Neuro NEXT

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

TACKLE ALS
"DONT BE SORRY LETS BEAT THIS"

Berry Consultants
Statistical Innovation

NETWORKS ACCELERATE THERAPY DEVELOPMENT

ALS PLATFORM TRIAL

ACCELERATING ALS THERAPY DEVELOPMENT

BRAINSTORMING NEURODEGENERATION
CIRM 4/15/2019

Agenda

1. Why now?

- ✓ Lessons from NeuroNEXT
- ✓ The Healey Center and NEALS
- ✓ Scientific breakthroughs and the ALS drug development pipeline

2. Platform Trial for ALS

- ✓ Definition
- ✓ Operational and scientific efficiencies
- ✓ Design considerations
- ✓ Platform for other Neurodegenerative Disorders

Conduct studies in neurological diseases through partnership with academia, private foundations and industry

Expand the NINDS capability to:

- *Respond quickly as new opportunities arise* to test promising therapies for people with neurological disorders
- *Test promising new therapies (5-7 in 7 years)*
- *Increase efficiency of clinical trials* before embarking on larger studies

Highlights of Network Success

Rich Pipeline

- 9 studies funded to date
- 5 completed; 3 actively enrolling;
  1 in start-up

Operational Efficiency

- Decreased study start up time
- Meeting study recruitment and retention targets
- Innovative study design
- Exceptional data quality

Network Partnerships

- Expanded number of trained investigators
- Built cohesive network
- Partnerships with academics, foundations and industry

NeuroNEXT: Each study contributing to field: Versatile

- **NN 101 Spinal Muscular Atrophy Biomarker Study**
  Data shared with FDA for review of new SMA Rxs
- **NN102 Ibudilast in Progressive Multiple Sclerosis**
  Medicinova
- **NN103 Rituximab in Myasthenia Gravis**
- **NN104 3K3A-APC in Acute Stroke,** First X01, ZZ Biotech
- **NN105 SRX246 for Irritability in Huntington's Disease**
  First SBIR Azevan
- **NN106 Cytochome C as Biomarker in Glioblastoma Multiforme**
- **NN107 AFQ056 (Novartis) for language learning in Fragile X**
- **NN108 Topiramate for Cryptogenic Peripheral Neuropathy**
- **NN109 ManNAc for GNE Myopathy**

Contributions to Neuro Community

- Model Network for executing clinical trials
  - Rapid study start up (central IRB, contracting)
  - Efficient on schedule enrollment
  - High quality data and optimized study close out
  - Optimized safety monitoring
    - single DSMB, medical monitoring and safety reporting
  - Sharing SOPs publically and with other networks
- Cohesive, well-functioning Network
  - Clinical trial experts from diverse neurologic fields learning from each other
  - Integrating rather than fragmenting neurological subspecialists
  - Training new investigators in trial design and leadership

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

130 academic sites

20+ years experience

Academic Contract Research Organization

- **57 studies** (21,113 participants **(21 industry-sponsored trials)**
- **PRO-ACT** (patient data > 10,000 ALS participants in clinical trials)
- **ANSWER ALS** (1000 participants)
- **Biorepository** (>90,000 cryovials)
- **Central IRB**
- **Trainings** (>1,800 trained; Investigators, Outcomes, Site Management, Patients)

- **NEW 2019 : PLATFORM TRIAL & FAST DIAGNOSTIC CENTERS**

PRESSING NEED TO INNOVATE ALS TRIALS

- Breakthroughs in our understanding of disease genetics and mechanisms
- **Growing pipeline of therapeutic candidates**
- Urgency to improve care for people affected by this serious illness + increase access to trials

Early Phase Pipeline Pressure

ALS PLATFORM TRIAL DESIGN COMMITTEE

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

Jinsy Andrews,
MD
Columbia University

James Berry,
MD, MPH
Healey Center

Merit Cudkowicz,
MD, MSc
Healey Center

Sabrina Paganoni,
MD, PhD
Healey Center

Jeremy Shefner,
MD, PhD
Barrow Neurological Institute

Kristine Broglio,
MS
Berry Consultants

Melanie Quintana,
PhD
Berry Consultants

Berry Consultants
Statistical Innovation

NEALS ADVISORY PANEL

Senda Ajroud-Driss
Ettore Beghi
Michael Benatar
Robert Bowser
Amy Chen
Sheena Chew
Americo Fernandes
Matthew Harms
Bjorn Oskarsson
Steve Kolb
Shafeeq Ladha
Erik Pioro
Jeffrey Rosenfeld
Zachary Simmons
Nimish Thakore
David Walk
Jim Wymer

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

The Status Quo

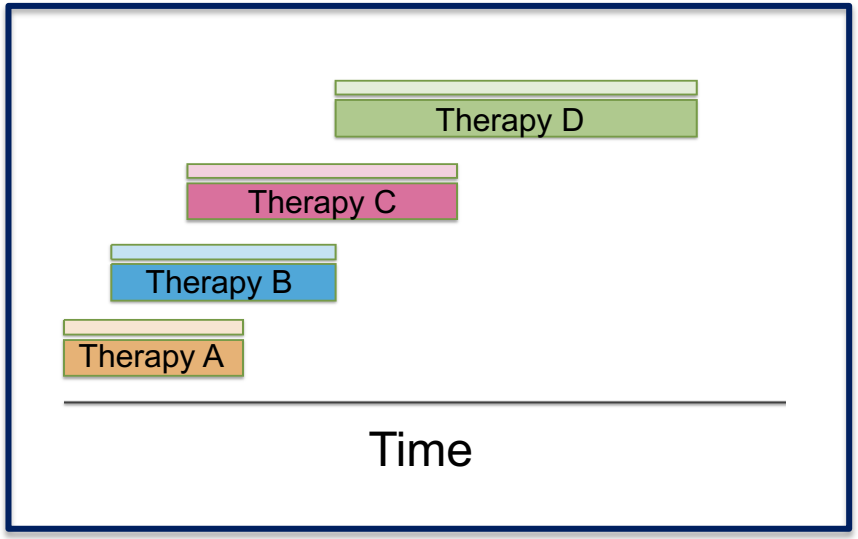
- We rebuild a new stadium every time we run a trial
- Rules are different in every match and nobody can watch the game

What if we had <u>one</u> arena and we all played at the same time, learning as we go along?

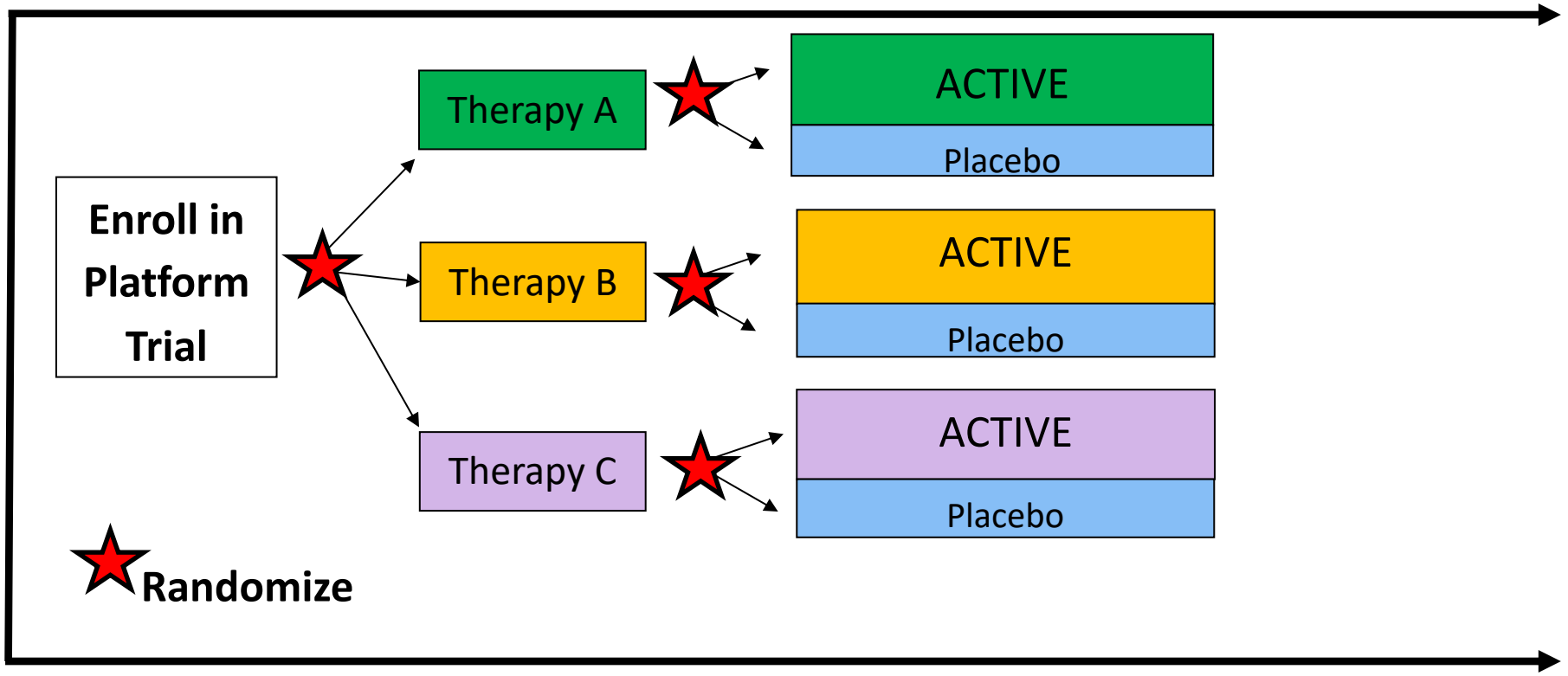
[Analogy adapted from Scott Berry, DIA Master Protocol Workshop 2018]

Platform Trial - definition

To study **multiple therapies** in the context of a single disease in a **perpetual** manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm



Platform Trial – patient experience



Pooled Placebo

- Highest statistical power comes from 1:1 randomization
- People with ALS prefer to minimize placebo
- We can achieve both of these by **pooling placebo** participants and **"sharing" power**

Operational Efficiencies

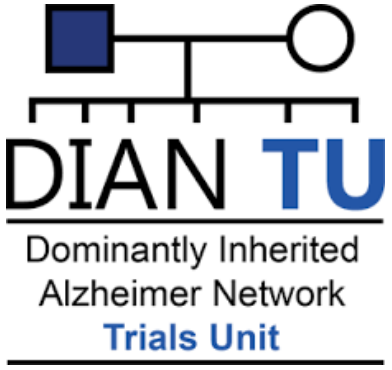
- ✓ **Faster start-up**
  - ✓ Trial-ready sites
  - ✓ Master Contracts
  - ✓ Central IRB
  - ✓ Ready EDC
- ✓ **High-quality execution**
  - ✓ Network of selected investigators and sites
  - ✓ Uniform data and samples
  - ✓ Recruitment and retention strategies
  - ✓ Robust monitoring

Scientific Efficiencies

- ✓ **Shared placebo**
  - ✓ Sample size savings
  - ✓ Appealing for patients
- ✓ **Test more therapies**
- ✓ **Learn** about disease and novel endpoints/biomarkers

  (speech analysis, neurofilaments, WGS, EIM, HHD)
- ✓ **Adapt** trial methodology

Examples of Platform Trials



Basket Trial Design
(ALS/AD/FTD Basket trial in design stage)

- One Treatment
- Multiple Diseases/Populations

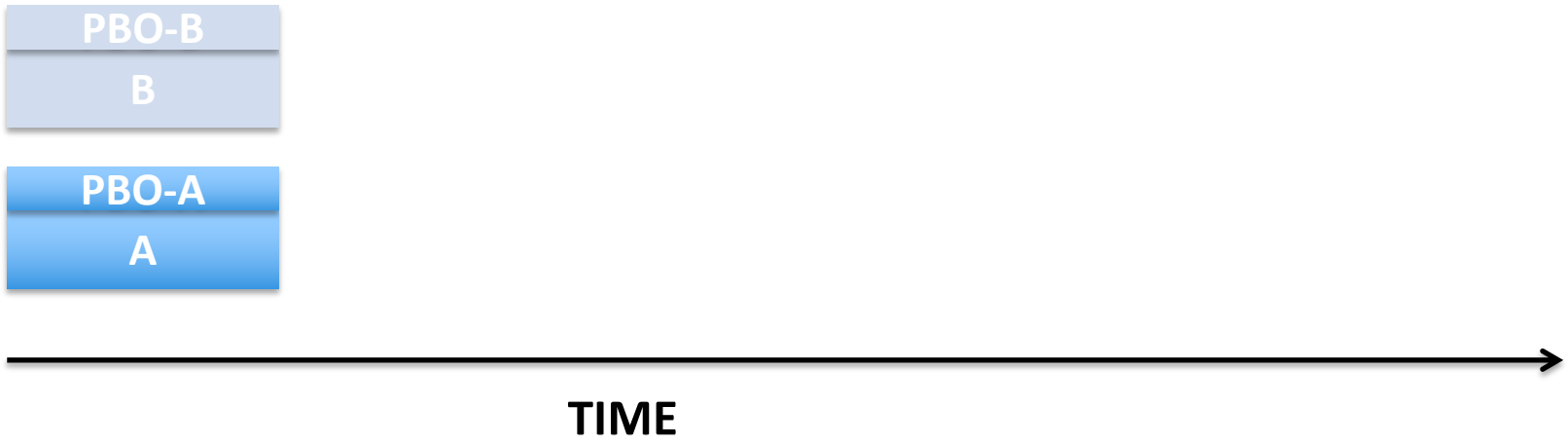
Disease	Treatment
Type A	?
Type B	?
Type C	?
…	
Type K	?
…	

Berry Consultants
Statistical Innovation

VISION FOR FIRST ALS PLATFORM TRIAL

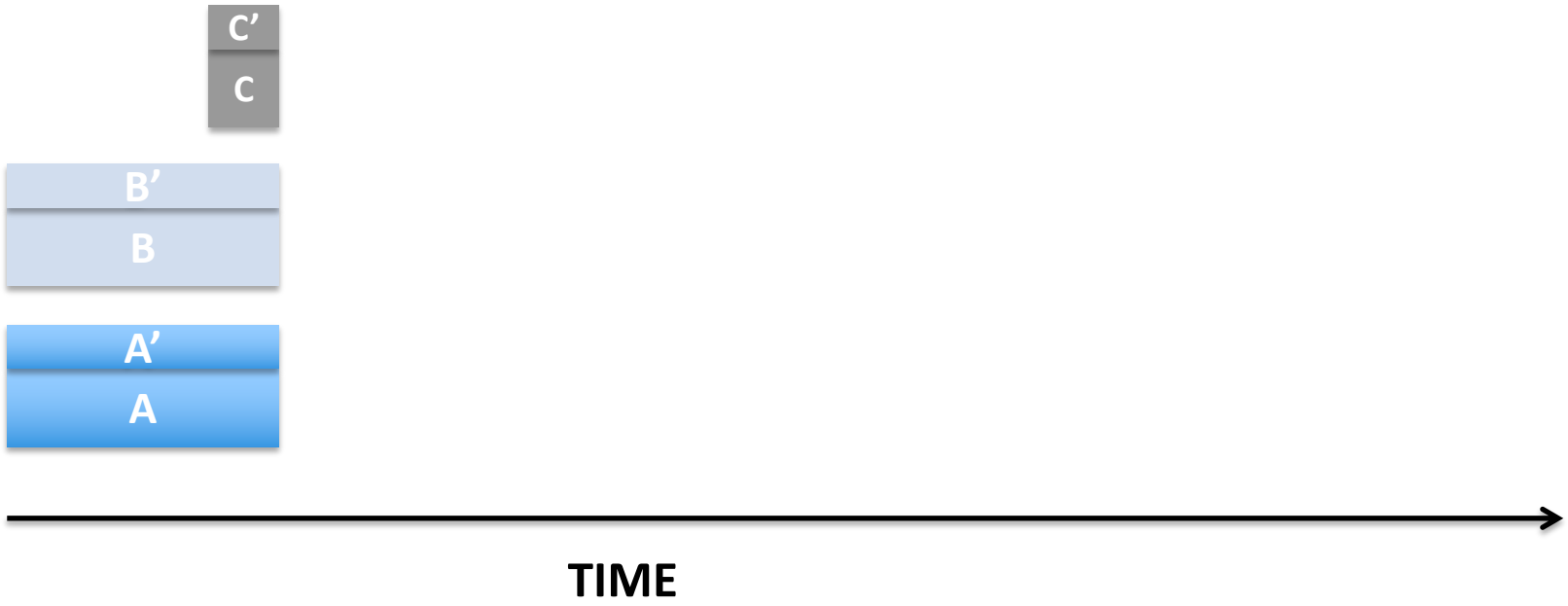
Example Regimen Journeys

- Randomized equally to all enrolling regimens
- Within a regimen randomize 3:1 Active:PBO



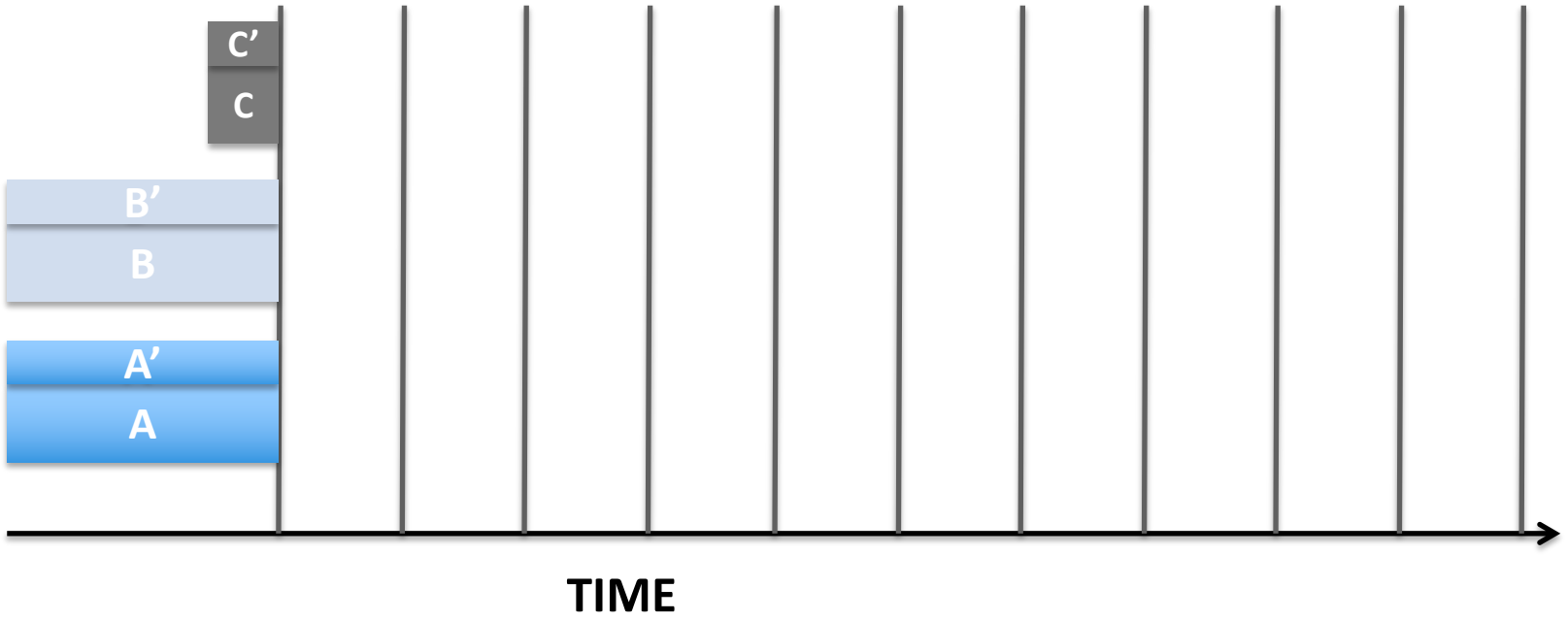
Example Regimen Journeys

- Can add treatment regimens “as appropriate”
  - Available, Enrollment support, …
  - Not a protocol change!



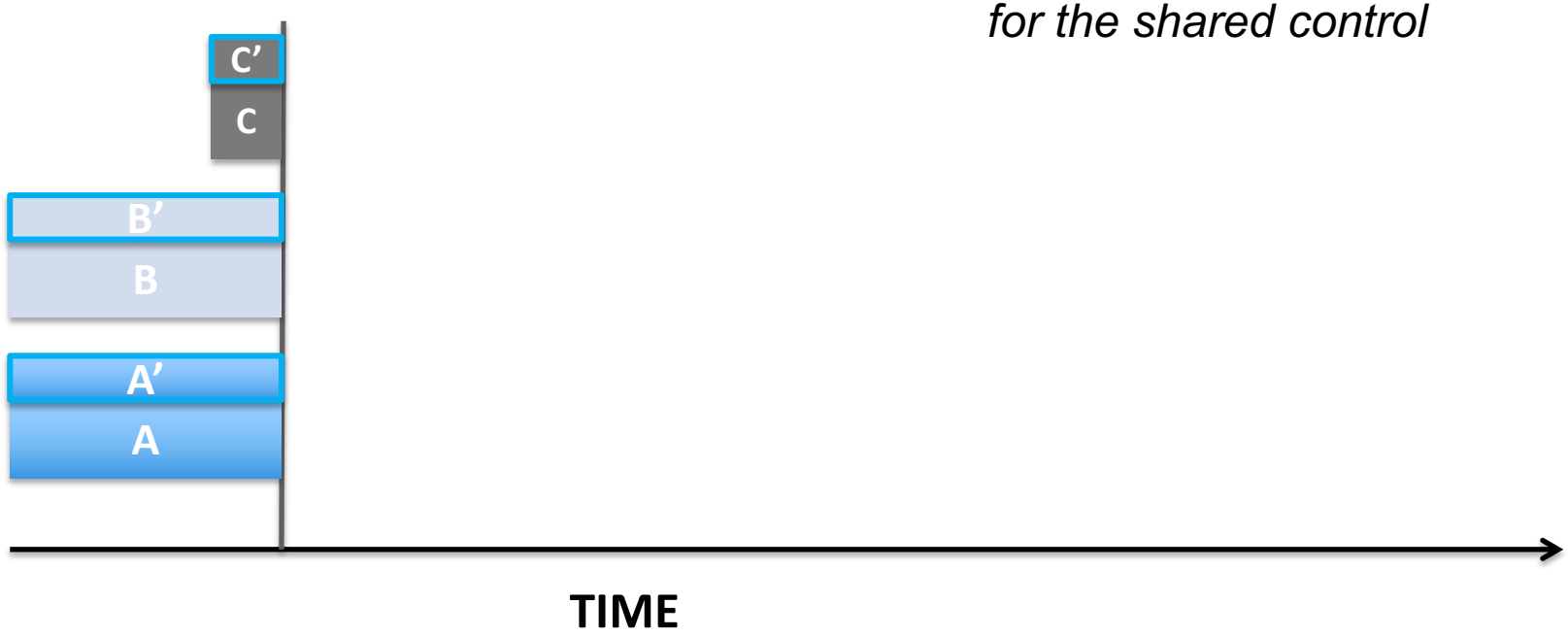
Example Regimen Journeys

- Interim Analyses:
  - Occur every 3 months for platform
  - Some regimens “actionable” at interim: Min. amount of data observed



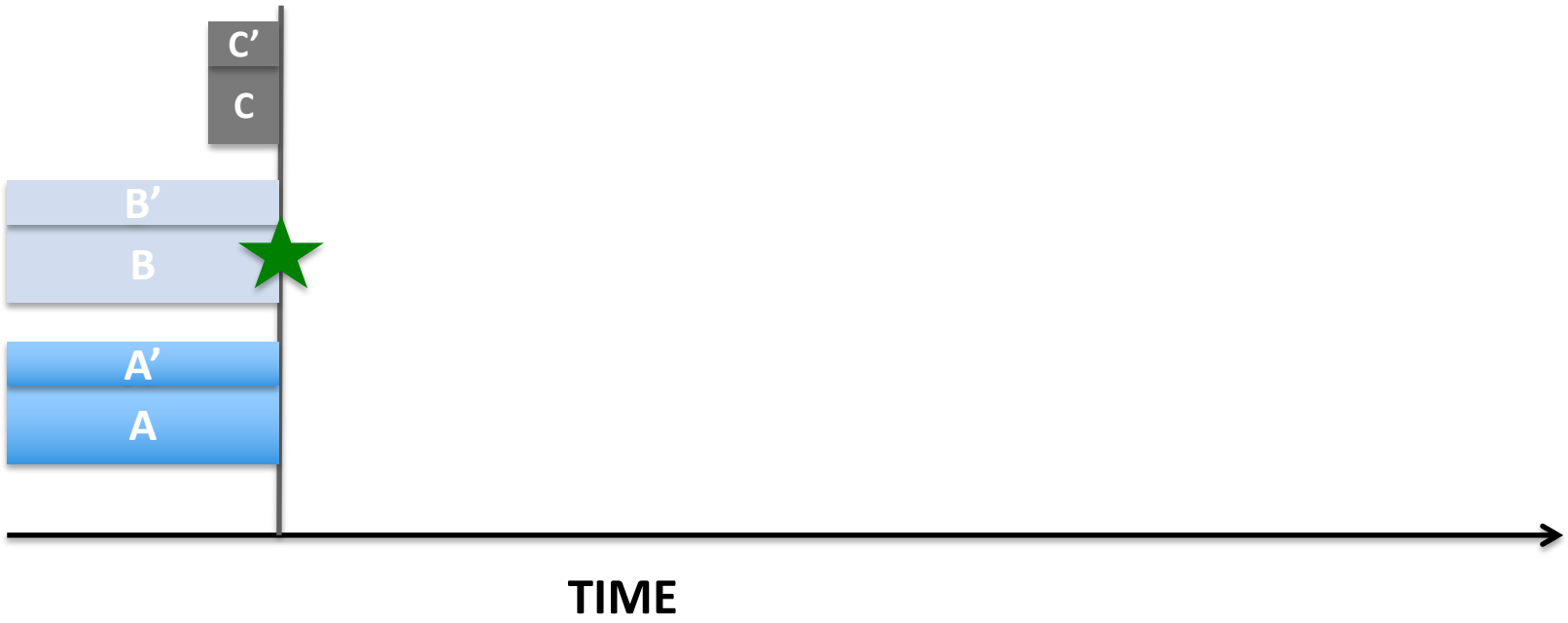
Example Regimen Journeys

- Interim Analysis Regimen A:
  - Combine all control participants together for analyses for each regimen
    - *Different routes of administration*
    - *Pool all routes of administration for the shared control*

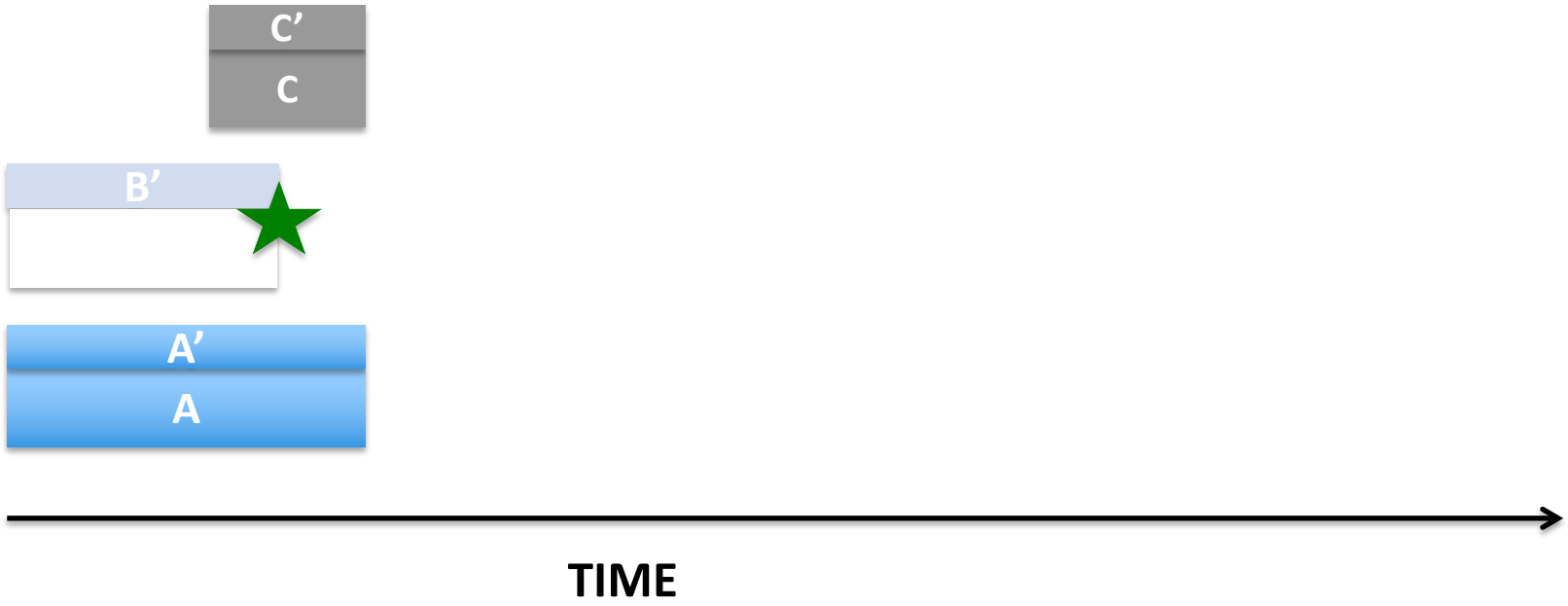


Example Regimen Journeys

- Interim Analyses:
  - Demonstrate early efficacy on ALSFRS-R
  - Option to start OLE or continue follow-up for safety or seamless phase II / III

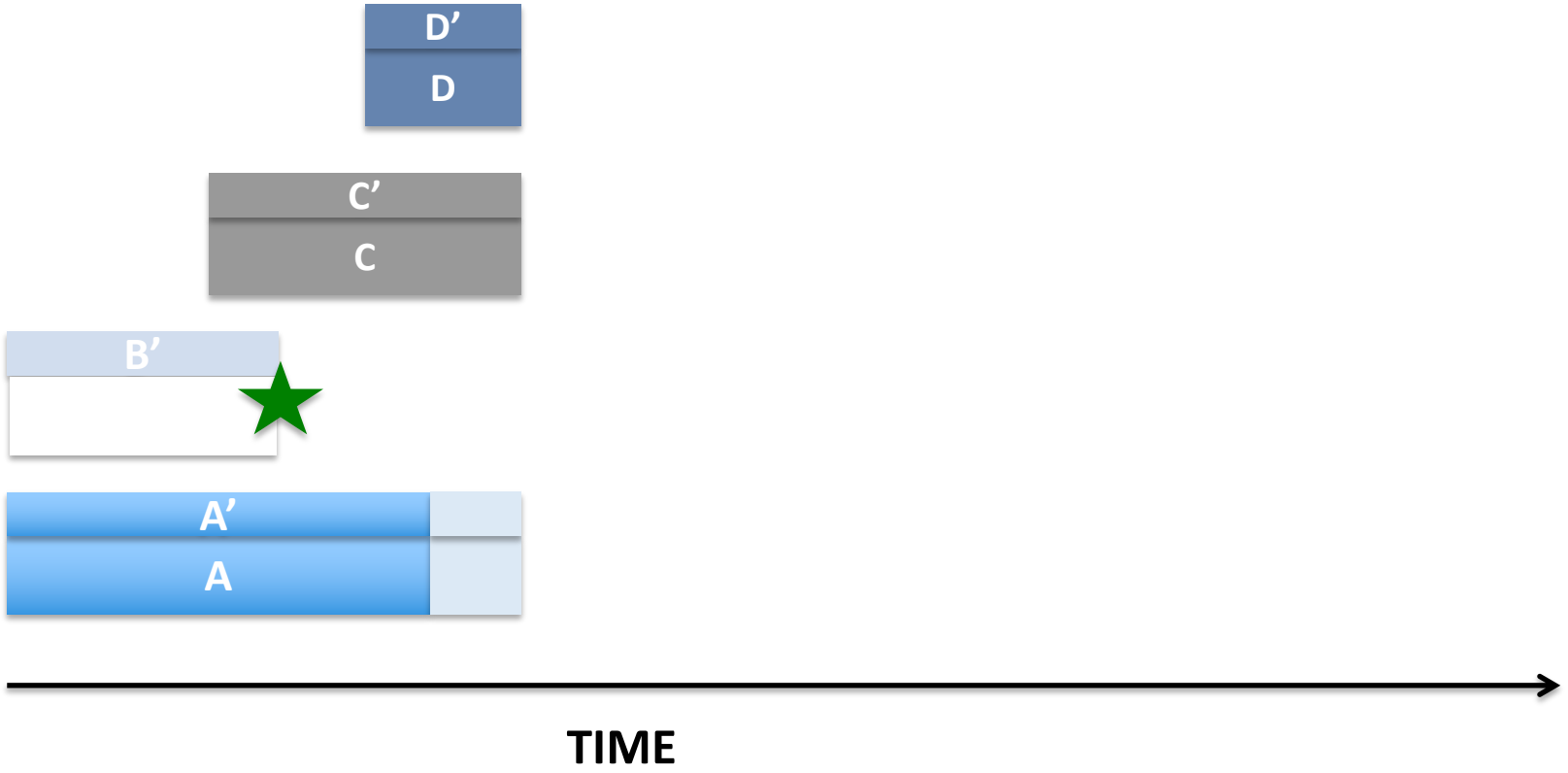


Example Regimen Journeys



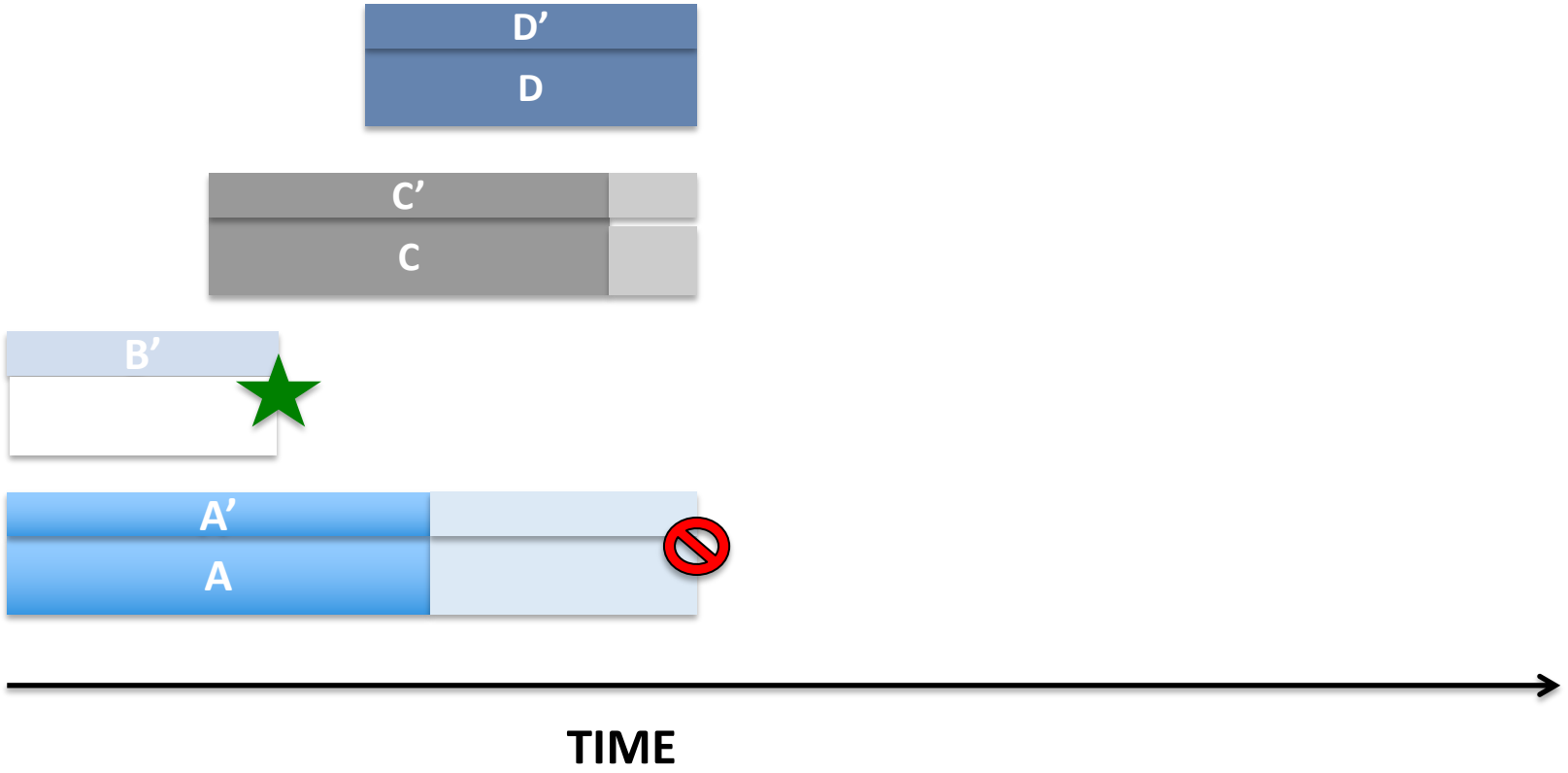
Example Regimen Journeys

- Another regimen added ….
- Enrollment to A ended, still follow…



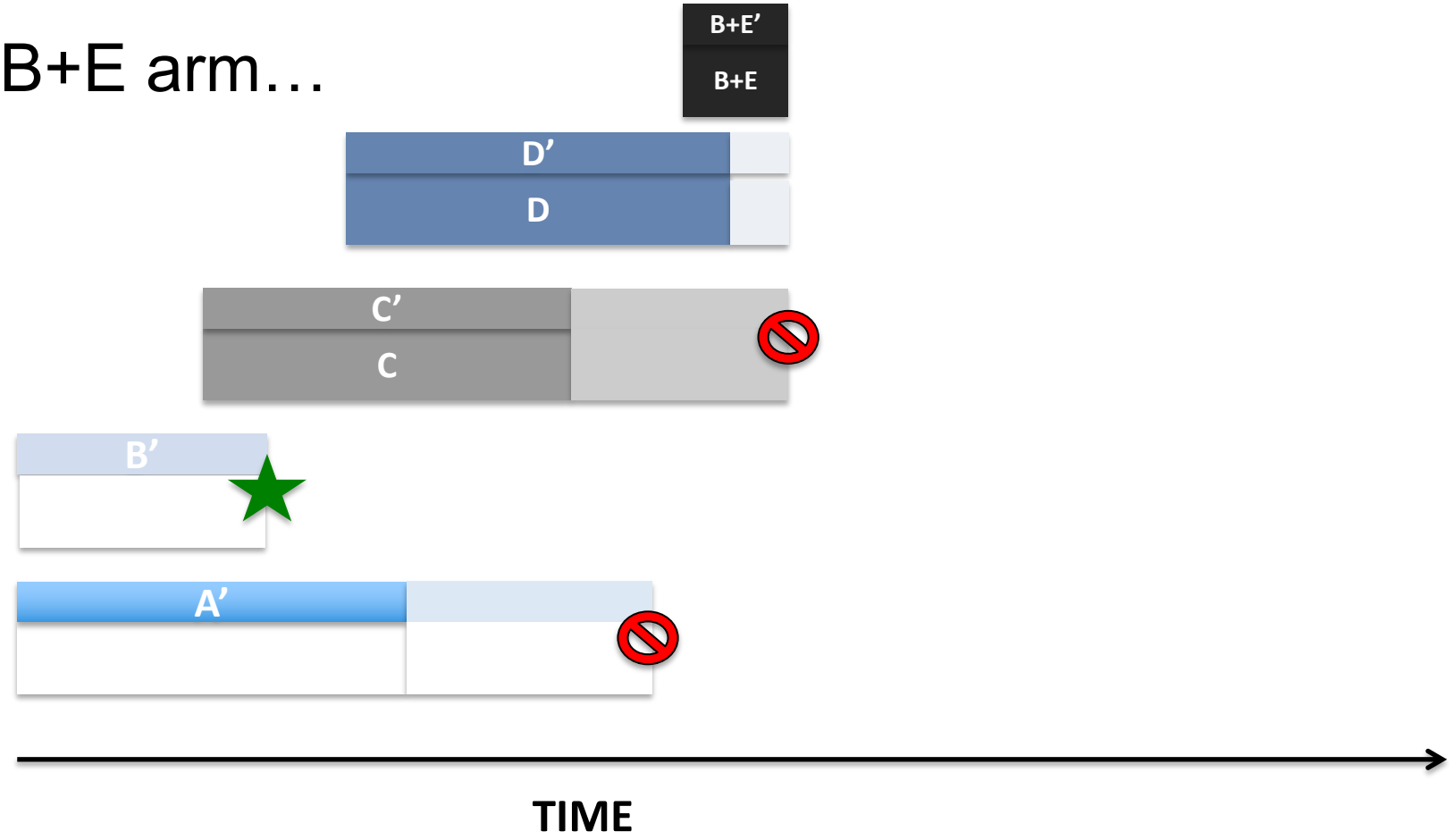
Example Regimen Journeys

- Drop a regimen for futility based on lack of efficacy
- Option to re-randomize participants



Example Regimen Journeys

- Stopped C
- Added B+E arm…



Master Protocol Vs Regimen Appendix

Master Protocol

- Trial Eligibility
- Visit schedule & data collection
- Sample Size: 120 per reg.
- Randomization: 3:1 Active:PBO
- Follow-up Time: 6 Months
- Recommended
  - Primary Endpoint: ALSFRS-R
  - Primary Analysis: Bayesian mixed effects repeated measures model
  - Success Criteria: Prob. Slow Progression > Thresh. (OF)
    - Overall Type I error = 5%
  - Futility Criteria: Prob. Slow Progression by at least 10% < .05

Regimen Flexibility

- Additional restrictions on Inclusion/exclusion: Due only to safety / MOA
- Additional endpoints to be collected
- Specifics on
  - Prespecified subgroups
  - Primary Endpoints and analyses
  - Alt. thresh. for success; spending function; type I error
  - More aggressive futility

Key Challenge

- Find Balance of Synergy vs. Flexibility
  - What is specified in the Master Protocol vs. Appendix
  - Too much in the Master Protocol – hard to reach consensus
  - Too much left to the Appendix – lose efficiencies

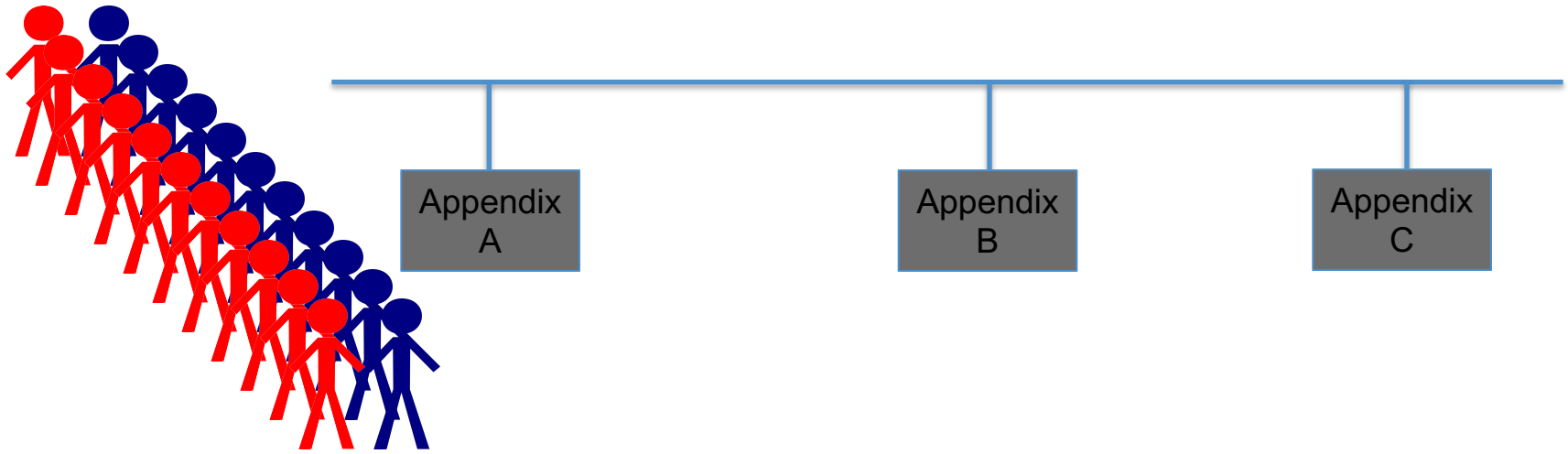
Specific Considerations for ALS: Endpoints

- Clinical and functional endpoints such as ALSFRS-R
- Novel endpoints such as HHD, Voice, EIM, Neurofilaments
- Platform trial as “Endpoint Engine”
  - Plan to collect a set of clinical and novel endpoints on all patients
  - Analyze the relationships between the novel endpoints and ALSFRS-R
  - Developing the candidate set of early, phase II endpoints, in particular model their ability to predict Phase III success on the clinical endpoints
- Potentially have a protocol defined suggested endpoint and analysis, but allow flexibility in each appendix

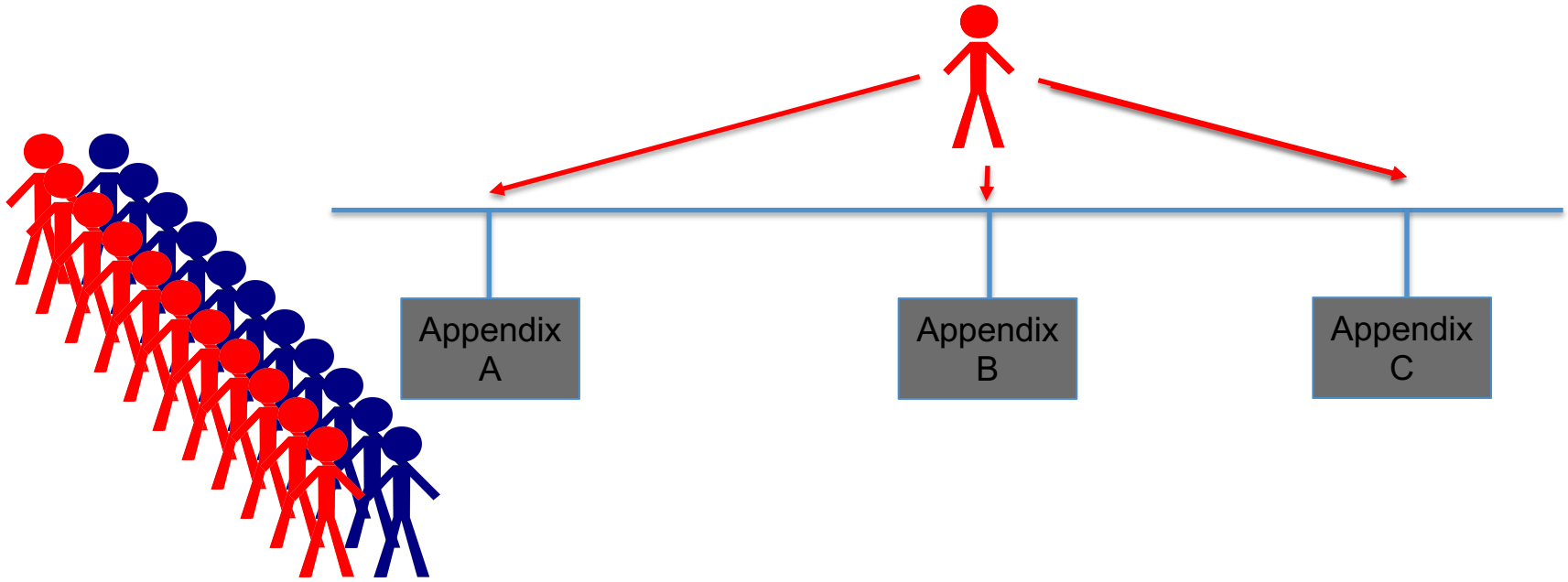
Specific Considerations for ALS: Subgroups

- *Under discussion*
- Subgroups may be of interest for
  - Clinical homogeneity
  - Because of a biomarker that corresponds to a particular MOA
- Every appendix having its own population of interest has the potential to negatively impact the shared control arm as well as enrollment to other appendices
- Likely only consider appendix-specific subgroup enrollment restrictions for MOA purposes

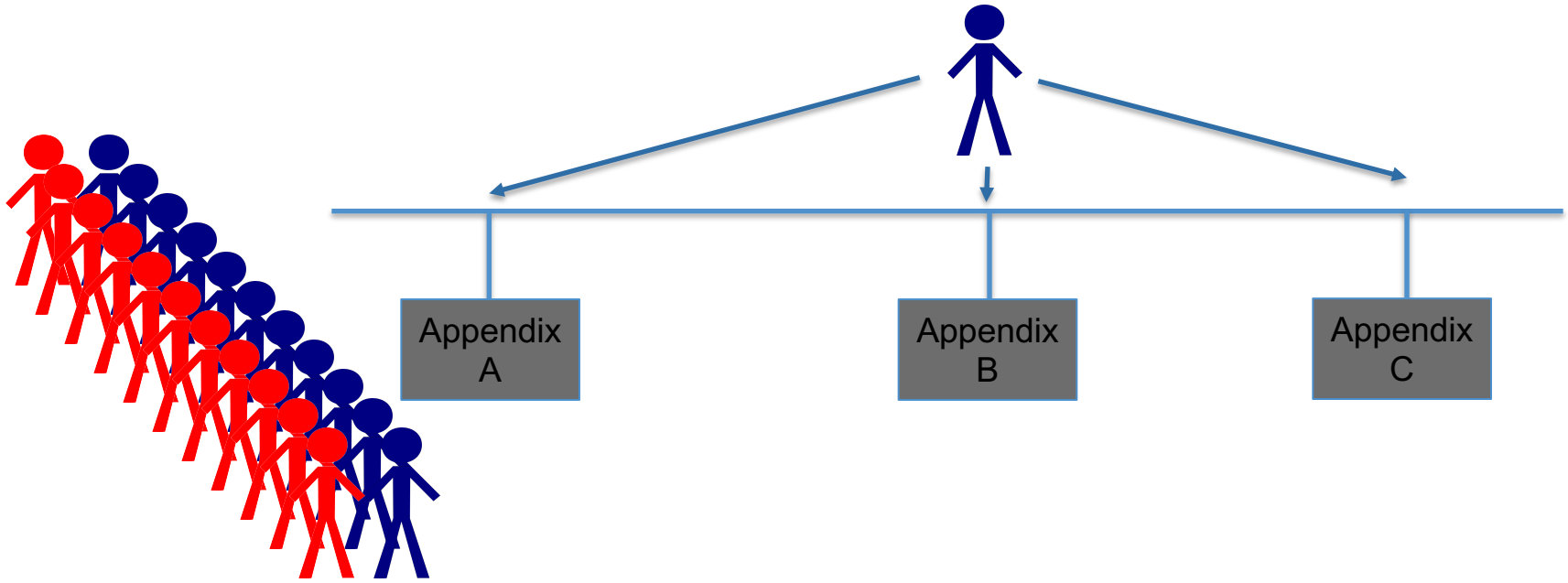
Specific Considerations for ALS: Subgroups



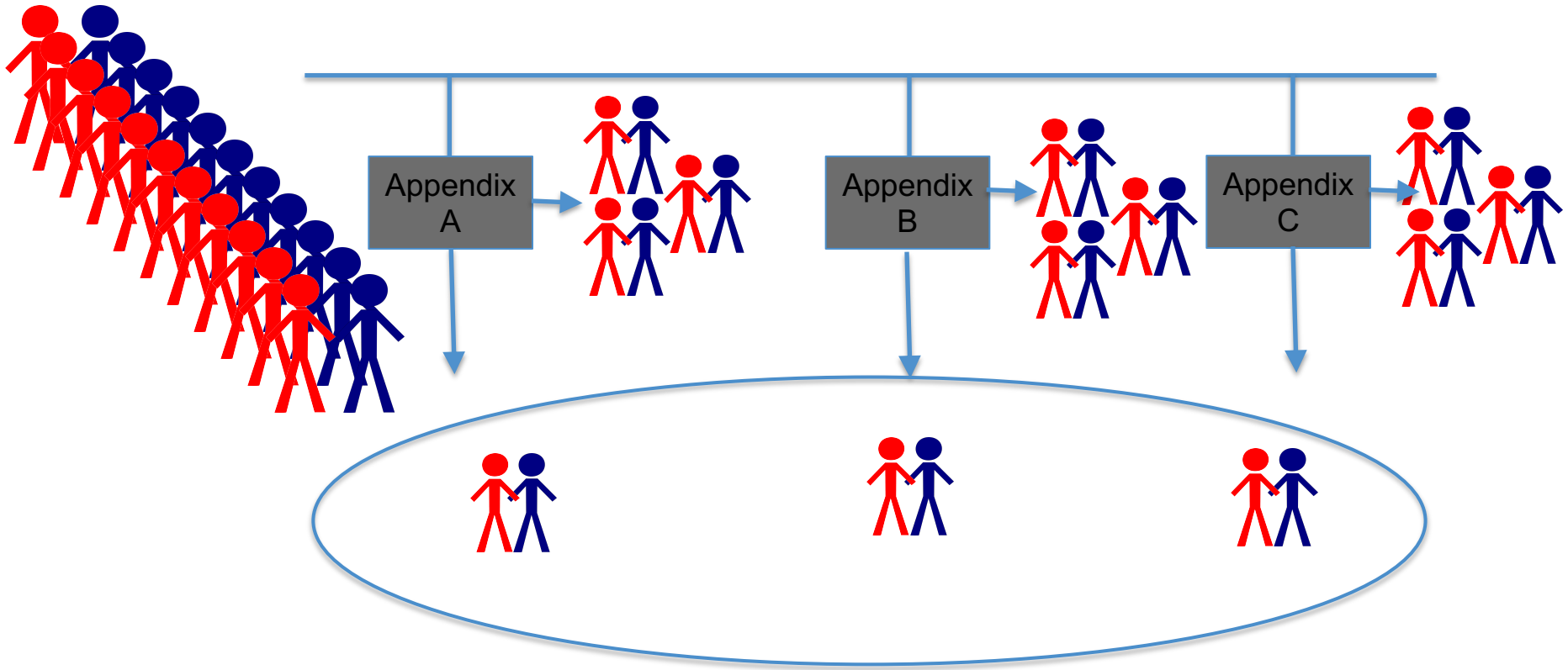
Specific Considerations for ALS: Subgroups



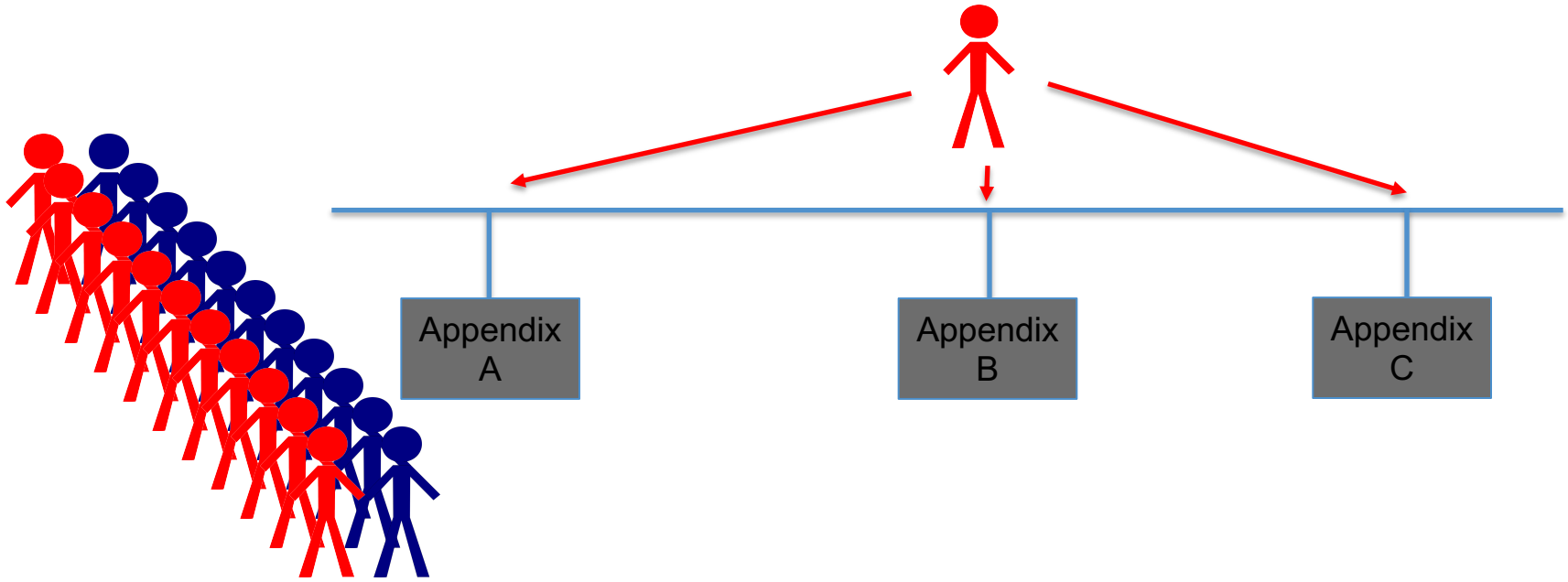
Specific Considerations for ALS: Subgroups



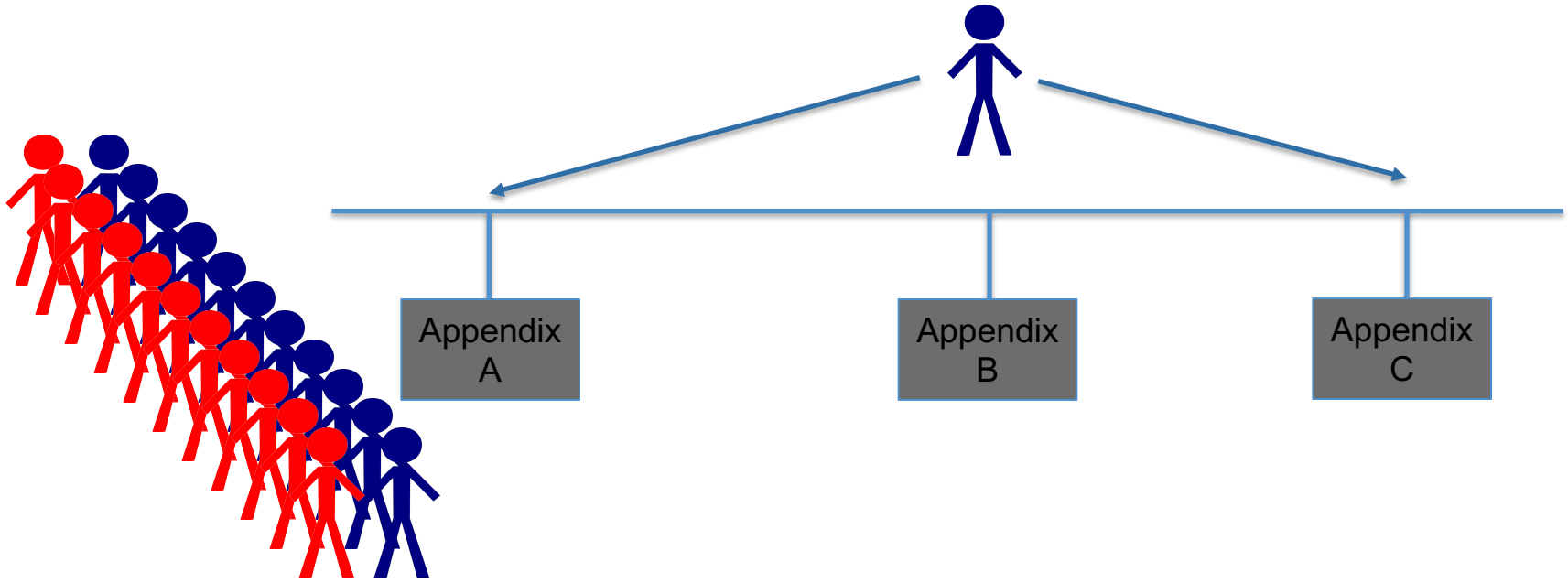
Specific Considerations for ALS: Subgroups



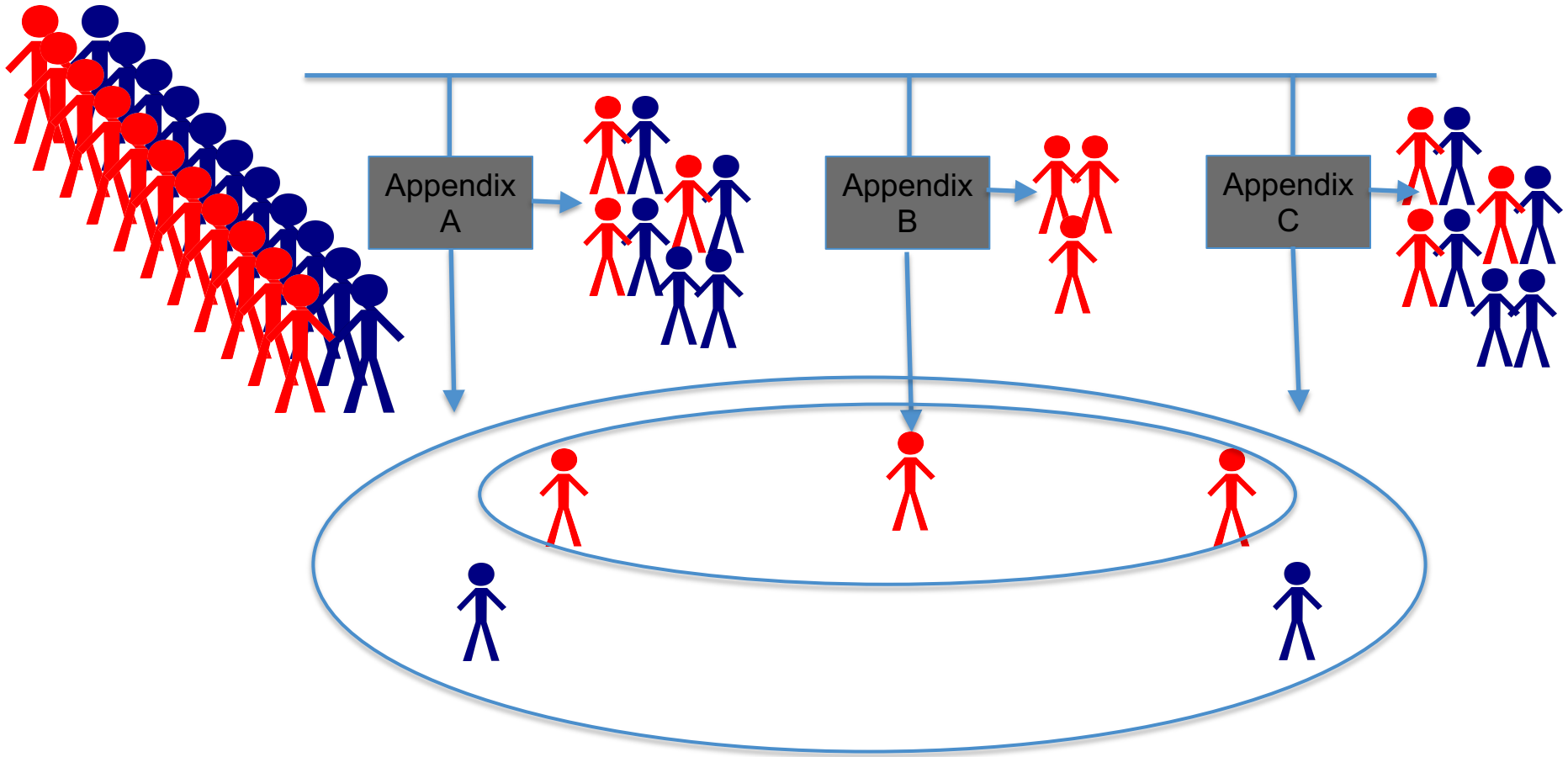
Specific Considerations for ALS: Subgroups



Specific Considerations for ALS: Subgroups



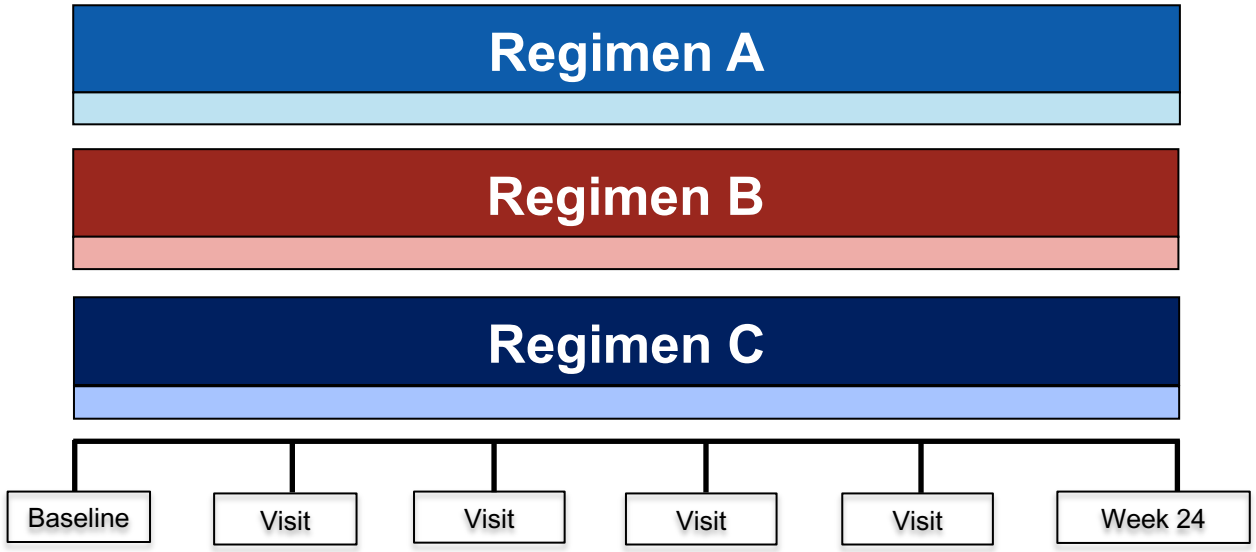
Specific Considerations for ALS: Subgroups



ALS PLATFORM TRIAL

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

Phase 2



Regimen flexibility to be discussed with industry partners

- Additional restrictions on inclusion/exclusion due to safety / MOA
- Additional endpoints to be collected
- Specifics on
  - Prespecified subgroups
  - Primary Endpoints and analyses
  - Alternative threshold for success; spending function; type I error
  - More aggressive futility

Clinical measures

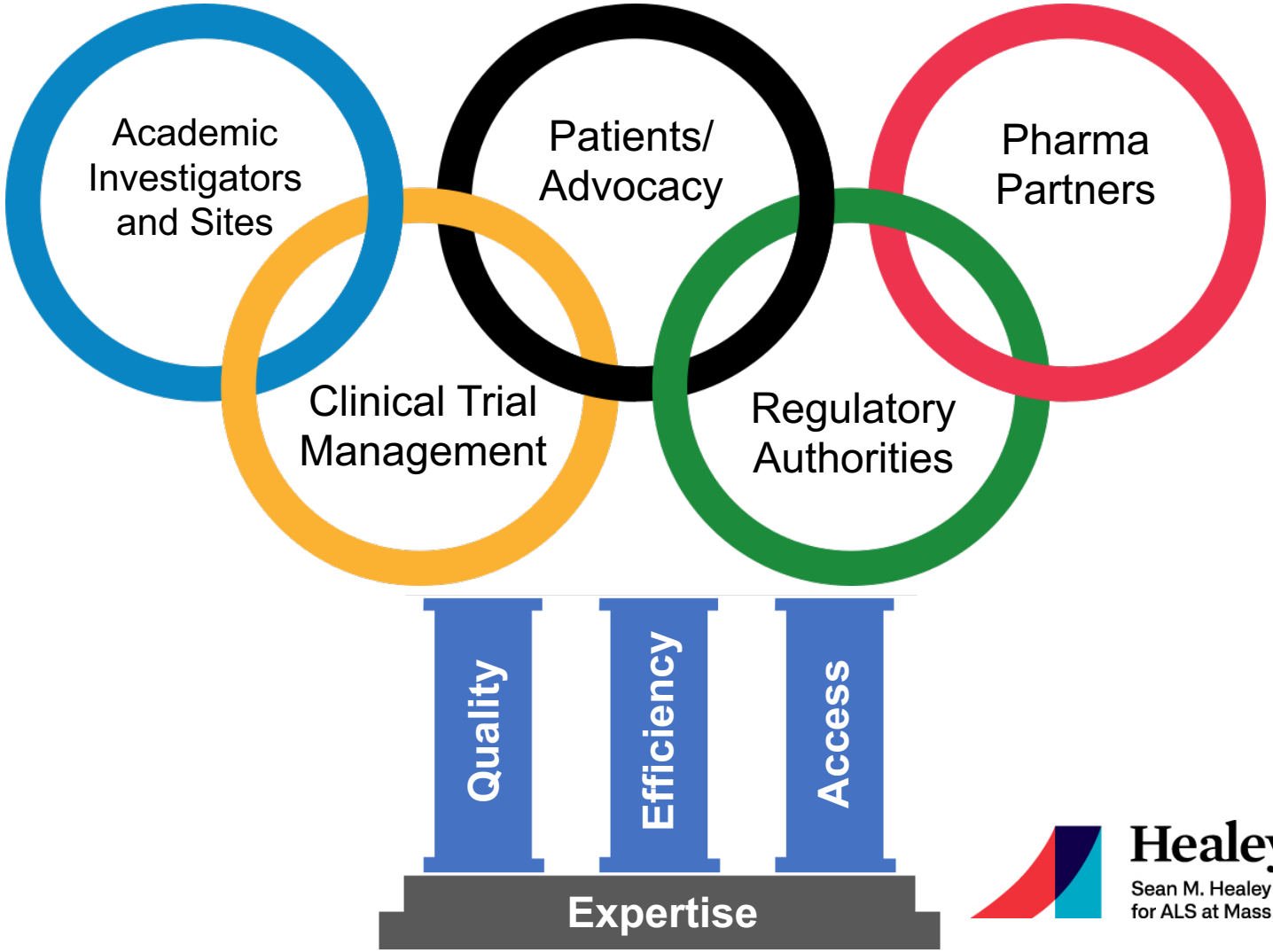
ALSFRS-R
SVC
Muscle Strength (HHD)
Speech Analysis
Electrical Impedance Myography

Biomarkers and samples

WGS
Neurofilament levels
Urine p75ecd
+/- bank biofluids (Sponsor decision)

Engaging the entire community

Test multiple therapies and learn faster, using less resources



Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

ALS PLATFORM TRIAL

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

Request for Proposals of Therapies

Application Due Date: Wednesday May 8th, 2019
Notification of therapy selection: End of May or early June 2019

RFP includes: CDA template; ALS Platform Trial Therapy Application Form

Review Criteria:

- Relevance of target in human disease
- Pre-clinical data to support target and therapy
- Clinical trial readiness (availability of compound and placebo, IND)
- Availability of relevant biomarkers

TACKLE ALS
"DONT BE SORRY LETS BEAT THIS"

NEALS
Northeast Amyotrophic Lateral Sclerosis Consortium

Berry Consultants
Statistical Innovation