Clinical Trial Designs to Accelerate Progress in the Treatment of TBI

Innovation Trends in Technologies for the Prevention, Treatment, and Management of Traumatic Brain Injury: A Workshop
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Financial Disclosures

- Academic Affiliation and Employment
  - County of Los Angeles, Department of Health Services
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- Other
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Introduction

- Similar to other challenging therapeutic areas, there are multiple challenges facing later-stage (phase II/III) development and evaluation of new treatments for TBI
- Complexity and heterogeneity of patient populations & injuries
- Likely complexity of effective treatment strategies
  - Combination treatments
  - Sequences of treatments, influences by prior individual response
  - Matching of therapies to responding subsets defined by biomarkers, imaging patterns, clinical phenotypes (heterogeneity of treatment effect)
- Progress has likely been slowed by the disconnect between how we design trials (simple) and how we deliver care (complex)

Learning Efficiently and Clinical Trials in TBI

- Across therapeutic areas, there has been marked progress in accelerating the evaluation of new treatments through innovative clinical trial design
- There is (almost) nothing unique about designing better trials of treatments for TBI
  - The statistical process of learning is agnostic to disease
- However, diffusion of innovation across areas is slow:
  - “But, has that type of trial been run in Disease X?”
  - “Did the FDA approve the drug/biologic/device?”

Some Example Goals of Innovative Trial Design

- Reduce risk of failure—failure to get a definitive answer to the motivating question—avoiding "anticipated regret"
- Fail efficiently at the level of the individual therapy
- Achieve greater efficiency, often through multiple "paths"
  - Structural efficiency, e.g., shared control groups, factorial designs
  - Operational efficiency, e.g., platform trials, master protocols
  - Inferential efficiency, e.g., adaptive designs, response-adaptive randomization, hierarchical modeling of HTE, seamless phase II/III
- Mirror clinical care, e.g., sequences of treatments driven by patient response, personalized and combination therapies

Example Trial Designs (1)

- **Adaptive**: Prespecified use of incoming data to modify trial characteristics, to improve treatment of patients, statistical efficiency, or mitigate risk of failure
  - Frequent interim analyses, response-adaptive randomization, early stopping for predicted success or futility
  - Time-to-information is critical
- **Adaptive Enrichment**: Modification of eligibility criteria to focus future enrollment on responding population(s)
  - Examples: DAWN and ENRICH in ischemic and hemorrhagic stroke

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Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

R.G. Nogueira, A.P. Jadhav, D.C. Haussen, A. Bonafe, R.F. Budzik, P. Bhuva, D.R. Yavagal, M. Ribo, C. Cognard, R.A. Hanel, C.A. Sila, A.E. Hassan, M. Millan, E.I. Levy, P. Mitchell, M. Chen, J.D. English, Q.A. Shah, F.L. Silver, V.M. Pereira, B.P. Mehta, B.W. Baxter, M.G. Abraham, P. Cardona, E. Veznedaroglu, F.R. Hellinger, L. Feng, J.F. Kirmani, D.K. Lopes, B.T. Jankowitz, M.R. Frankel, V. Costalat, N.A. Vora, A.J. Yoo, A.M. Malik, A.J. Furlan, M. Rubiera, A. Aghaebrahim, J.-M. Olivot, W.G. Tekle, R. Shields, T. Graves, R.J. Lewis, W.S. Smith, D.S. Liebeskind, J.L. Saver, and T.G. Jovin, for the DAWN Trial Investigators*

ABSTRACT

BACKGROUND

The effect of endovascular thrombectomy that is performed more than 6 hours after the onset of ischemic stroke is uncertain. Patients with a clinical deficit that is disproportionately severe relative to the infarct volume may benefit from late thrombectomy.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Jovin at the University of Pittsburgh Med-

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ORIGINAL ARTICLE

Trial of Early Minimally Invasive Removal of Intracerebral Hemorrhage

G. Pradilla, J.J. Ratcliff, A.J. Hall, B.R. Saville, J.W. Allen, G. Paulon, A. McGlothlin, R.J. Lewis, M. Fitzgerald, A.F. Caveney, X.T. Li, M. Bain, J. Gomes, B. Jankowitz, G. Zenonos, B.J. Molyneaux, J. Davies, A. Siddiqui, M.R. Chicoine, S.G. Keyrouz, J.A. Grossberg, M.V. Shah, R. Singh, B.N. Bohnstedt, M. Frankel, D.W. Wright, and D.L. Barrow, for the ENRICH trial investigators*

ABSTRACT

BACKGROUND

Trials of surgical evacuation of supratentorial intracerebral hemorrhages have generally shown no functional benefit. Whether early minimally invasive surgical removal would result in better outcomes than medical management is not known.

METHODS

In this multicenter, randomized trial involving patients with an acute intracerebral hemorrhage, we assessed surgical removal of the hematoma as compared with medical management. Patients who had a lobar or anterior basal ganglia hemorrhage with a hematoma volume of 30 to 80 ml were assigned, in a 1:1 ratio, within 24 hours after the time that they were last known to be well, to minimally invasive

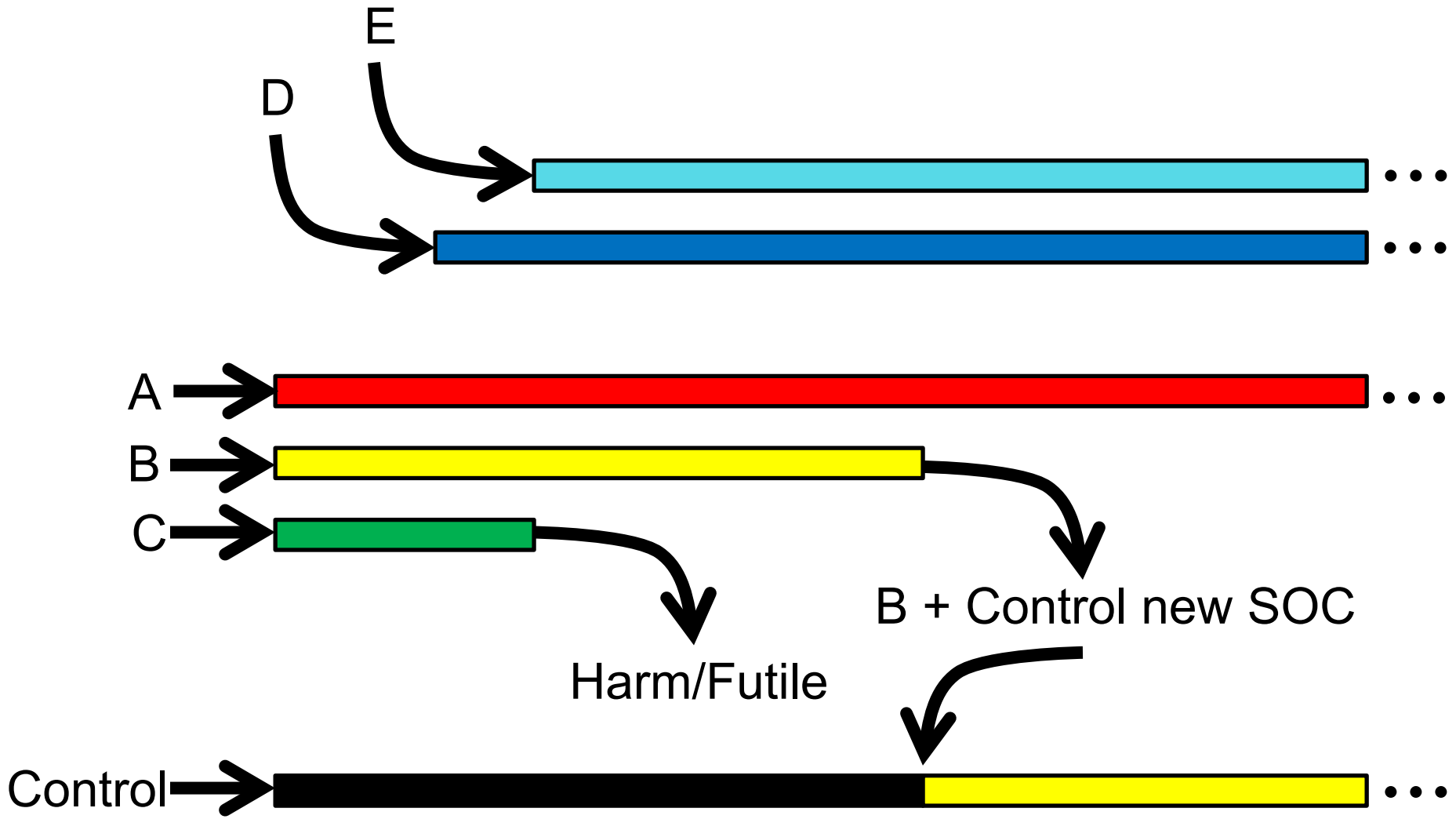
The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Pradilla can be contacted at gpradil@emory.edu or at the Department of Neurosurgery, Emory University School of Medicine, 1365 Clifton Rd. NE, Suite B6200, Atlanta, GA 30322.

*A complete list of collaborators, sites, and ENRICH trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

Example Trial Designs (2)

- **Platform**: Allows the dynamic modification of available treatment options
  - Addition of promising therapies when available
  - Dropping of therapies for success or futility/failure
  - Avoid “rebuilding the stadium for each match”
- **Multifactorial Platform**: Allows treatment combinations
- **Sequential Multiple Assignment Randomized Trial (SMART):** Evaluates treatment sequences that depend on individual responses to prior therapies

Potential Features of a Platform Trial



Examples of Platform Trials

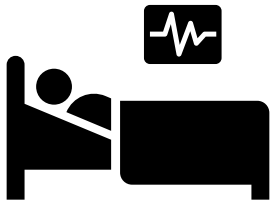
- REMAP-CAP (community acquired pneumonia and COVID)
- RECOVERY (COVID)
- GBM Agile (glioblastoma multiforme)
- Precision Promise (pancreatic cancer)
- Healey ALS Platform Trial (amyotrophic lateral sclerosis)
- STEP (acute ischemic stroke)

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

Multifactorial Platform Trial

- Patients may be eligible for more than one domain of treatment, and thus be randomized to multiple treatments, with one chosen from each domain



Neuroprotectant
None
NP A
NP B

Hemostatic Tx
None
Hemostatic Tx

Multifactorial Platform Trial

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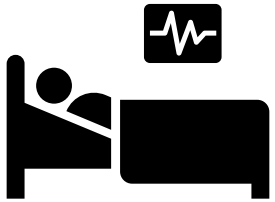

Neuroprotectant
None
NP A
NP B

Neuroprotectant
NP A

Hemostatic Tx
None
Hemostatic Tx

Hemostatic Tx
Hemostatic Tx

Randomization

Regimen
NP A
Hemostatic Tx

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-

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JAMA Guide to Statistics and Methods

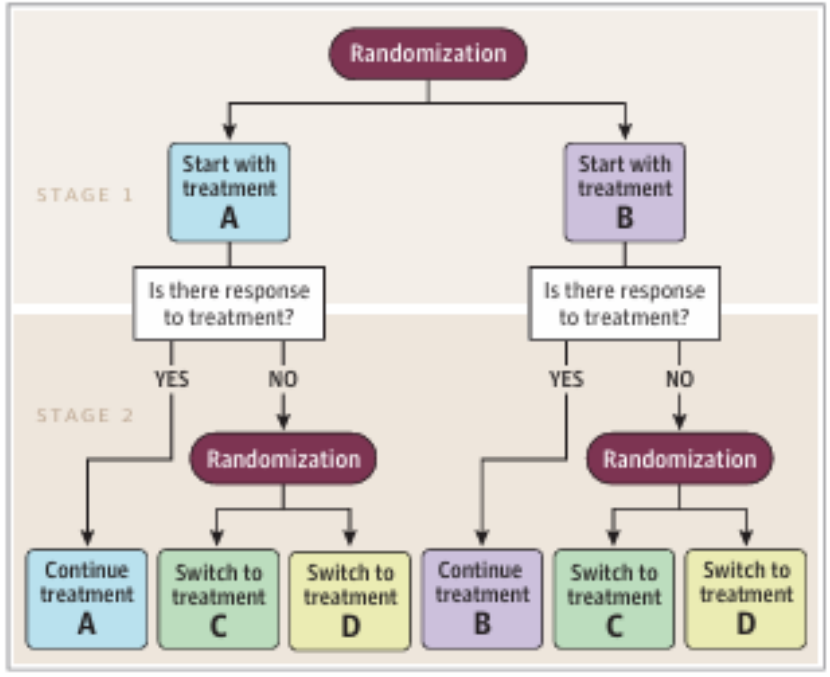
Sequential, Multiple Assignment, Randomized Trial Designs

Kelley M. Kidwell, PhD; Daniel Almirall, PhD

An adaptive intervention is a set of diagnostic, preventive, therapeutic, or engagement strategies that are used in stages, and the selection of the intervention at each stage is based on defined decision rules. At the beginning of each stage in care, treatment may be changed by the clinician to suit the needs of the patient. Typical adaptations include intensifying an ongoing treatment or adding or switching to another treatment. These decisions are made in response to changes in the patient's status, such as a patient's early response to, or engagement with, a prior treatment. The patient experiences an adaptive intervention as a sequence of personalized treatments.

Adaptive interventions are necessary because, for many disorders, the optimal sequence of interventions differs among patients. Not all patients respond the same way or have the same adverse event profile; not all patients engage with treatment in the same way; many disorders have a waxing and waning course; and comorbidities arise or become more salient during the course of care. The trial by Fortney et al[1] constructed a 2-stage, adaptive telecare intervention to treat complex psychiatric disorders in underserved, rural, primary care settings. The investigators used a sequential, multiple assignment, randomized trial (SMART)[2] design to answer questions concerning the most effective mode of intervention delivery at 2 critical decision points in the adaptive telecare intervention.

Figure. An Example of a SMART Design

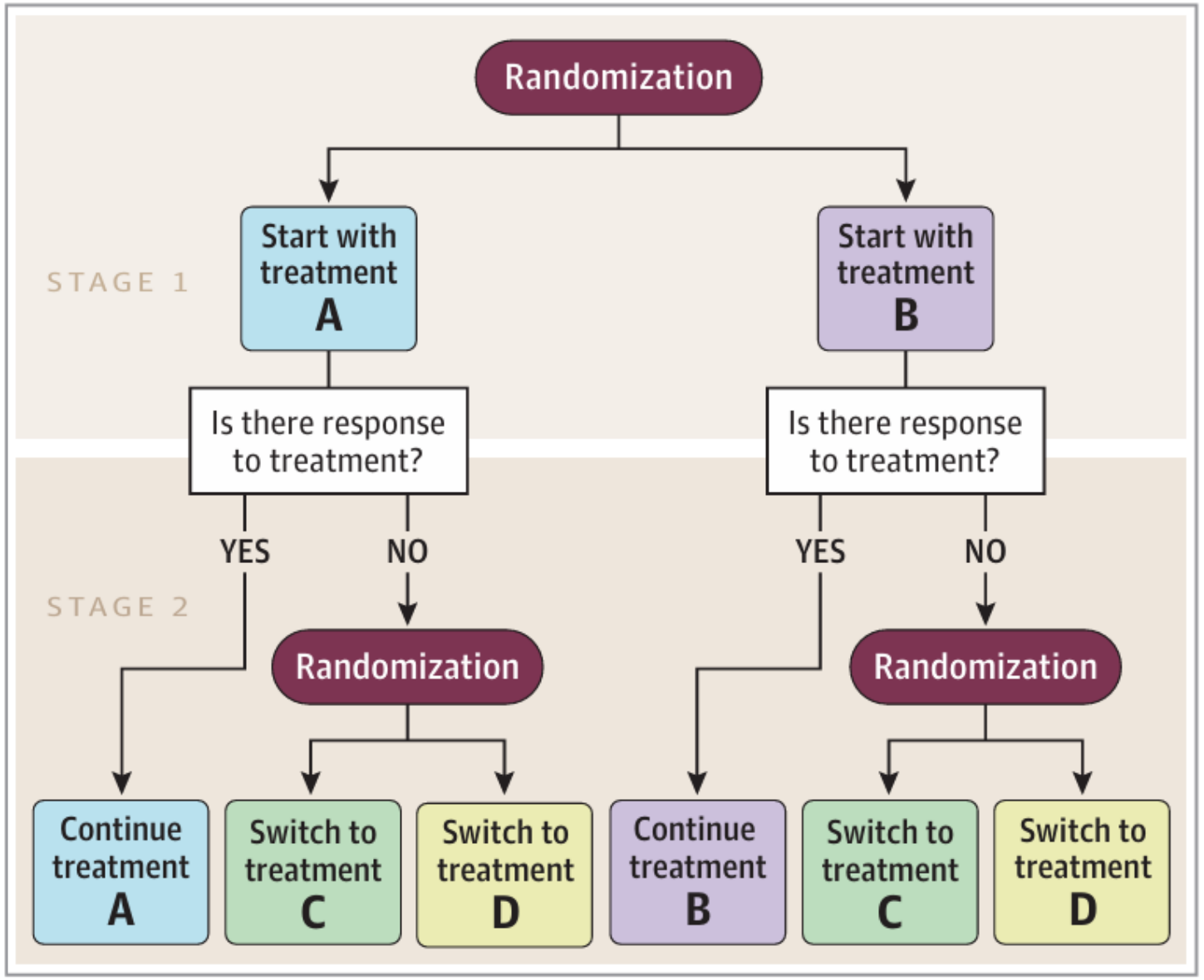


SMART indicates sequential, multiple assignment, randomized trial.

they can be varied due to pragmatic considerations. For example, in the Figure, stage 2 treatments C and D need not be the same for

JAMA. 2023;329(4):336–337.

Figure. An Example of a SMART Design



SMART indicates sequential, multiple assignment, randomized trial.

JAMA. 2023;329(4):336–337.

Potential Benefits of Example Trial Designs

Trial Design	Key Characteristic or Goal					
	Better Treatment of Patients	Reduced Risk of Failure*	Inferential Efficiency	Operational Efficiency	Comb. Therapies	Treatment Sequences
Adaptive	+++	+++	++	+/-	++	+
Adaptive Enrichment	+++	+++	++	++	+	?
Platform	+++	++/+++	+++	+++	++	+
Multifactorial Platform	+++	++/+++	+++	+++	+++	+
SMART	+++	++/+++	+	+	+	+++

* Depends on definition of failure

Common Pitfalls to Avoid

- Believing trial design in TBI is “special”
- Confusing careful thinking with information in trial design (e.g., dose selection, responding patient population) rather than designing a trial to address uncertainty
- Blaming prior failures on
  - The trial design
  - The primary outcome chosen
- Failure to conduct phase II with phase III in mind (e.g, to determine predictive probability of phase III success)

Conclusions

- The design of clinical trials in TBI can be improved by incorporating progress in other therapeutic areas
- Adaptive, platform, and SMART trials can yield substantial operational and inferential efficiencies and improve patient-centeredness
- The careful matching of the trial design strategy to the true threats to success is critical
- Success is a trial that efficiently and definitively answers the motivating question, whether positive or negative