Adaptive and Platform Clinical Trial Design

HEmostatic REsuscitation and Trauma Induced Coagulopathy (HERETIC)
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HERETIC

Berry Consultants
Statistical Innovation

Financial Disclosures

- Academic Affiliation and Employment
  - County of Los Angeles, Department of Health Services
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- Other
  - Statistical Editor, *JAMA*

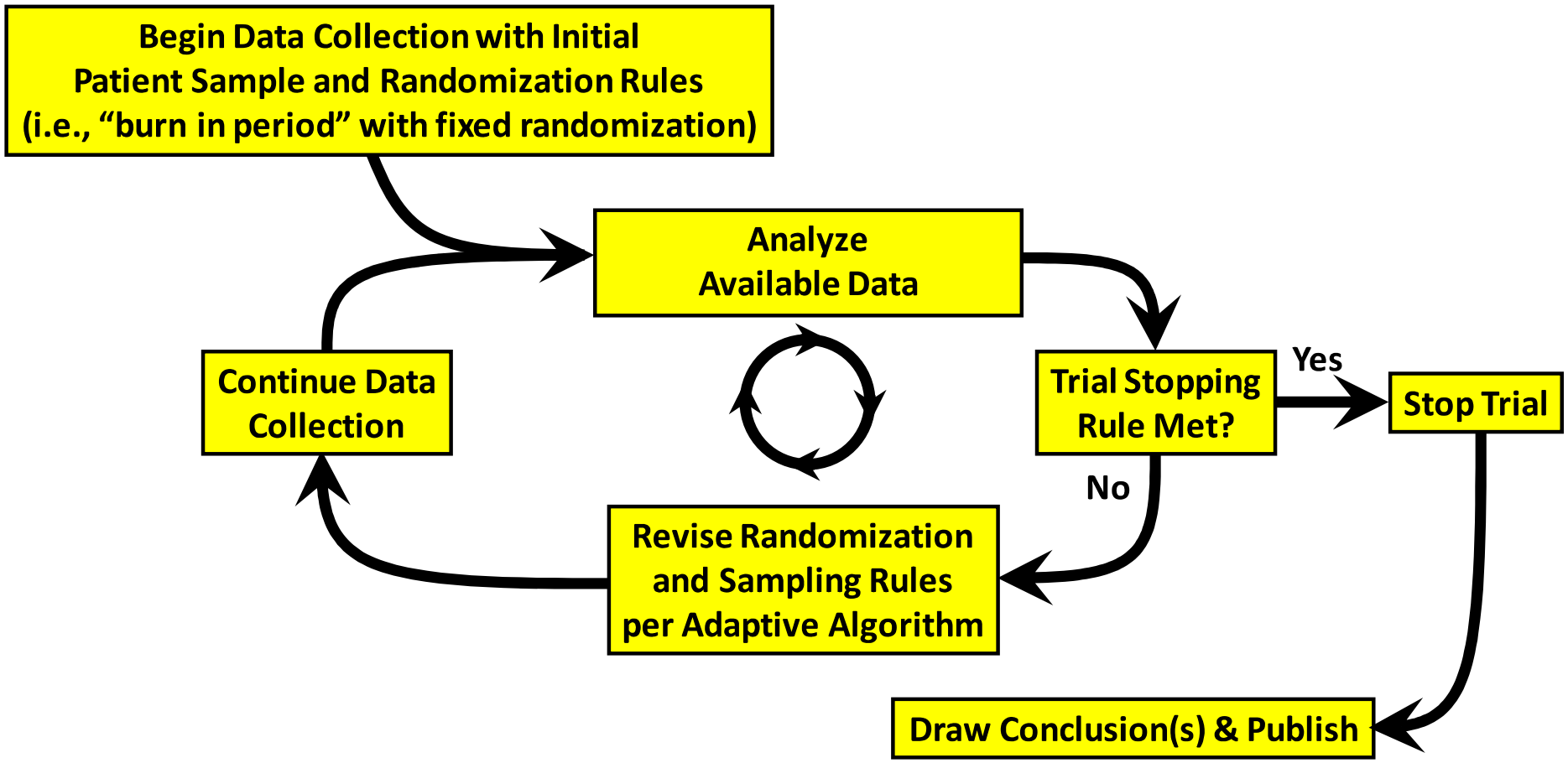
Motivation for Adaptive Trials

- When designing a clinical trial there is substantial uncertainty (e.g., best measure of benefit, outcome event rates, best treatment or dose, best duration, responsive target population)
- This creates uncertainty in the optimal trial design
- Traditionally, all key trial parameters are defined before first patient is enrolled and held constant during execution
  - Can lead to increased risk of a negative or a failed trial, even if an experimental treatment is inherently effective
  - Can miss an opportunity to treat patients more effectively within the trial

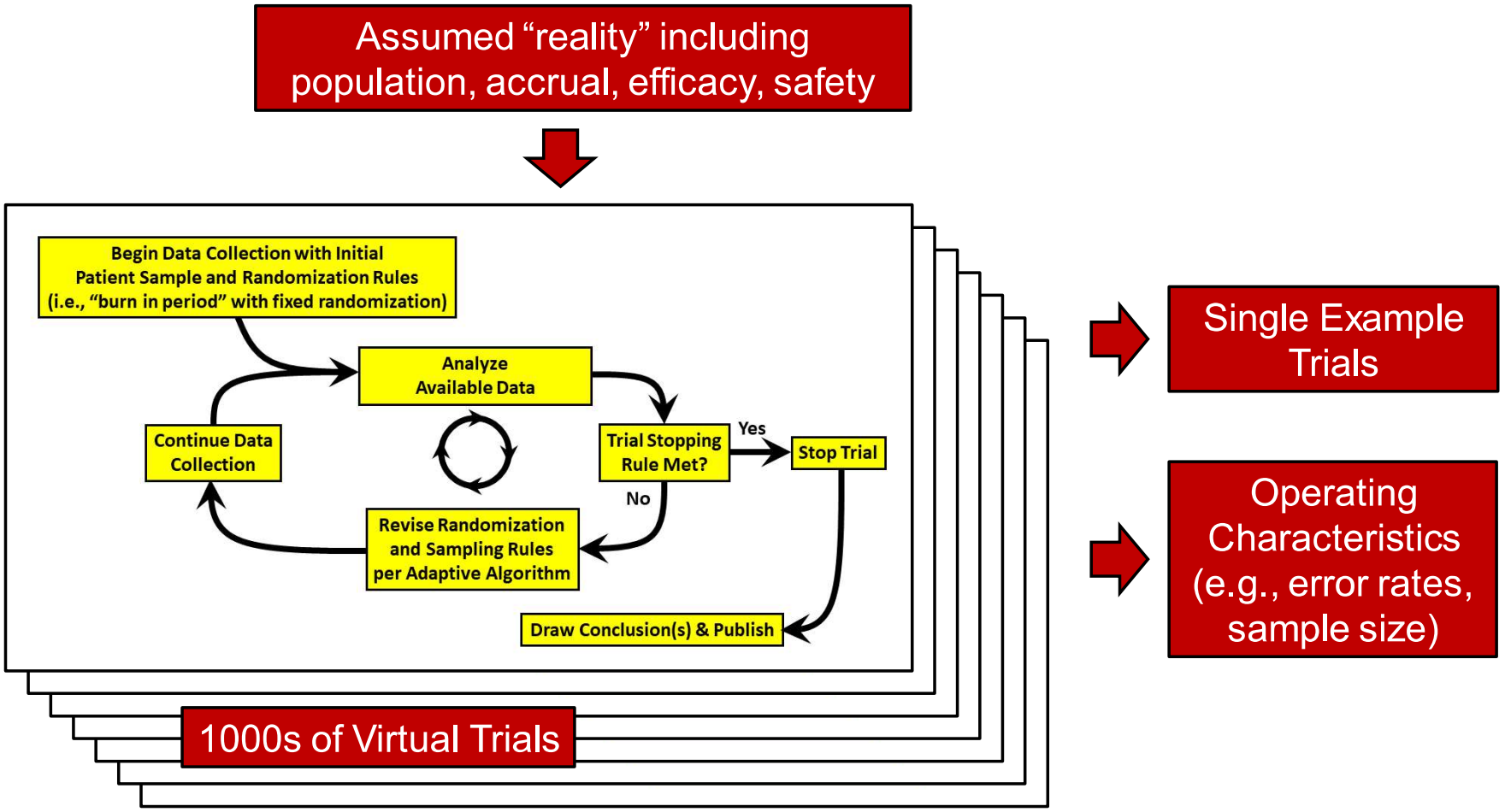
Key Advantage of an Adaptive Trial

- Once patients are enrolled and at least some outcomes are known, information accumulates that reduces 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
- By incorporating prespecified rules, the designs can be rigorous with well-defined operating characteristics
- This can, in some circumstances, increase the probability of getting the right answer at the end of the trial, improve trial efficiency, or improve patient outcomes within the trial

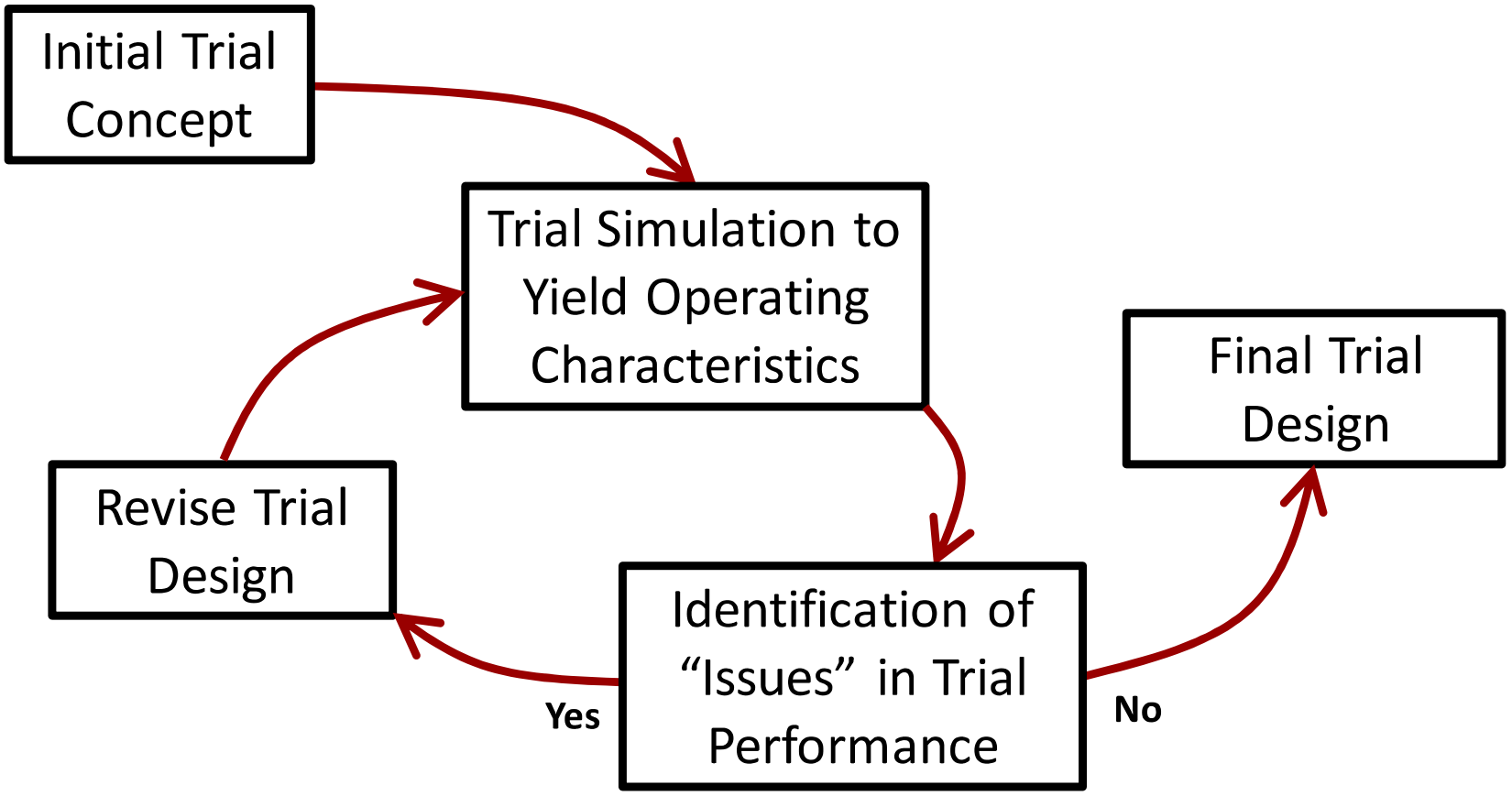
The Adaptive Process for a Randomized Clinical Trial



Trial Simulation



The Adaptive Trial Design Process



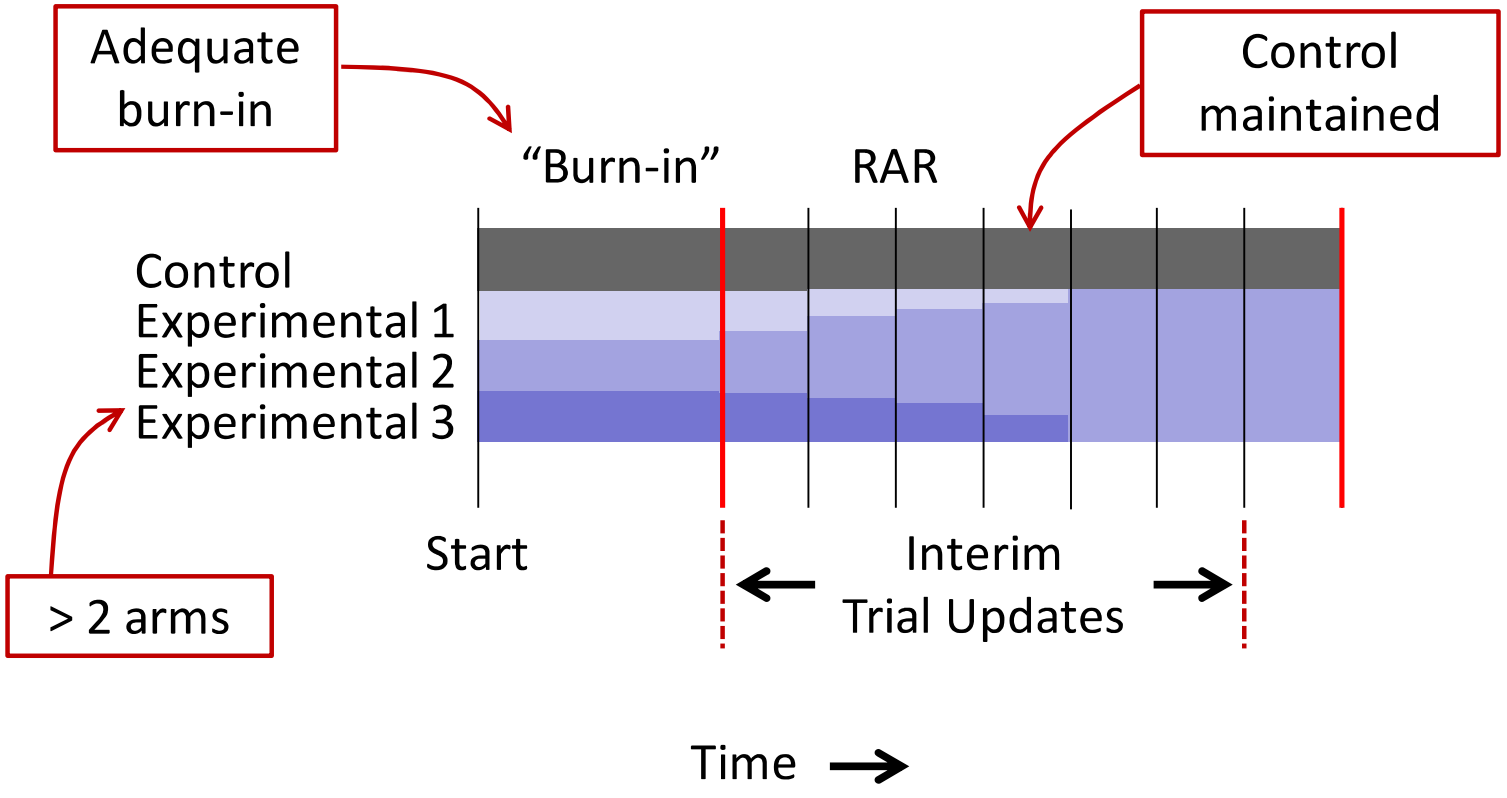
Potential Adaptive Strategies

- Frequent interim analyses at which adaptations are possible
- "Goldilocks" sample size re-estimation
- Response-adaptive randomization
  - Includes adding or dropping of arms or even groups of treatment options
- Explicit decision rules based on Bayesian posterior or predictive probabilities at each interim analysis
  - Early stopping for success
  - Early stopping for futility
- Enrichment of study population
- Seamless transition from phase II to phase III

A Toolset Rather than a Bookshelf

- Adaptive design is ideally a creative process of matching methodological solutions to specific threats to trial success, considering
  - Available resources, patient population
  - Acceptable error rates, potential threats to validity
  - Whether trial results are intended to influence future research efforts, regulatory decision making, or clinical practice
- While specific examples can illustrate benefits of adaptive design, anchoring on specific examples can erroneously suggest adaptive trials are just another limited set of inflexible options

Typical RAR Strategy



Motivation for a Platform Trial

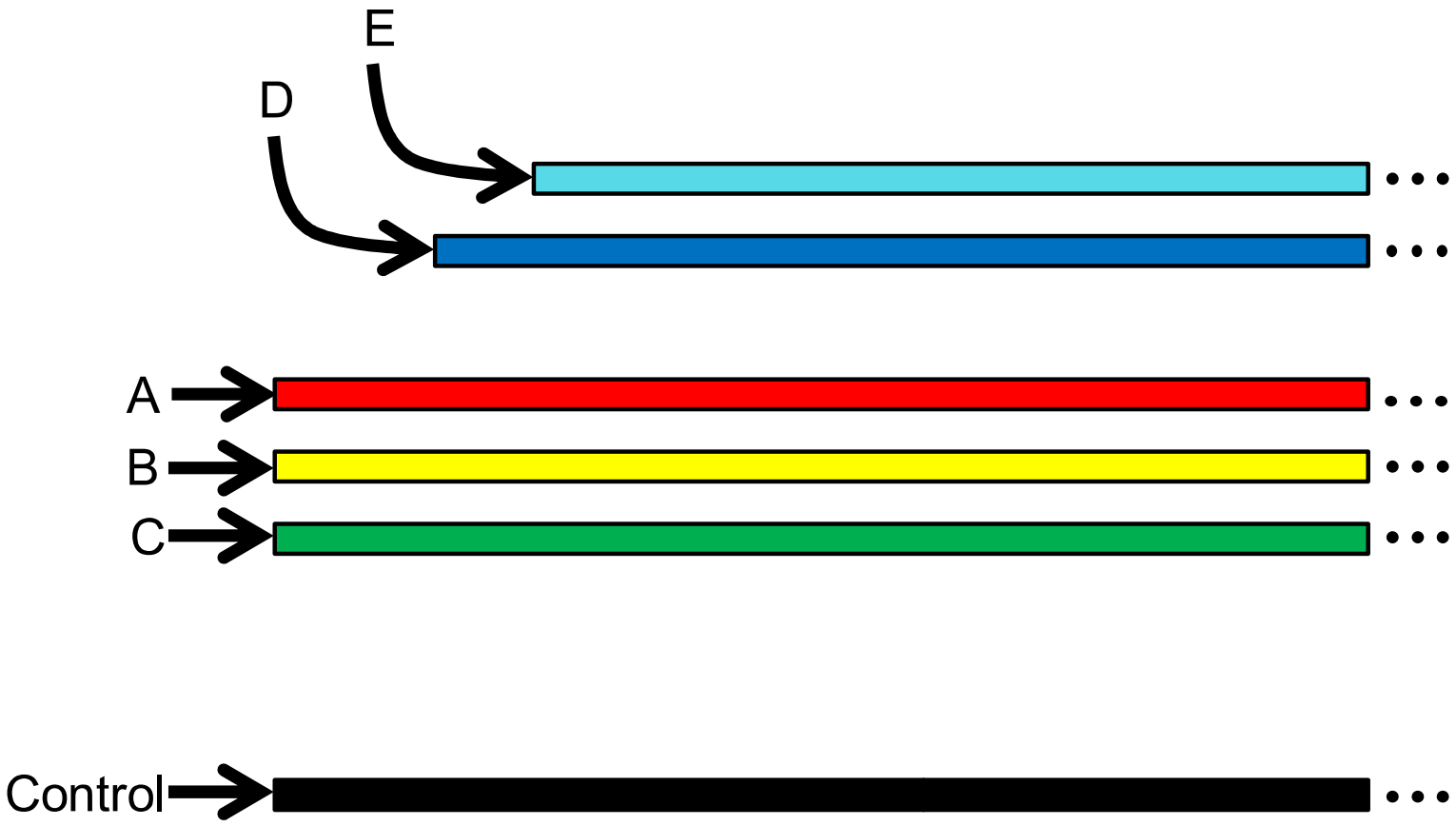
- The list of treatments worthy of investigation often changes rapidly, relative to the time required to design, fund, implement, and complete a modern randomized clinical trial (RCT)
- In some cases, the current list of promising therapies is already long, and a traditional trial is ill-suited to evaluating all efficiently
- If forced to focus on only a few treatments, the initial selection of experimental arm(s) may miss the effective ones, or more promising therapies may become available after the trial begins
- **Some diseases require combinations of treatments for benefit**
- These considerations may result in a traditional, simple trial having reduced value or being unethical to complete

Platform Trial

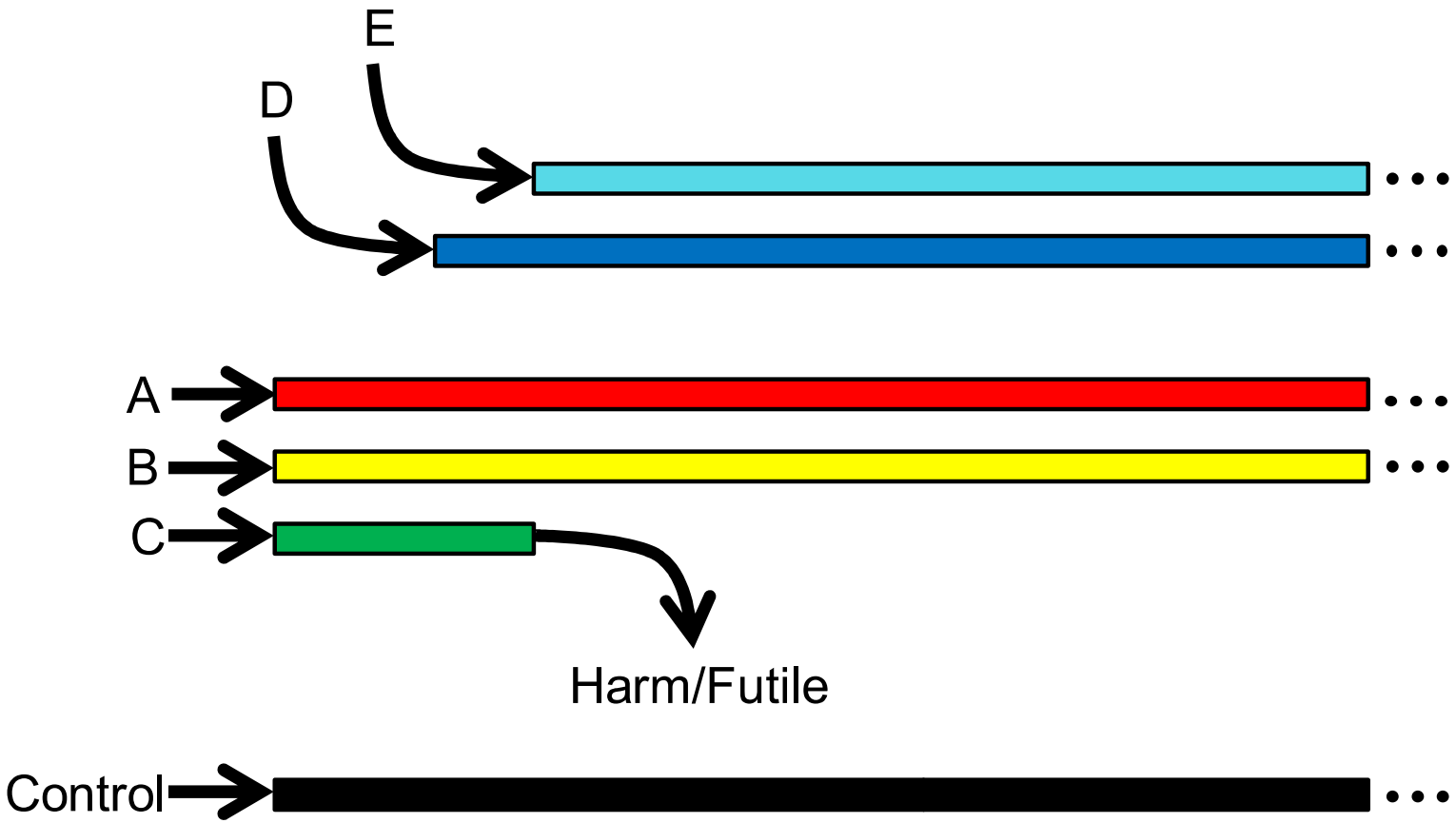
- An experimental infrastructure to evaluate multiple treatments, often for a group of diseases, intended to continue beyond the evaluation of any individual treatment
  - Multiple treatments and often administered in combination
  - Often a group of related diseases or subgroups
  - Dynamic list of available treatments, potentially assigned with response-adaptive randomization
  - Preferred treatments may depend on health system, patient, or disease-level characteristics
  - Focus is on effective treatment of disease

Potential Features of a Platform Trial

Potential Features of a Platform Trial



Potential Features of a Platform Trial



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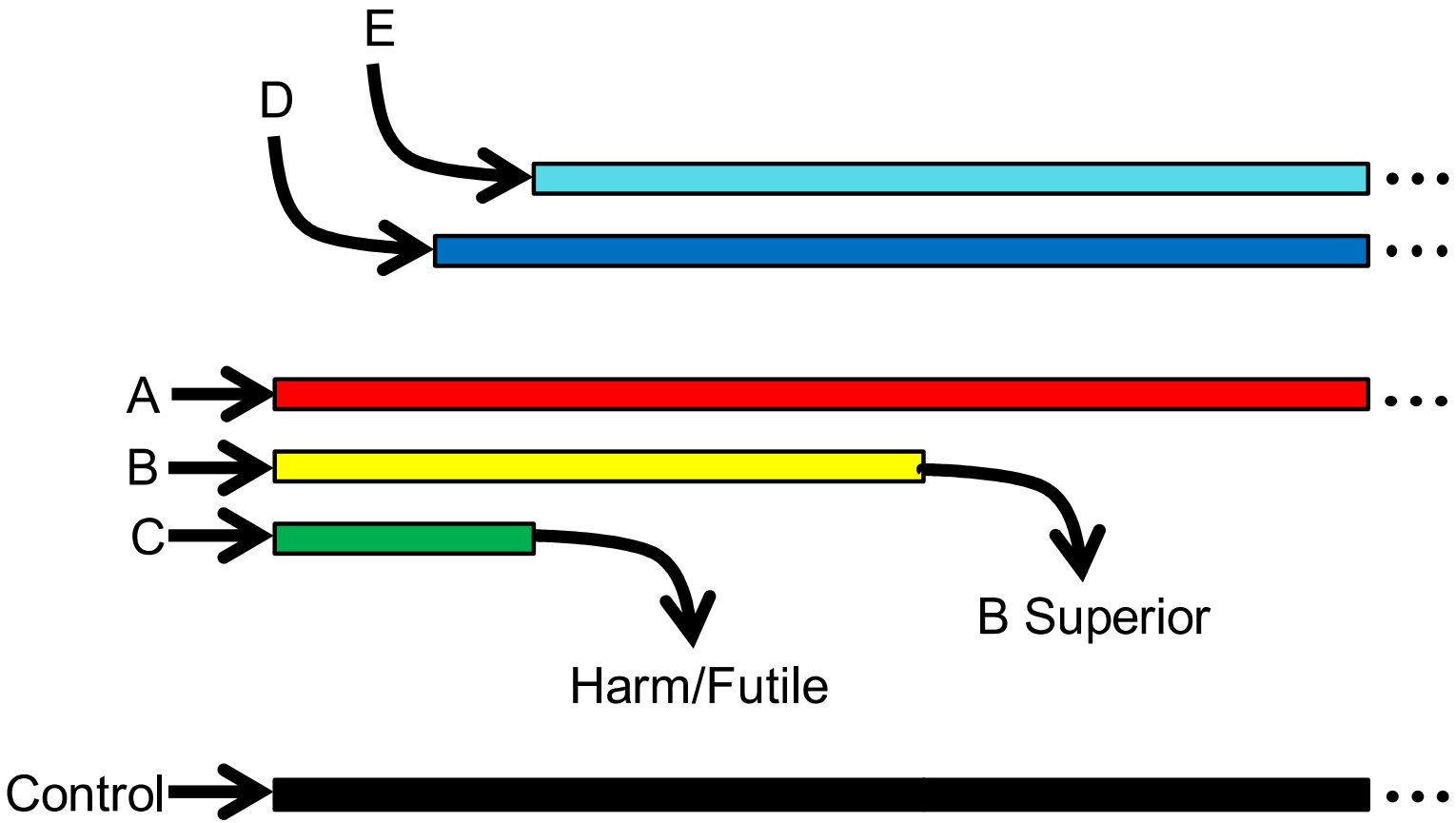

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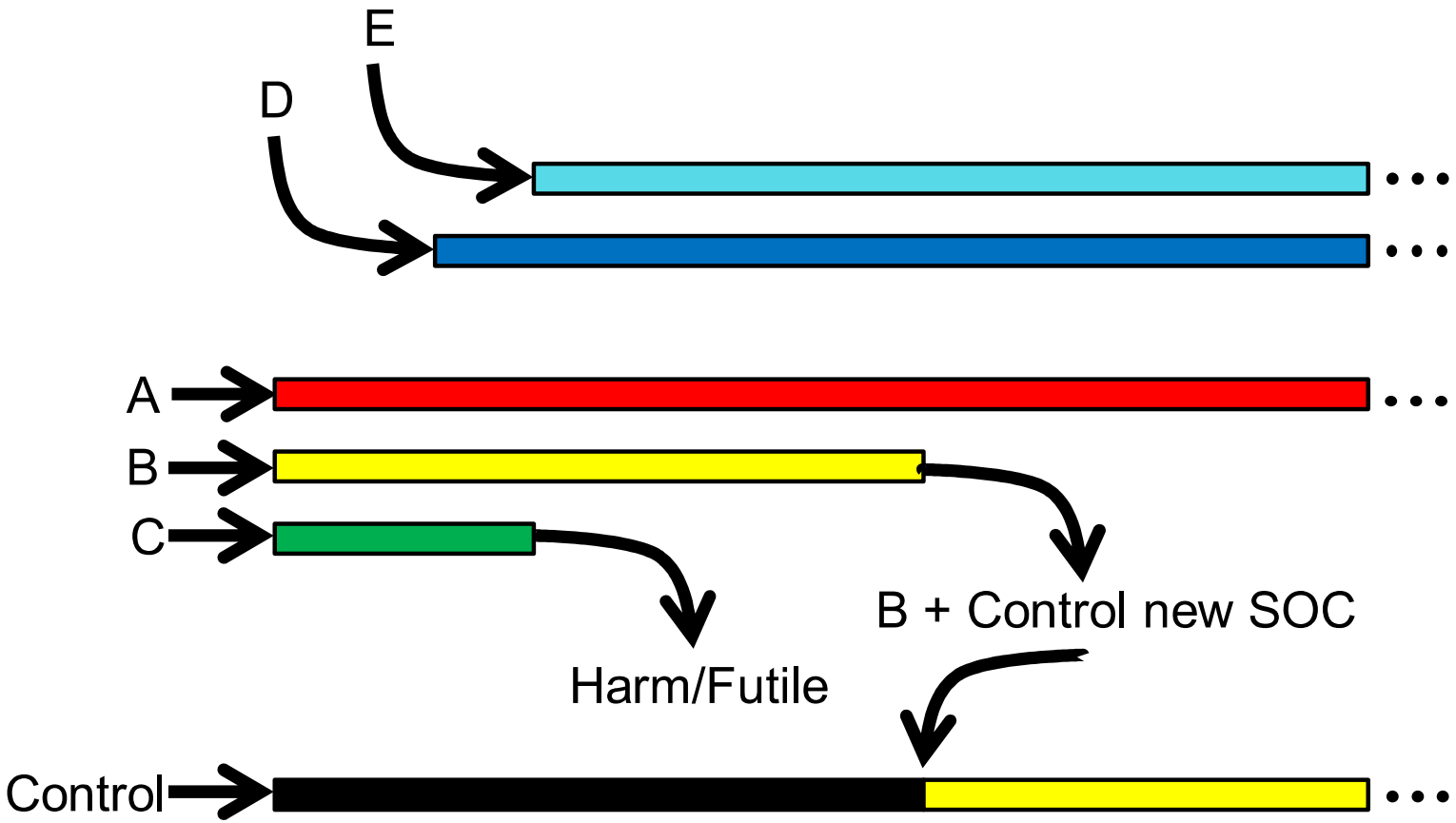
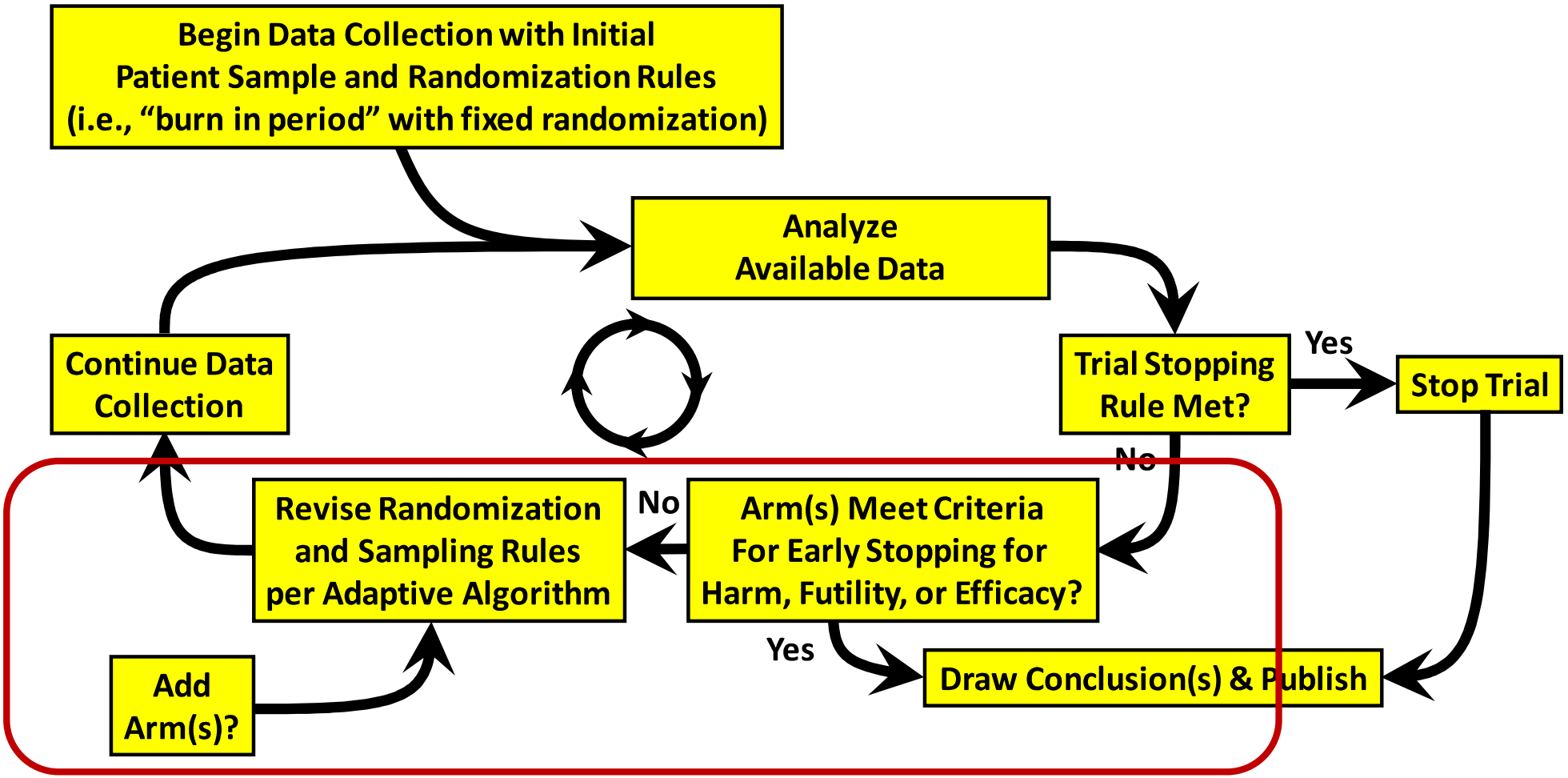


A Few Examples of Platform Trials

- REMAP-CAP (community acquired pneumonia and COVID)
- RECOVERY (COVID)
- AntiCOV (outpatient treatment of COVID in Africa)
- GBM Agile (glioblastoma multiforme)
- Precision Promise (pancreatic cancer)
- Healey ALS Platform Trial (amyotrophic lateral sclerosis)

The Adaptive Process for a Platform Trial



Potential Efficiencies

- Structural
  - Shared control group
  - Informative endpoints (e.g., utility functions)
  - Disease progression models
- Adaptations
  - Response adaptive randomization
  - Early stopping
  - Enrichment
- Statistical Approaches
  - Hierarchical Models with “borrowing”
  - Subgroup- or disease-specific inferences and treatment assignments

Article

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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.

Keywords

Platform trial, master protocol, multi-arm, adaptive, Bayesian, clinical trial design

VIEWPOINT

Fusing Randomized Trials With Big Data
The Key to Self-learning Health Care Systems?

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Randomized clinical trials (RCTs) have revolutionized medicine by providing evidence on the efficacy and safety of drugs, devices, and procedures. Today, more than 40 000 RCTs are reported annually, their quality continues to increase, and oversight mechanisms ensure adequate protection of participants. However, RCTs have at least 4 related problems: (1) they are too expensive and difficult; (2) their findings are too broad (average treatment effect not representative of benefit for any given individual) and too narrow (trial population and setting not representative of general practice); (3) randomizing patients can make patients and physicians uncomfortable, especially when comparing different types of existing care; and (4) there are often long delays before RCT results diffuse into practice.

The new alternative is "big data." Because medical care is increasingly digitized in electronic health record (EHR) data sets and linked biological and genetic data banks, proponents suggest that health care systems are at the dawn of an era in which a patient's prognosis and optimal therapy will be generated from rapid analysis of these data sets using sophisticated machine-learning strategies. The information is relatively inexpensive, generated as a by-product of patient care (overcoming the cost problem), and both specific to

access to massive amounts of data, the Achilles' heel is lack of causal inference. No matter how detailed the measurement and how sophisticated the adjustment for all known variables, big data cannot eliminate unmeasured factors coincident with a particular treatment assignment that could explain an apparent change in outcome.[2]

Thus, each approach has complementary strengths: RCTs offer causal inference, and big data offers the potential for low-cost, high-volume, nuanced answers with immediate feedback. Rather than debate which is better, the greatest promise may come from fusing them.

Fixing Problem 1—Cost and Difficulty

Conducting RCTs as freestanding enterprises requires considerable infrastructure, much of which is duplicative with clinical care. Many argue better integration with the EHR could reduce RCT costs and overcome some logistic difficulties. For example, EHR screening tools are often used to identify potential patients. For patients enrolled in RCTs, the burden of data collection is frequently eased by automated download from the EHR. The interventions being tested also could be nested in the EHR, including both the order entry for the intervention and the recording of intervention

JAMA. 2015;314(8):767-768. doi:10.1001/jama.2015.7762.

Randomized Embedded, Multifactorial, Adaptive Platform (REMAP) trial

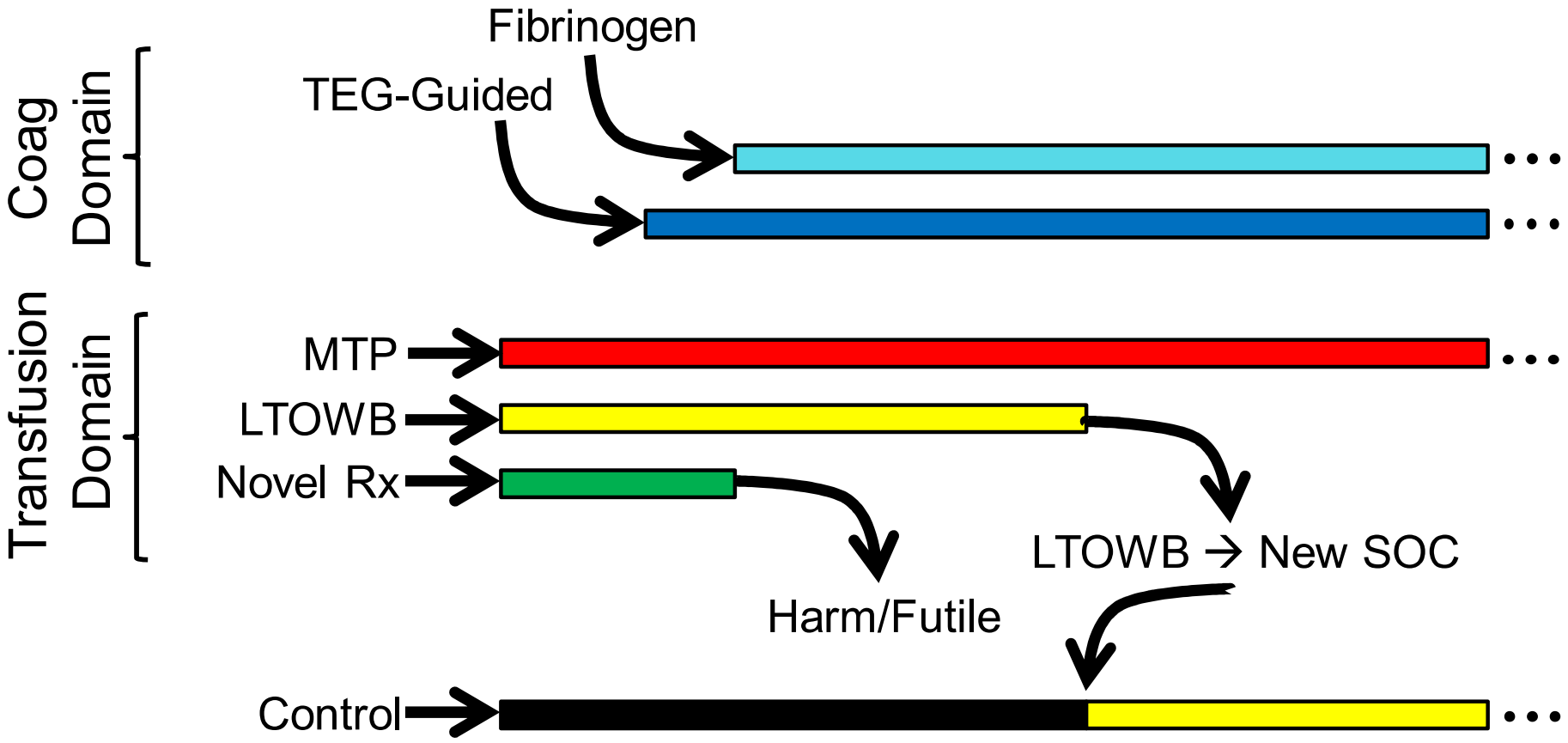
- Randomized
- Embedded
- Multifactorial
- Adaptive
- Platform

Thanks to Derek C. Angus, MD, MPH, University of Pittsburgh Medical Center, for “REMAP”

Multifactorial Platform Trial Terminology

- Domain
  - A domain of treatment
  - E.g., Transfusion strategy, Coagulation, Hemorrhage control
- Factor
  - One particular treatment within a domain
  - E.g., TEG-guided management of coagulation
- Regimen (or treatment regimen)
  - The assigned collection of factors from multiple domains

Potential Features of a Multifactorial Platform



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ADAPTIVE PLATFORM TRIAL DESIGN

TRANSFUSION

An adaptive platform trial for evaluating treatments in patients with life-threatening hemorrhage from traumatic injuries: Rationale and proposal

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ADAPTIVE PLATFORM TRIAL DESIGN

TRANSFUSION

An adaptive platform trial for evaluating treatments in patients with life-threatening hemorrhage from traumatic injuries: Planning and execution

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ADAPTIVE PLATFORM TRIAL DESIGN

TRANSFUSION

An adaptive platform trial for evaluating treatments in patients with life-threatening hemorrhage from traumatic injuries: Ethical and US regulatory considerations

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Goldkind SF, Brosch LR, Lewis RJ, et al. Transfusion. 2022 Aug;62 Suppl 1:S255-S265.

Strata in a Platform Trial for Hemorrhagic Shock

- Patient strata define the smallest group of patients in which a separate conclusion regarding treatment efficacy can be drawn
- The strata should generally be based on criteria present at enrollment, and reflect the structure of clinical decision making

Possible Strata
Adult, no concomitant head injury
Adult, concomitant head injury
Child, no concomitant head injury
Child, concomitant head injury

Clinical Challenges to Address

Clinical Research Challenge	Pertinent Platform Trial Feature
Variable mechanisms of injury, sources of bleeding, and injury severity	Estimation of treatment effects separately for prespecified clinically distinct patient subgroups or strata; adjustment for baseline characteristics
Multiple phases and sites of care (e.g., prehospital, emergency department, operating room, intensive care unit)	Trial can accommodate multiple time points at which a patient becomes eligible for a treatment, with the allocation to later treatments only revealed when needed
Simultaneous administration of multiple treatments with the possibility of interactions between treatments	Separate randomization in each domain of care allows simultaneous investigation of multiple therapies; evaluation of efficacy at the level of the regimen (the combination of all assigned treatments or factors) allow for the possibility of interactions or synergy among treatments.
Both early and longer-term outcomes of interest	The primary endpoint will be 6-hour all-cause mortality; however, in cases in which informing clinical care requires consideration of longer-term outcomes, the 28-day all-cause mortality will be considered
Difficulty in obtaining consent, will require an emergency exception from informed consent (e.g., 21 CFR 50.24)	The trial will be designed to hold "out the prospect of direct benefit to the subjects" as required in 21 CFR 50.24(a)(3) both through the investigation of promising treatments and through the use of response-adaptive randomization to improve outcomes within the trial
Changes in the effectiveness of care over time; secular trends	Explicit adjustment for time-based trends in the primary inferential model rather than only as a secondary or post-hoc sensitivity analysis
Introduction of new standards of care	If a new standard of care is defined for one of the treatment domains, the prior standard of care can be removed from the trial and the new standard of care used as the control treatment or factor going forward. This can be accommodated without any pause in the trial or change to the underlying trial and statistical methodology

Efficiencies of a Multifactorial Platform Trial

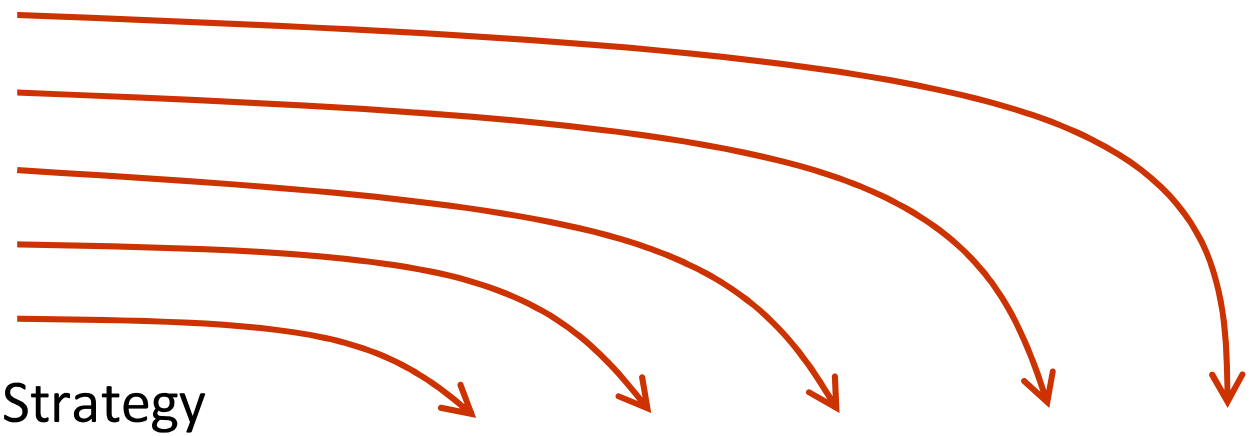
Platform Trial Characteristic	Associated Efficiency
Simultaneous evaluation of multiple therapeutic options within each domain	No requirement to duplicate control subjects for the evaluation of each experimental treatment within a domain
Evaluation of multiple therapeutic domains	Simultaneous investigation of multiple domains of care, reducing the average time and number of enrolled subjects required per result generated. This supports the goal of exposing the minimum number of subjects possible to address each clinical question.
Dynamic set of treatment options	The trial utilizes a dynamic set of treatment options so that there is no stopping or pausing of the trial when a result is generated and minimal start up time when a new treatment is added.
Response-adaptive randomization	The randomization proportions for future subjects are adjusted, after a suitable burn in period, so that future subjects are preferentially allocated to the treatment regimens that are most likely to be effective. This increases the rate at which data are generated for the most promising therapies, even though the identity of the most promising therapies cannot be known at the beginning of the trial.[18-20]
Statistical modeling (e.g., hierarchical modeling) to yield efficient estimation of treatment effects within prespecified subgroups	Hierarchical modeling reduces the average mean-square error in the estimation of treatment effects across subgroups, while allowing for flexibility in the extent with which data across subgroups are pooled or considered independently.[37,38]
Ability to replace the control treatment strategy	The control treatment or factor within each domain can be replaced when the standard of care changes, eliminating the need to pause or terminate the trial with improvements in the standard of care.

Potential Domains and Factors/Treatments

Treatment Domain	Factors of Treatment Options within the Domain
Transfusion Strategy	1. Arm A: (Control) with 1:1:1 plasma:platelets:RBCs 2. Arm B: Low titer liquid cold stored whole blood (LTOWB) 3. Arm C: Fresh whole blood
Management of Coagulopathy	1. Arm A: (Control) plasma (FFP, thawed or liquid) 2. Arm B: Thromboelastography (TEG) guided management 3. Arm C: Fibrinogen concentrate first strategy 4. Arm D: (Back up) Lyophilized plasma 5. Arm E: (Back up) Prehospital freeze-dried plasma w TEG-guided ED management
Hemorrhage Control	1. Arm A: (Control) Stop the Bleed Interventions 2. Arm B: Prehospital hemorrhage control with wound packing using hemostatic agents 3. Arm C: Prehospital hemorrhage control with injectable sponges
Management of Acute Respiratory Distress Syndrome	1. Arm A: (Control) Low tidal volume ventilation 2. Arm B: ECMO to obviate need for ventilation 3. Arm C: Anti-inflammatory therapies
Treatment of TBI with Concomitant Traumatic Hemorrhage	1. Arm A: (Control) Permissive hypotension 2. Arm B: Titrate to MAP of 60 mmHg 3. Arm C: Titrate to MAP of 80 mmHg

Controls in a Multifactorial Platform Trial

- Management of Coagulopathy
  - Exp. Rx. 1
  - Exp. Rx. 2
  - Exp. Rx. 3
  - Exp. Rx. 4
  - Control
- Transfusion Strategy
  - Exp. Strategy 1
  - Exp. Strategy 2
  - Exp. Strategy 3
  - Standard/Control



Rx × 1	Rx × 2	Rx × 2	Rx × 2	Rx × 2
Rx × 1	Rx × 2	Rx × 2	Rx × 2	Rx × 2
Rx × 1	Rx × 2	Rx × 2	Rx × 2	Rx × 2
Rx × 0	Rx × 1	Rx × 1	Rx × 1	Rx × 1

Matching Domains and Factors to Strata

- Each stratum can be eligible for all or a subset of domains, as appropriate, and even to only a subset of the factors/treatment arms in the included domains
- E.g., a neuroprotectant domain can be limited to patients with head trauma
- Similarly, certain combinations of factors or treatments may be excluded from randomization and consideration, e.g., due to known drug-drug interactions or other considerations

What about Quality of Life?

- Some treatment domains are focused on quality-of-life rather than survival (e.g., rehabilitation strategies)
- QOL-focused domains can be “driven” by a different endpoint, e.g., a patient-reported outcome (PRO)
- Possible strategy
  - Primary outcome 6-hour all-cause mortality
  - Secondary outcomes: Longer term survival; QoL PRO
  - Use QoL as primary for domains targeting QoL

Conclusions

- An adaptive, multifactorial platform trial can be used to create a seamless process in which new evidence is immediately used to improve trial efficiency, decrease the time and cost necessary to evaluate individual and combination therapies, and improve the outcomes of patients treated within the trial
- This approach is highly promising for the accelerated evaluation of treatments for post-traumatic hemorrhagic shock
- A “roadmap” for such a trial including fundamental structure, implementation strategies and considerations, and ethical issues has been recently published

Key Elements in the Design of a Platform Trial (1)

- Overall Patient Population: Should generally be broadly defined to avoid overly limiting the population, given long time horizon
- Subpopulations/Strata: Exhaustive but mutually-exclusive subgroups, based on baseline characteristics, that define the smallest groups in which you may want to draw different conclusions regarding efficacy
- Initial Interventions: May be limited at the start of the trial
  - *Domains*: A group of therapeutic options sharing a common goal or mechanism (e.g., anti-fibrotics, immunosupressives)
  - *Factors*: The set of mutually exclusive options within each domain (e.g., the choice of anti-fibrotic agent, or choice of dose of an agent)
  - *Combinations*: Must consider what combinations of factors across domains, if any, are excluded from consideration

Key Elements in the Design of a Platform Trial (2)

- Trial Endpoint: A single primary endpoint is generally chosen to "drive" the adaptive design
  - *Proximate outcomes*: more proximate outcomes can be used to inform interim decision-making allowing use of information from patients who have not yet reaching the primary endpoint
- Decisions Rules: The set of prespecified rules that comprise the adaptive design
  - *Stopping*: Criteria for stopping an arm (e.g., for harm or efficacy)
  - *Randomization*: Criteria for modifying randomization (e.g, RAR)
  - *Enrichment*: Criteria for restricting the randomization to selected subgroups of patients due to futility or harm in other subgroups
  - *Phase II/III transition*: Bringing a single treatment strategy forward to testing against control in a confirmatory setting