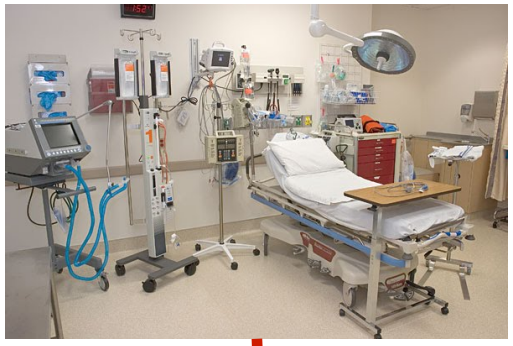

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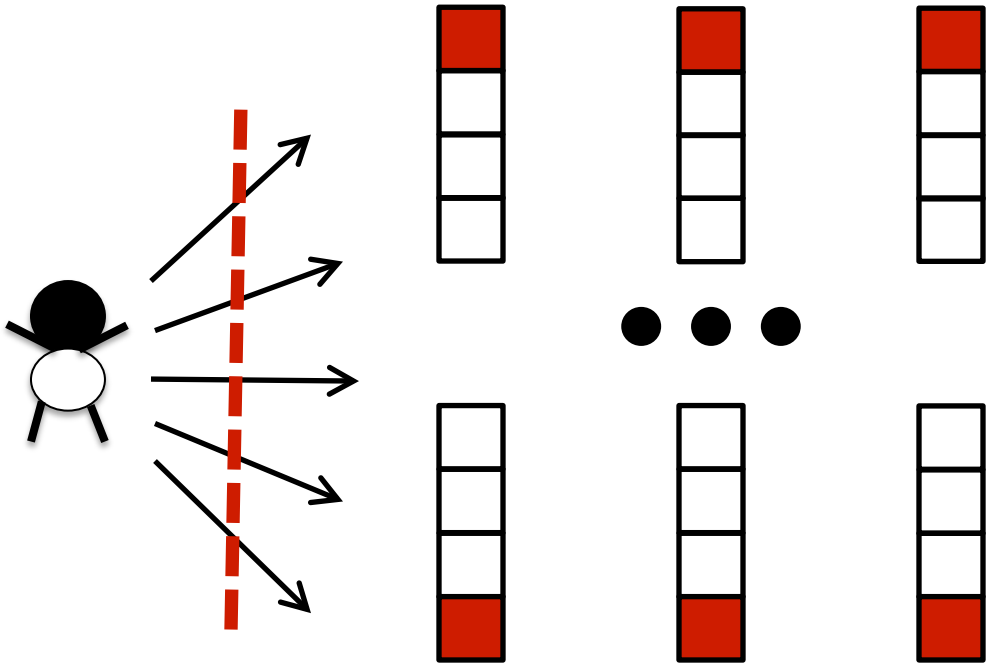
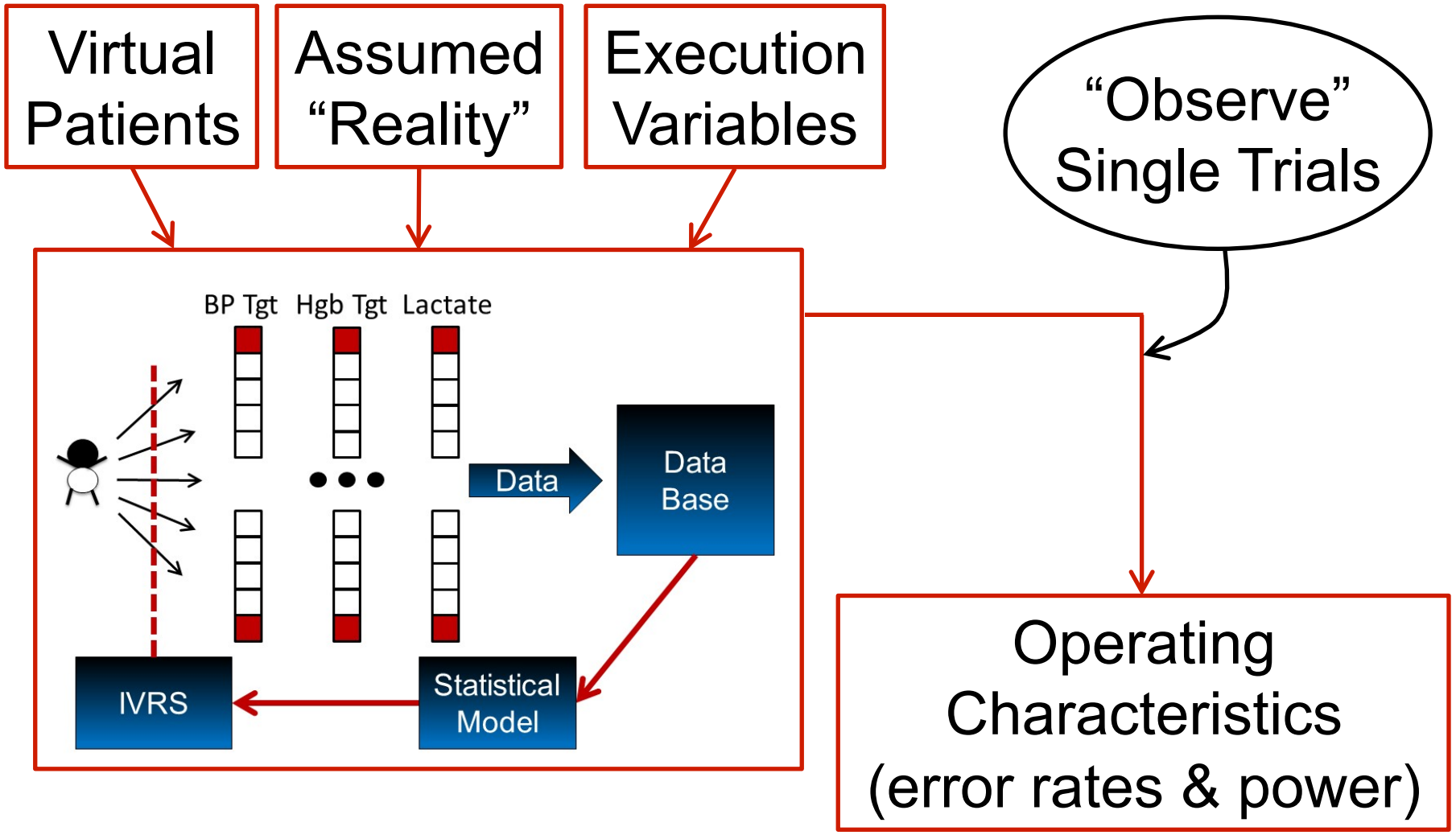


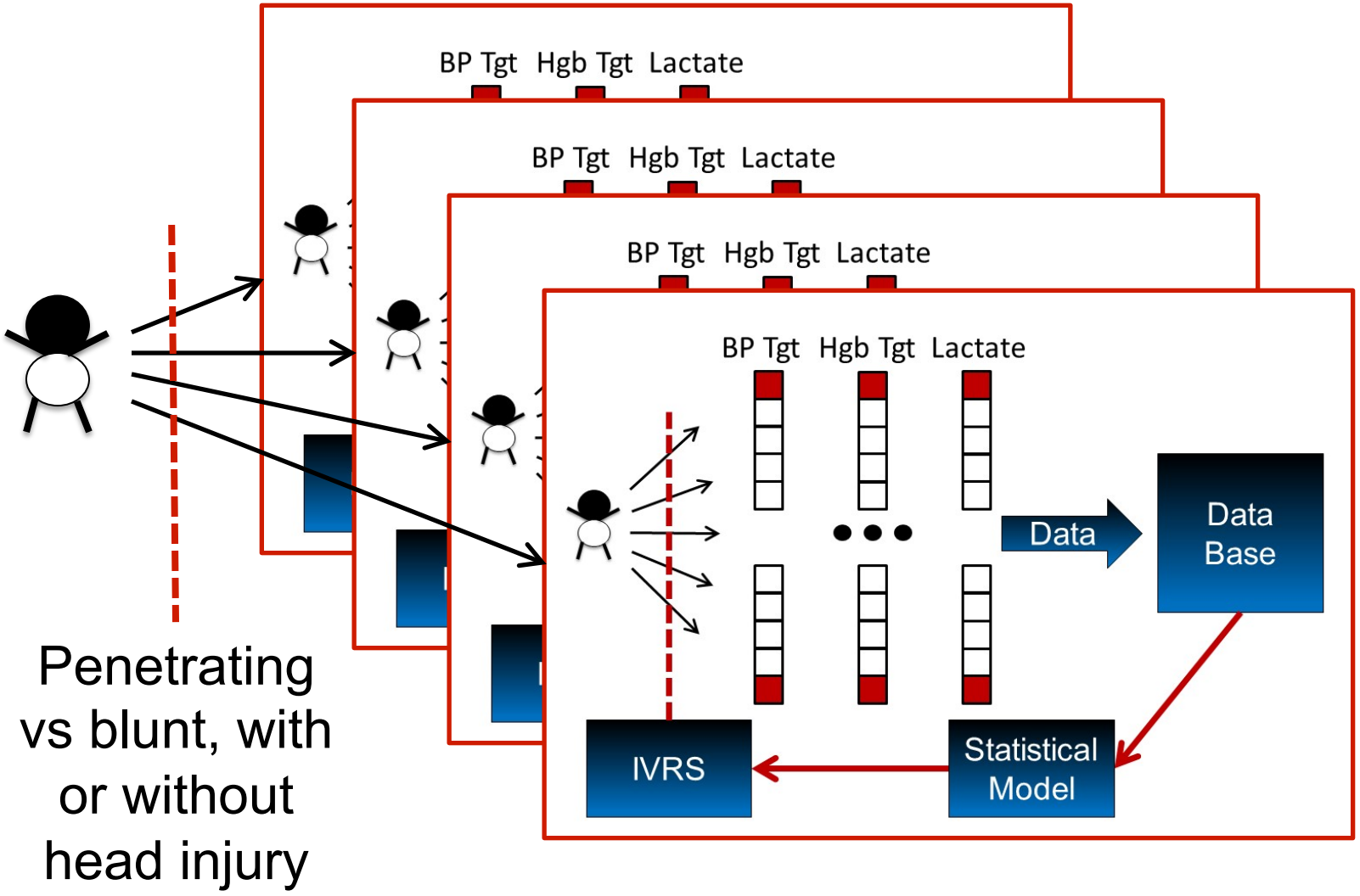
Data

Data Base

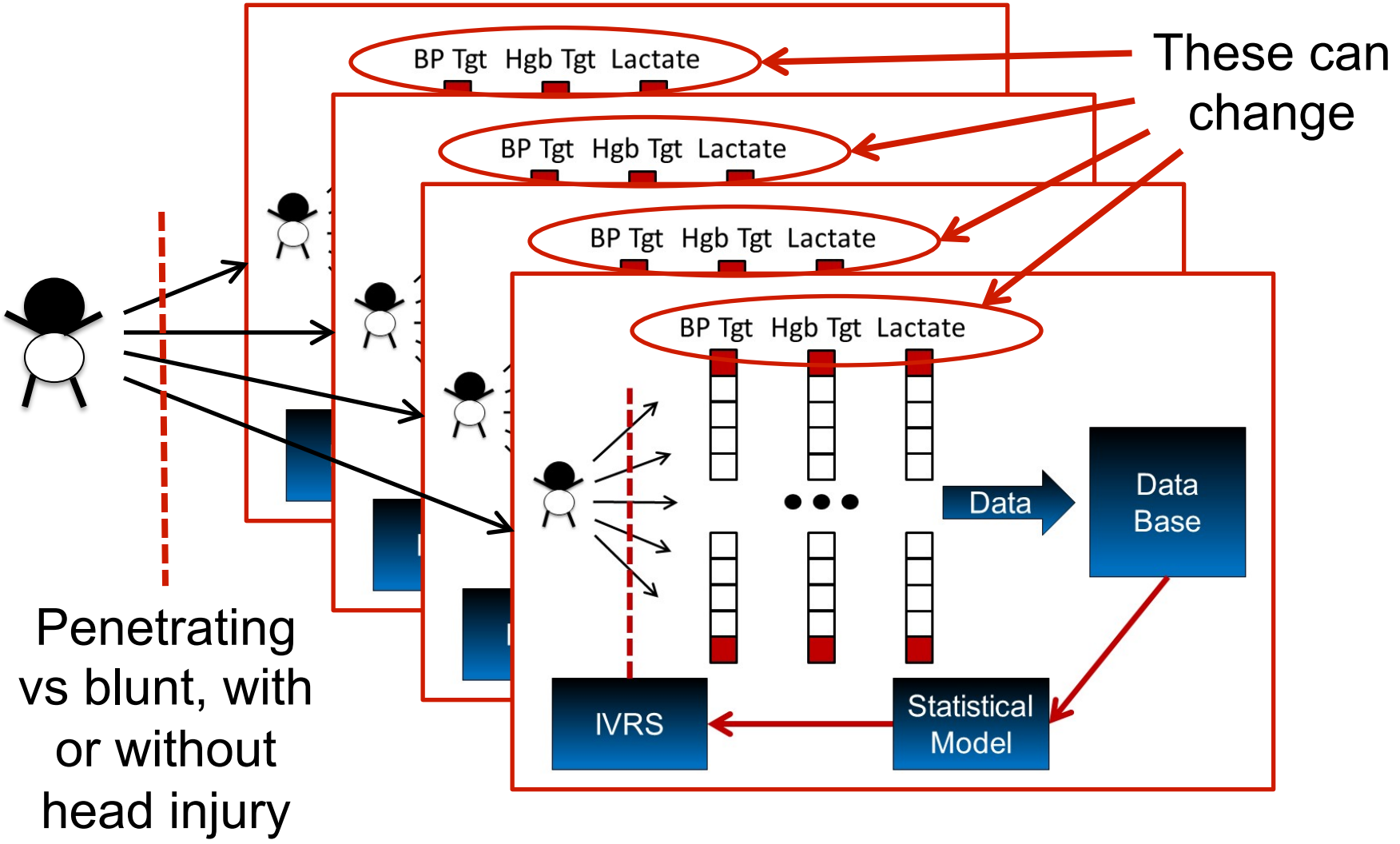
Trial Simulation



Platform Trial Schematic



Platform Trial Schematic



Conclusions

- Adaptive trial designs can be used to create a seamless process in which new evidence is immediately used to improve trial efficiency
- A platform trial can extend this process beyond a single treatment or few treatments and beyond a homogeneous population
- A well-designed platform trial is prespecified and carefully tailored to address the real threats to success in the clinical setting, while achieving greater statistical efficiency