Platform Trial Design: Application to Therapeutic Trials in Lyme IACI

Research for Lyme Infection-Associated Chronic Illnesses Treatment:
Broadening the Lens – A Workshop
July 11, 2024

Roger J. Lewis, MD, PhD
Senior Medical Scientist, Berry Consultants, LLC; Investigator, Lundquist Institute, Harbor-UCLA Medical Center; Professor of Emergency Medicine, David Geffen School of Medicine at UCLA

Email: roger@berryconsultants.com

Berry Consultants
Statistical Innovation

Financial Disclosures

- Academic Affiliation and Employment
  - David Geffen School of Medicine at UCLA
  - Lundquist Institute for Biomedical Innovation
  - Berry Consultants, LLC (multiple clients)
- Special Government Employee
  - Food and Drug Administration
- Other
  - Senior Statistical Editor, *JAMA*

Challenges in Testing Therapeutics for Lyme IACI

- Heterogeneous disease and patient population (e.g., primary symptomatology, time since initial infection, variability over time, possibility of multiple pathogens)
  - Prior trials with small fractions of screened patients ultimately enrolled
- Potential for multifactorial disease processes, likely requiring combination therapies for meaningful benefit (e.g., immune dysregulation, persistent infection, multiple pathogens)
  - Prior NIH trials focused on monotherapy, largely antimicrobials
- Burden and resources required to start and close out each clinical trial (universal problem if more than one therapy to be tested)
- Obvious analogies to long COVID

Avoiding Anticipated Regret

- A substantial fraction of all confirmatory trials fail despite promising preliminary results
- Investigators can anticipate the design decisions they are most likely to want to "take over" if the trial were to fail
- Areas of "anticipated regret" are promising targets for adaptations or trial innovation
- Major risk: investigating therapies that truly lack therapeutic benefit

Adaptive Multifactorial Platform Trial

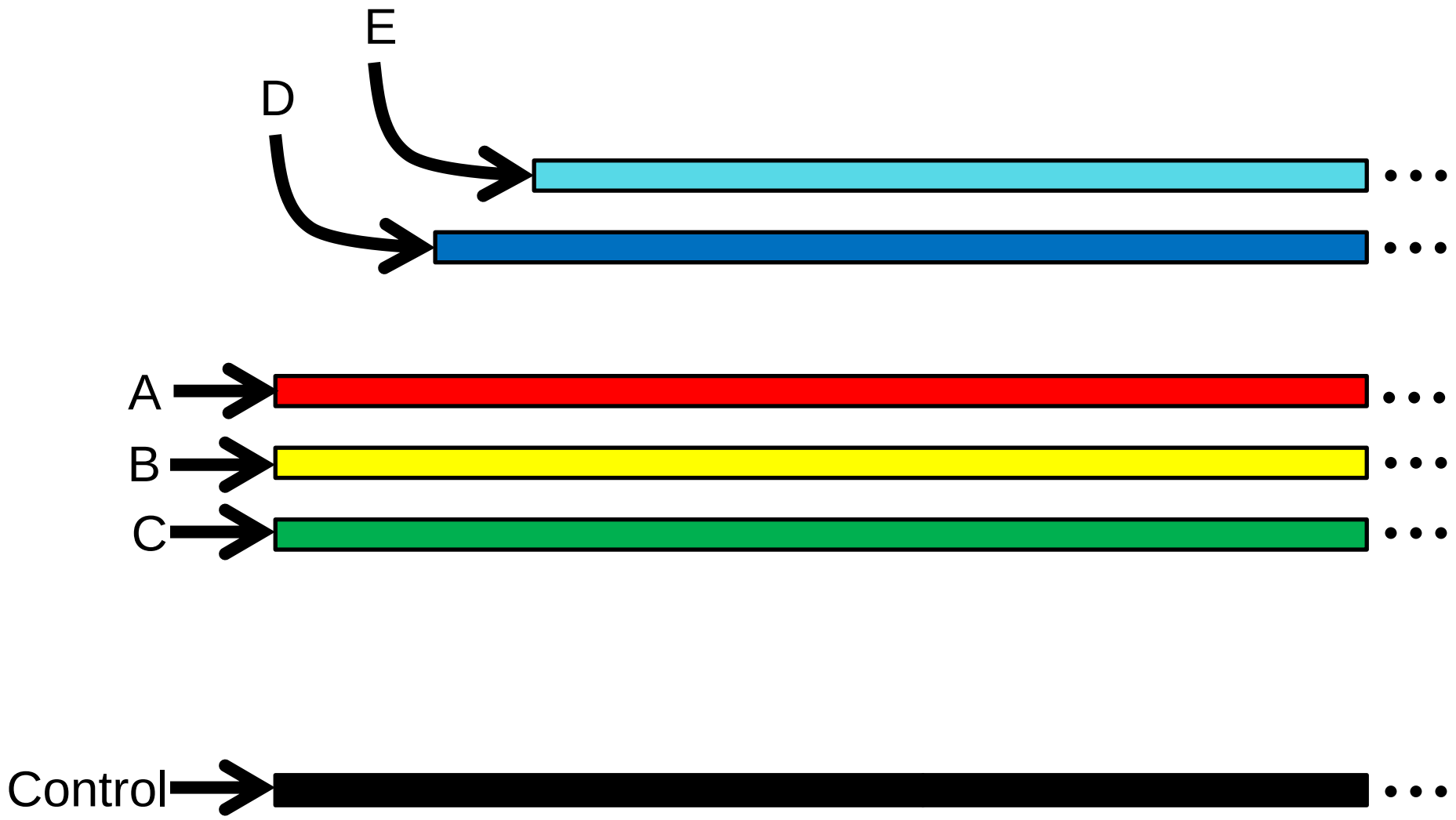
- An experimental infrastructure designed to evaluate multiple treatments, often for a heterogeneous disease, intended to continue beyond the evaluation of any individual treatment
  - Multiple treatments, often administered in combination
  - Often a broad group of related diseases or subgroups
  - 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

Adaptive Multifactorial Platform Trial

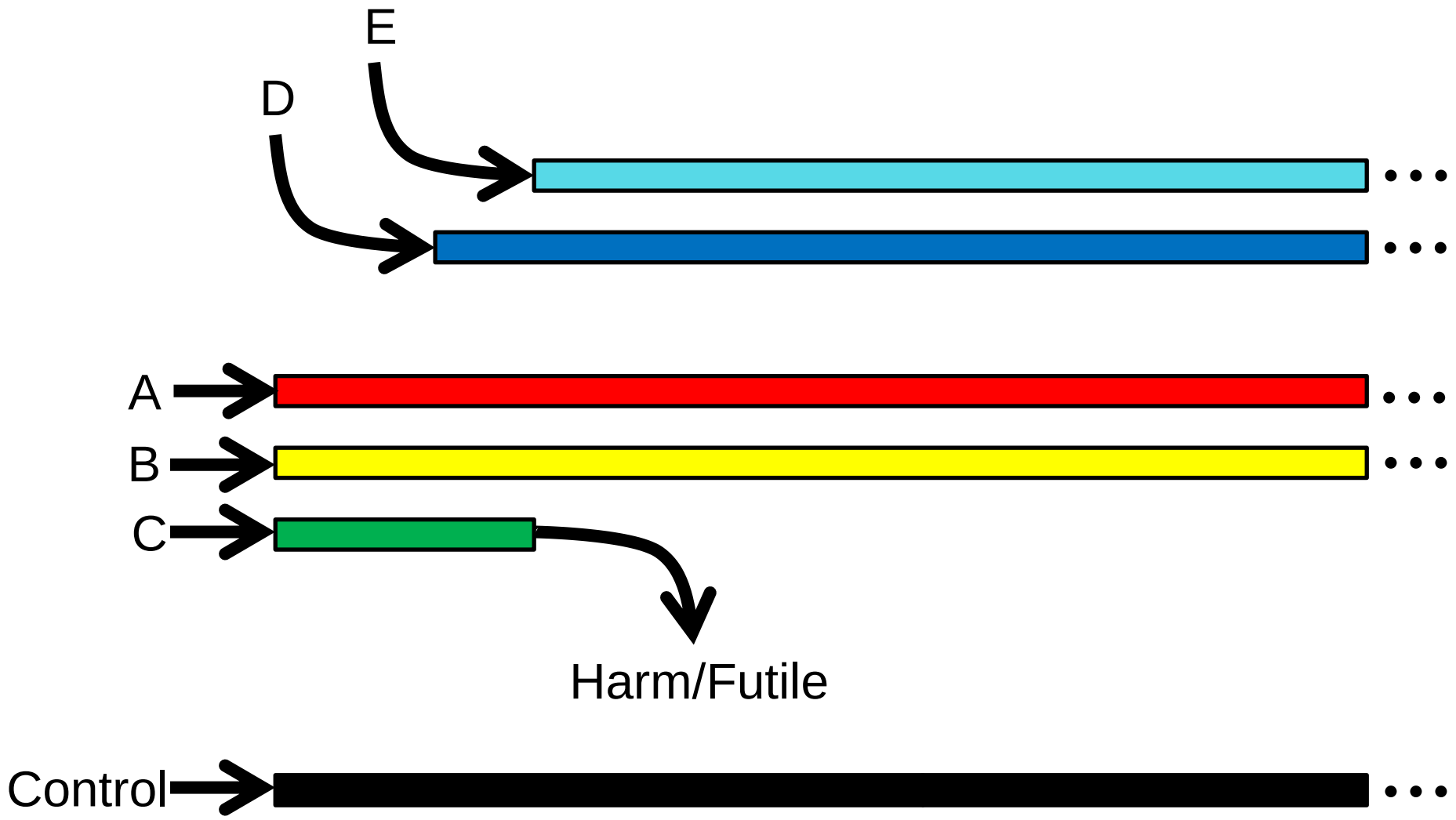
- Adaptive: Available arms, randomization ratios, etc. may change in response to accumulating data to treat patients more effectively within the trial or improve statistical efficiency
- Multifactorial: Multiple “domains” of treatment, with options available from each domain (e.g., antimicrobial, immunomodulatory, etc.)
- Platform: Intended to continue beyond the testing of initial treatment options, with the addition of new treatment options

Potential Features of a Platform Trial

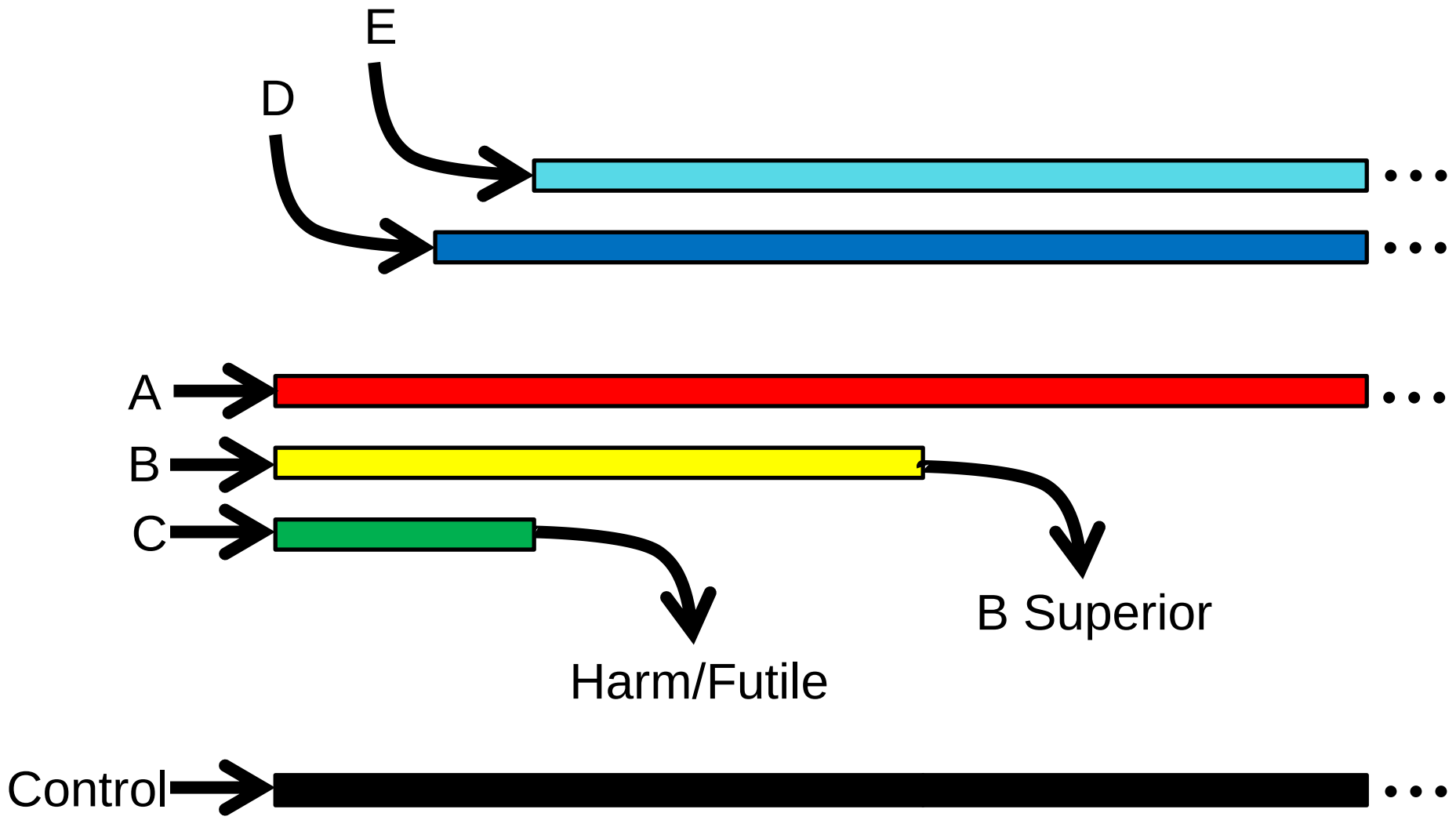
Potential Features of a Platform Trial



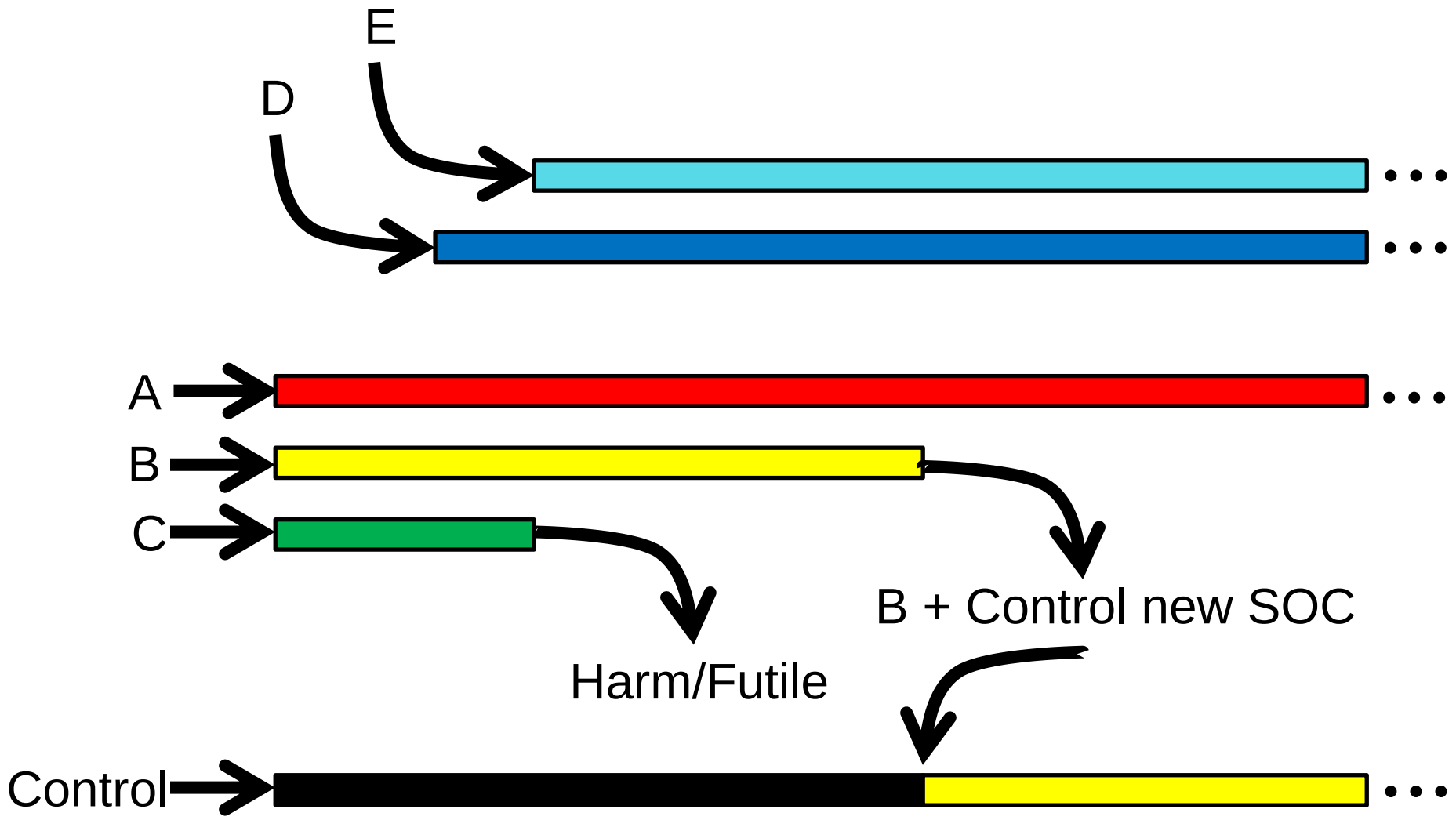
Potential Features of a Platform Trial



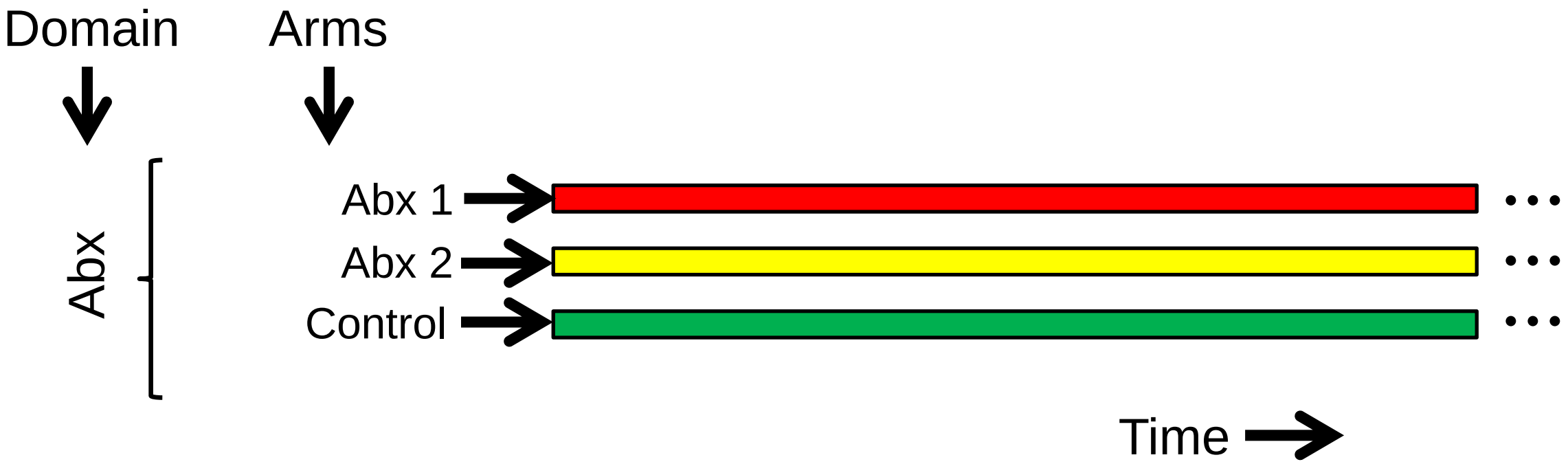
Potential Features of a Platform Trial



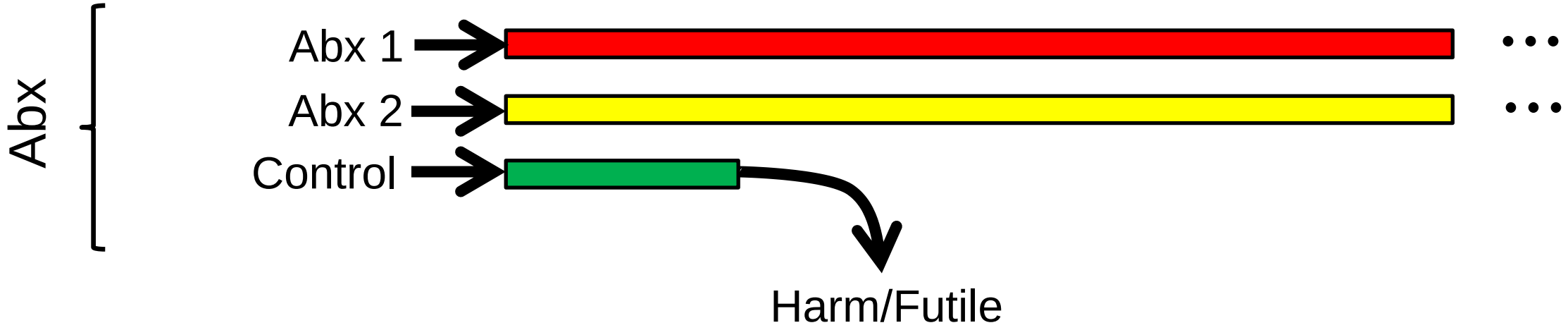
Potential Features of a Platform Trial



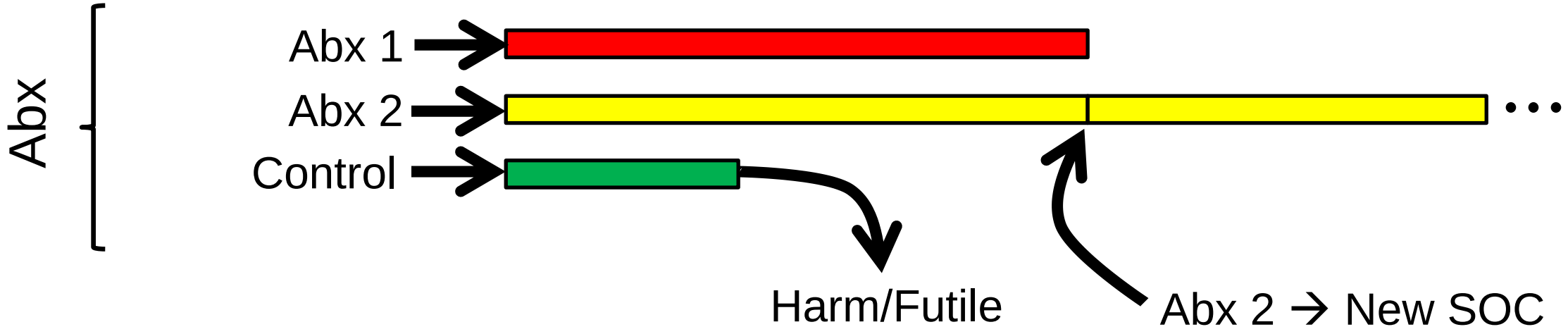
Multifactorial Platform for Lyme IACI



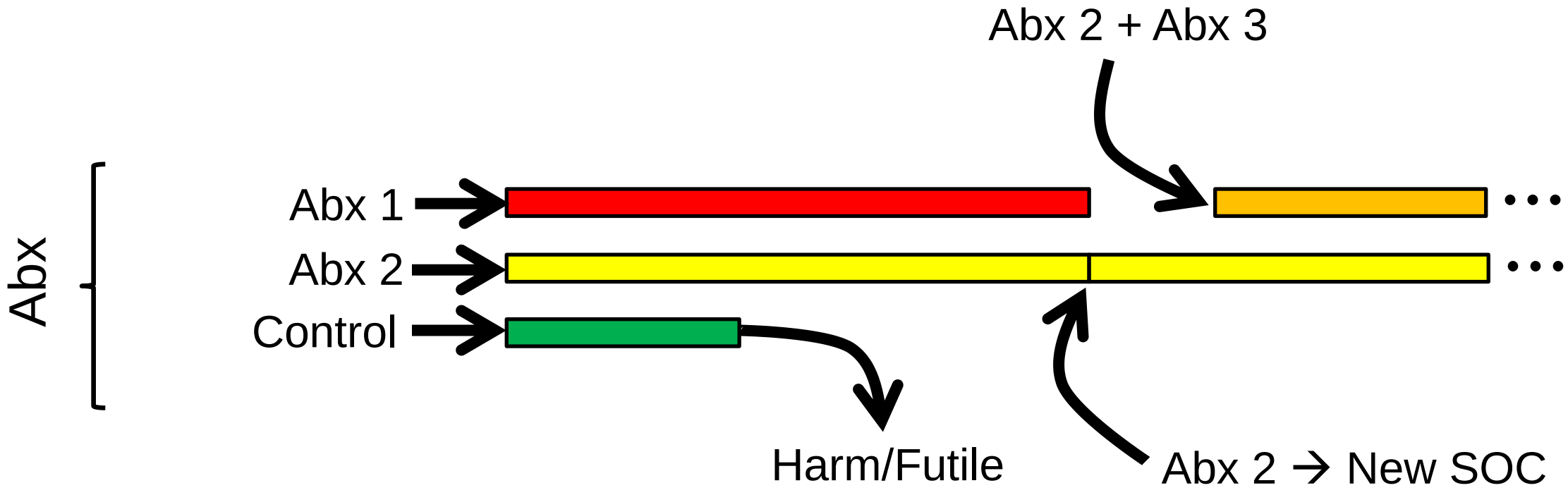
Multifactorial Platform for Lyme IACI



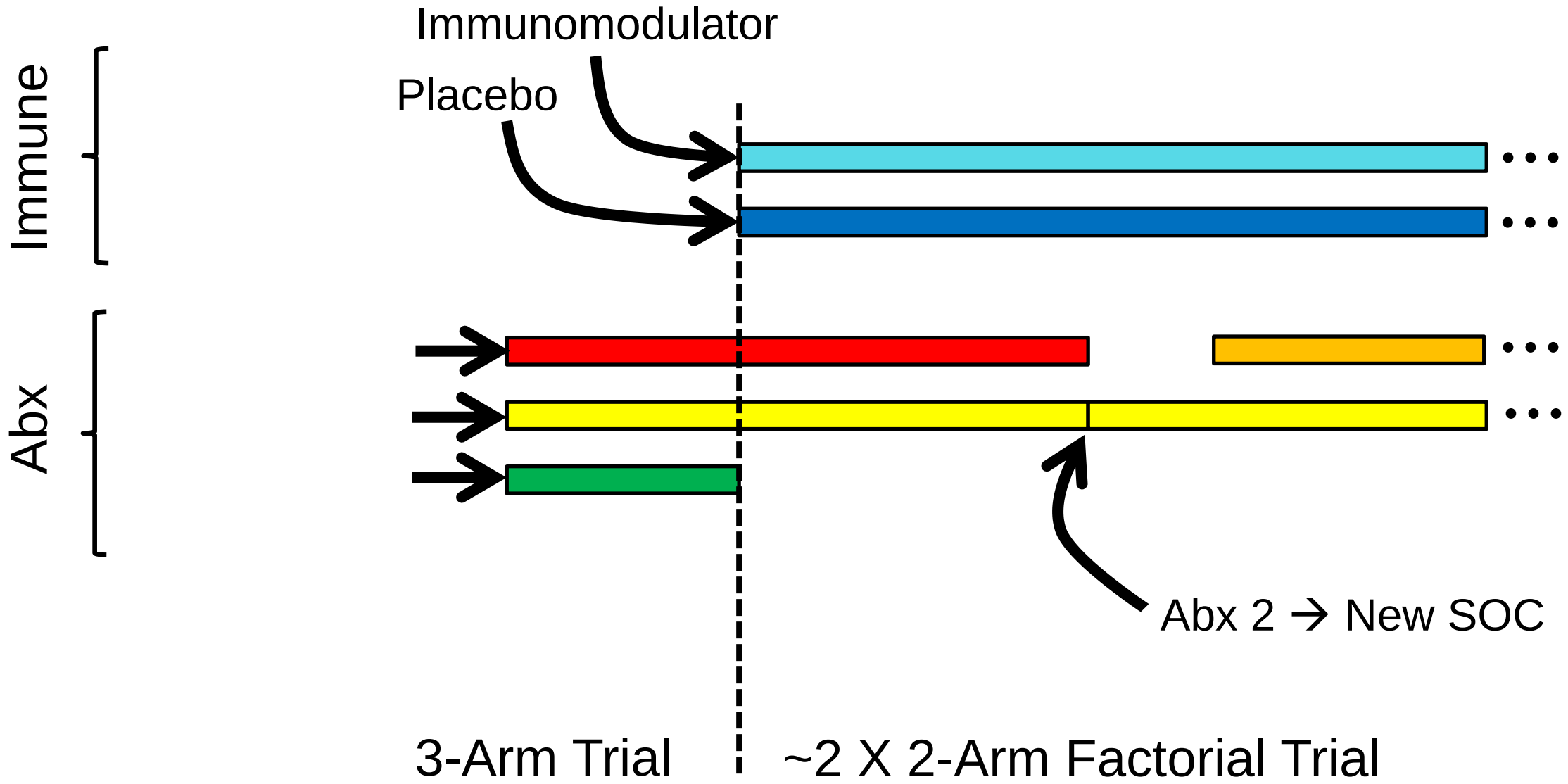
Multifactorial Platform for Lyme IACI



Multifactorial Platform for Lyme IACI

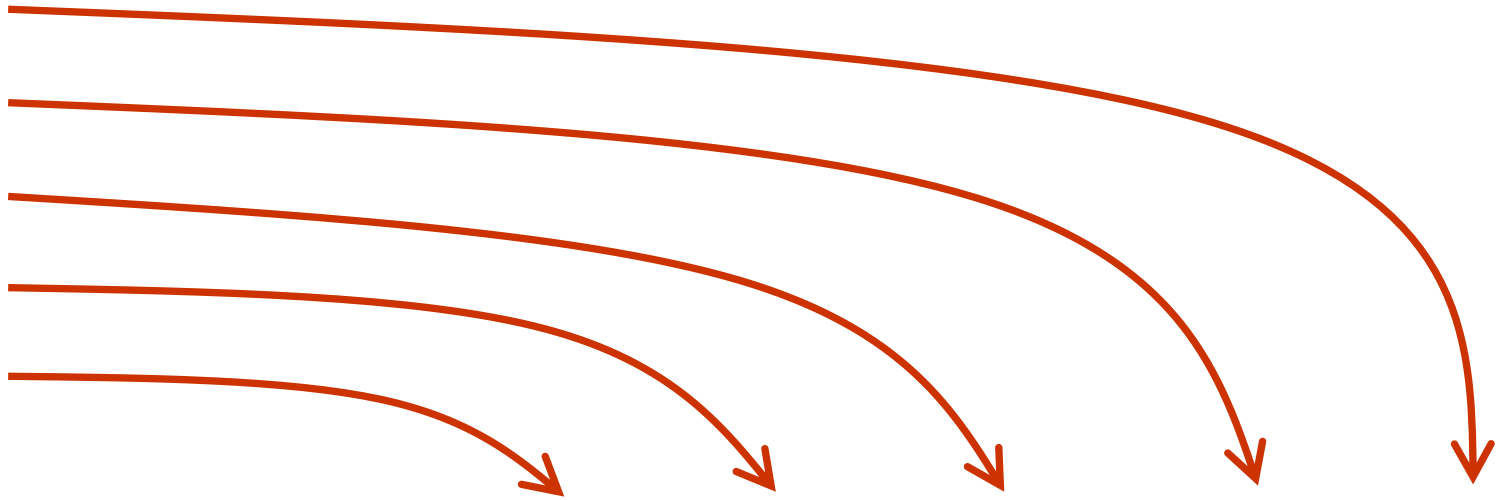


Multifactorial Platform for Lyme IACI



Controls in a Multifactorial Platform Trial

- Domain 1
  - Exp. Rx. 1
  - Exp. Rx. 2
  - Exp. Rx. 3
  - Exp. Rx. 4
  - Control
- Domain 2
  - 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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators*

ABSTRACT

BACKGROUND

The efficacy of interleukin-6 receptor antagonists in critically ill patients with coronavirus disease 2019 (Covid-19) is unclear.

METHODS

We evaluated tocilizumab and sarilumab in an ongoing international, multifactorial, adaptive platform trial. Adult patients with Covid-19, within 24 hours after starting organ support in the intensive care unit (ICU), were randomly assigned to receive tocilizumab (8 mg per kilogram of body weight), sarilumab (400 mg), or standard care (control). The primary outcome was respiratory and cardiovascular organ support–free days, on an ordinal scale combining in-hospital death (assigned a value of –1) and days free of organ support to day 21. The trial uses a Bayesian statistical model with predefined criteria for superiority, efficacy, equivalence, or futility. An odds ratio greater than 1 represented improved survival, more organ support–free days, or both.

The members of the writing committee (A.C. Gordon, P.R. Mouncey, F. Al-Beidh, K.M. Rowan, A.D. Nichol, Y.M. Arabi, D. Annane, A. Beane, W. van Bentum-Puijk, L.R. Berry, Z. Bhimani, M.J.M. Bonten, C.A. Bradbury, F.M. Brunkhorst, A. Buzgau, A.C. Cheng, M.A. Detry, E.J. Duffy, L.J. Estcourt, M. Fitzgerald, H. Goossens, R. Haniffa, A.M. Higgins, T.E. Hills, C.M. Horvat, F. Lamontagne, P.R. Lawler, H.L. Leavis, K.M. Linstrum, E. Litton, E. Lorenzi, J.C. Marshall, F.B. Mayr, D.F. McAuley, A. McGlothlin, S.P. McGuinness, B.J. McVerry, S.K. Montgomery, S.C. Morpeth, S. Murthy, K. Orr, R.L. Parke, J.C. Parker, A.E. Patanwala, V. Pettilä, E. Rademaker, M.S. Santos, C.T. Saunders, C.W. Seymour, M. Shan-

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*

ABSTRACT

BACKGROUND

Thrombosis and inflammation may contribute to morbidity and mortality among patients with coronavirus disease 2019 (Covid-19). We hypothesized that therapeutic-dose anticoagulation would improve outcomes in critically ill patients with Covid-19.

METHODS

In an open-label, adaptive, multiplatform, randomized clinical trial, critically ill patients with severe Covid-19 were randomly assigned to a pragmatically defined regimen of either therapeutic-dose anticoagulation with heparin or pharmacologic thromboprophylaxis in accordance with local usual care. The primary outcome was organ support–free days, evaluated on an ordinal scale that combined in-hospital death (assigned a value of –1) and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge.

The members of the executive writing committee and the block writing committee assume responsibility for the overall content and integrity of this article. The full names, academic degrees, and affiliations of the members of the executive writing committee and the block writing committee are listed in the Appendix. Address reprint requests to Dr. Zarychanski at the Sections of Hematology/Oncology and Critical Care, University of Manitoba, Winnipeg, MB, Canada R3E 0V9, or at rzarychanski@cancercare.mb.ca.

*The full list of investigators and collaborators is provided in the Supplementary Appendix, available at NEJM.org.

ORIGINAL ARTICLE

Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

The ATTACC, ACTIV-4a, and REMAP-CAP Investigators*

ABSTRACT

BACKGROUND

Thrombosis and inflammation may contribute to the risk of death and complications among patients with coronavirus disease 2019 (Covid-19). We hypothesized that therapeutic-dose anticoagulation may improve outcomes in noncritically ill patients who are hospitalized with Covid-19.

METHODS

In this open-label, adaptive, multiplatform, controlled trial, we randomly assigned patients who were hospitalized with Covid-19 and who were not critically ill (which was defined as an absence of critical care–level organ support at enrollment) to receive pragmatically defined regimens of either therapeutic-dose anticoagulation with heparin or usual-care pharmacologic thromboprophylaxis. The primary outcome was organ support–free days, evaluated on an ordinal scale that combined in-hospital death (assigned a value of –1) and the number of days free of cardio-

The members of the executive writing committee and the block writing committee assume responsibility for the overall content and integrity of this article. The full names, academic degrees, and affiliations of the members of the executive writing committee and the block writing committee are listed in the Appendix. Address reprint requests to Dr. Zarychanski at the Sections of Hematology/Oncology and Critical Care, University of Manitoba, Winnipeg, MB, Canada R3E 0V9, or at rzarychanski@cancercare.mb.ca; or to Dr. Hochman at New York University Grossman School of Medicine, New York University Langone Health, 530 First Ave., Skirball 9R, New York, NY,

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Convalescent Plasma on Organ Support–Free Days in Critically Ill Patients With COVID-19
A Randomized Clinical Trial

Writing Committee for the REMAP-CAP Investigators

IMPORTANCE The evidence for benefit of convalescent plasma for critically ill patients with COVID-19 is inconclusive.

OBJECTIVE To determine whether convalescent plasma would improve outcomes for critically ill adults with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS The ongoing Randomized, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) enrolled and randomized 4763 adults with suspected or confirmed COVID-19 between March 9, 2020, and January 18, 2021, within at least 1 domain; 2011 critically ill adults were randomized to open-label interventions in the immunoglobulin domain at 129 sites in 4 countries. Follow-up ended on April 19, 2021.

INTERVENTIONS The immunoglobulin domain randomized participants to receive 2 units of high-titer, ABO-compatible convalescent plasma (total volume of 550 mL ± 150 mL) within 48 hours of randomization (n = 1084) or no convalescent plasma (n = 916).

Supplemental content

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Antiplatelet Therapy on Survival and Organ Support–Free Days in Critically Ill Patients With COVID-19
A Randomized Clinical Trial

REMAP-CAP Writing Committee for the REMAP-CAP Investigators

IMPORTANCE The efficacy of antiplatelet therapy in critically ill patients with COVID-19 is uncertain.

OBJECTIVE To determine whether antiplatelet therapy improves outcomes for critically ill adults with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS In an ongoing adaptive platform trial (REMAP-CAP) testing multiple interventions within multiple therapeutic domains, 1557 critically ill adult patients with COVID-19 were enrolled between October 30, 2020, and June 23, 2021, from 105 sites in 8 countries and followed up for 90 days (final follow-up date: July 26, 2021).

INTERVENTIONS Patients were randomized to receive either open-label aspirin (n = 565), a P2Y12 inhibitor (n = 455), or no antiplatelet therapy (control; n = 529). Interventions were continued in the hospital for a maximum of 14 days and were in addition to anticoagulation thromboprophylaxis.

MAIN OUTCOMES AND MEASURES The primary end point was organ support–free days (days alive and free of intensive care unit–based respiratory or cardiovascular organ support)

Visual Abstract
Editorial
Supplemental content

Revisiting Challenges in Lyme IACI

- Heterogeneous disease and afflicted population
  - Enroll a broad population, maximize screen “successes”
  - Explicitly address/model heterogeneity, including the possibility that best treatment(s) depend on subgroup/disease characteristics
- Potential for multifactorial disease processes, likely requiring combination therapies for meaningful benefit
  - Factorial design to test combination treatments
  - Minimize fraction of participants randomized to pure control strategies
- Burden and resources required to start and close out each clinical trial
  - Seamless dropping and adding of treatment arms to minimize gaps and transition costs/delays

Final Comments

- An adaptive trial can create a seamless process in which new evidence is immediately used to improve trial efficiency, decrease the time and cost necessary to evaluate new therapies, and improve expected patient outcomes within the trial
- A platform trial extends this process beyond a single treatment or few treatments and beyond a homogeneous population, and accommodate treatment options that change over time
- A well-designed adaptive, or adaptive platform trial, is prespecified and tailored to address the most pressing threats to success, while achieving greater statistical efficiency and better patient outcomes within the trial

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
  - *Factors*: The set of mutually exclusive options within each domain
  - *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

Master Protocol vs Platform Trial

- Master Protocol: A set of standard definitions, procedures, data collection and management structures, etc. that can be used to implement multiple related clinical trials and yield important improvements in quality and operational efficiency.
- Platform Trial: An integrated clinical trial that has the capability to evaluate multiple treatments simultaneously, often in combination, and with the list of available treatments changing over time.
  - *Perpetual trial*: A platform trial that is designed so that it can continue indefinitely with the dropping and addition of new treatments as appropriate.

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

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

From the Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD. Address reprint requests to Dr. LaVange at the Office of Biostatistics, Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Blvd., Silver Spring, MD 20993, or at lisa.lavange@fda.hhs.gov.

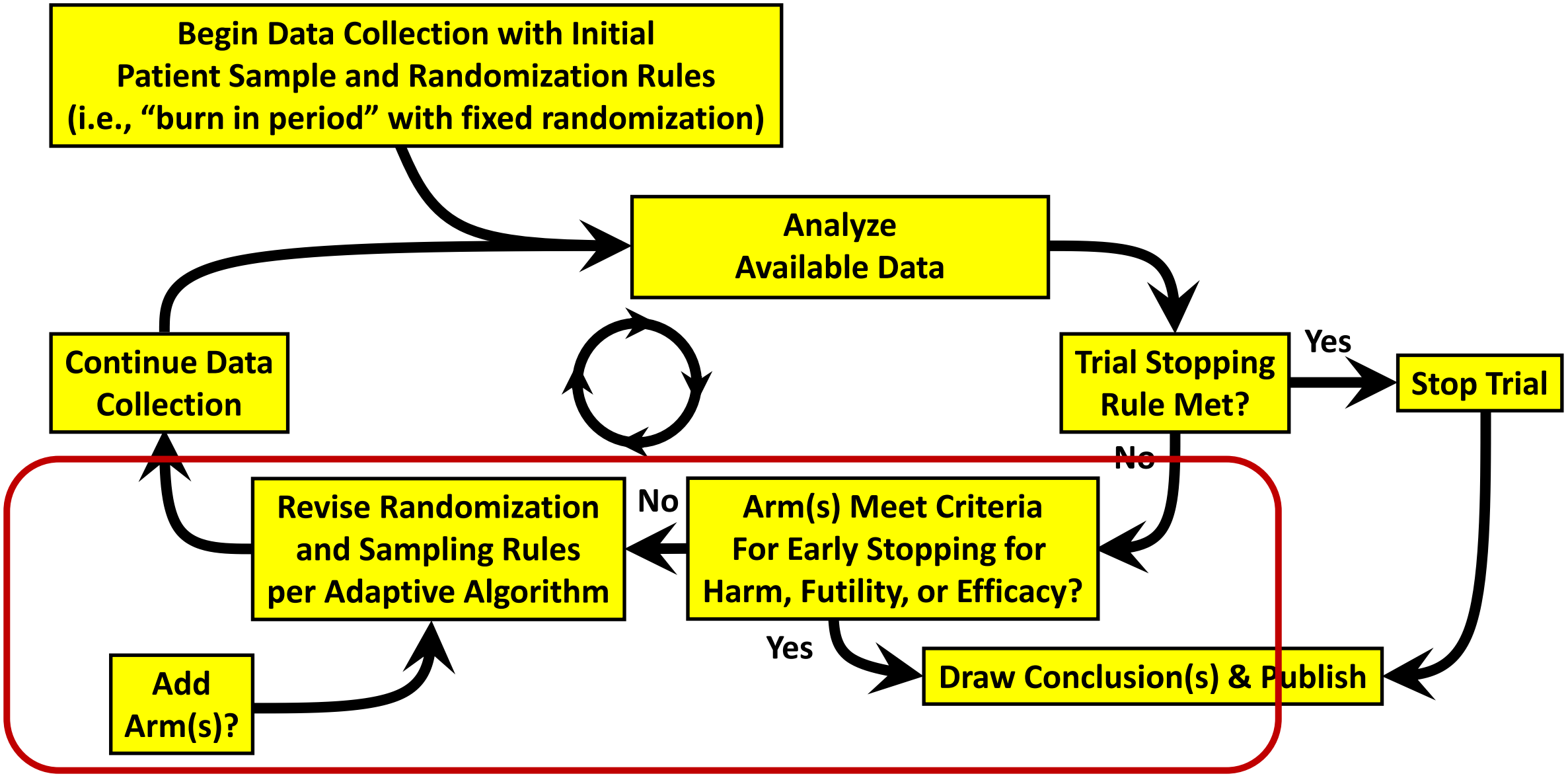
N Engl J Med 2017;377:62-70.
DOI: 10.1056/NEJMra1510062

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

NEJM 2017;377:62-70

The Adaptive Process for a Platform Trial



Potential Efficiencies or Enhancements

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