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at Massachusetts General Hospital

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Statistical Innovation

The HEALEY ALS Platform Trial: Efficient Design and Implementation of Regimens

Marianne Chase, Melanie Quintana, PhD,
Annette De Mattos, MPH, Brittney Harkey, PhD

2024
BOSTON

SCT | 45TH ANNUAL MEETING

Disclosures

- All presenters have no relevant disclosures to report

Overview of the HEALEY ALS Platform Trial

Marianne Chase
Senior Director of Clinical Trial Operations
Healey & AMG Center for ALS at Mass General

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Sean M. Healey & AMG Center for ALS
at Massachusetts General Hospital

The HEALEY ALS Platform Trial is grounded in robust academia – industry partnership

HARVARD MEDICAL SCHOOL

NEUROLOGICAL CLINICAL RESEARCH INSTITUTE

Massachusetts General Hospital
Founding Member, Mass General Brigham

Healey & AMG Center
Sean M. Healey & AMG Center for ALS
at Massachusetts General Hospital

TACKLE ALS "DON'T BE SORRY LETS BEAT THIS"

ALS ASSOCIATION

MDA Muscular Dystrophy Association

SALSA For a Cure

alsFINDINGaCURE

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

I AM ALS

TAMBOURINE

Berry Consultants Statistical Innovation

BARROW Neurological Institute

AMG The AMG Foundation

ucb

biohaven pharmaceuticals

CLene NANOMEDICINE

prilenia

SEELOS THERAPEUTICS

Calico

DENALI THERAPEUTICS

THE ARTHUR M. BLANK FAMILY FOUNDATION

ALS ONE

Engaged patient community
More than 250 companies in the ALS space
Many new investigational drugs waiting to be tested

HEALEY ALS Platform Trial

Traditional

	Intervention
Disease	Therapy A

Platform

	Intervention		
Disease	Therapy A	Therapy B	Therapy C

The HEALEY ALS Platform Trial aims to meet the needs of the ALS community

Several advantages over traditional trials

Reduces placebo

Cuts time

Cuts costs

Rapidly move drugs that are more likely to succeed to phase 3

Worked with the entire ALS Community to launch the trial efficiently

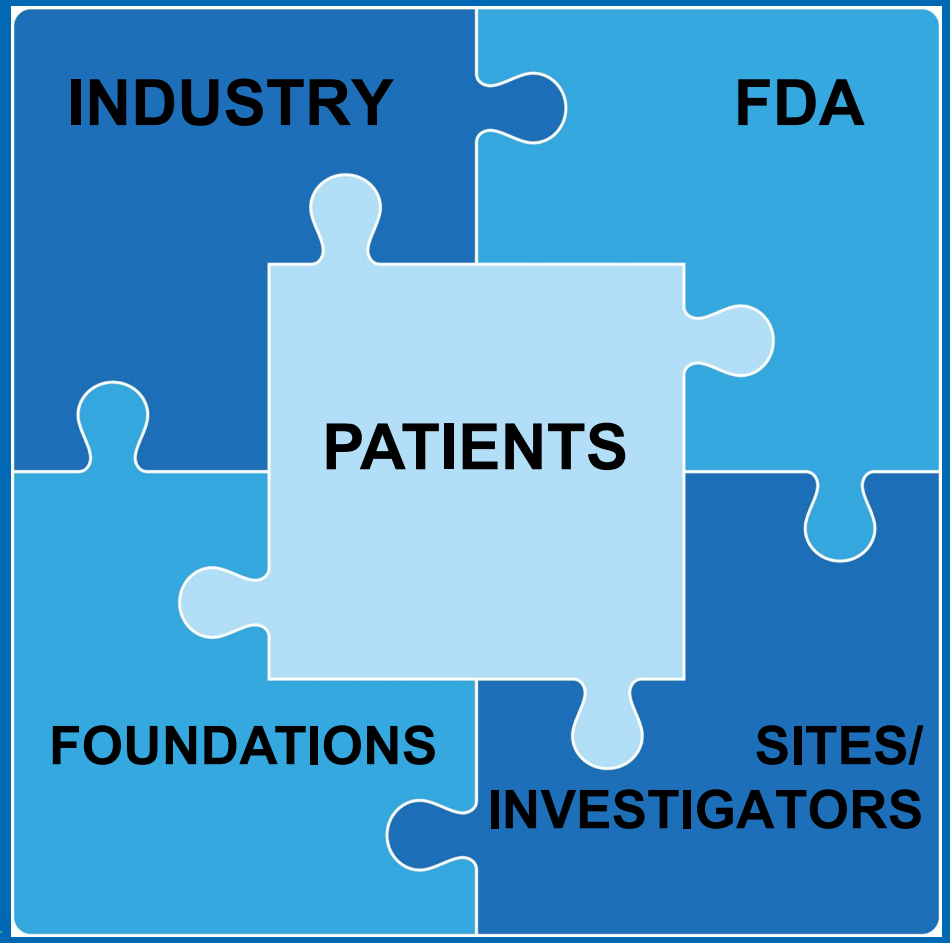
Platform trials are a win for all stakeholders

ALS Platform Trial Industry Workshop

"Platform trials may possibly be the best thing I have seen since diagnosis!"

★★★★★

***5-stars** Patient-Centric Trial Design (PaCTD) Rating*



NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

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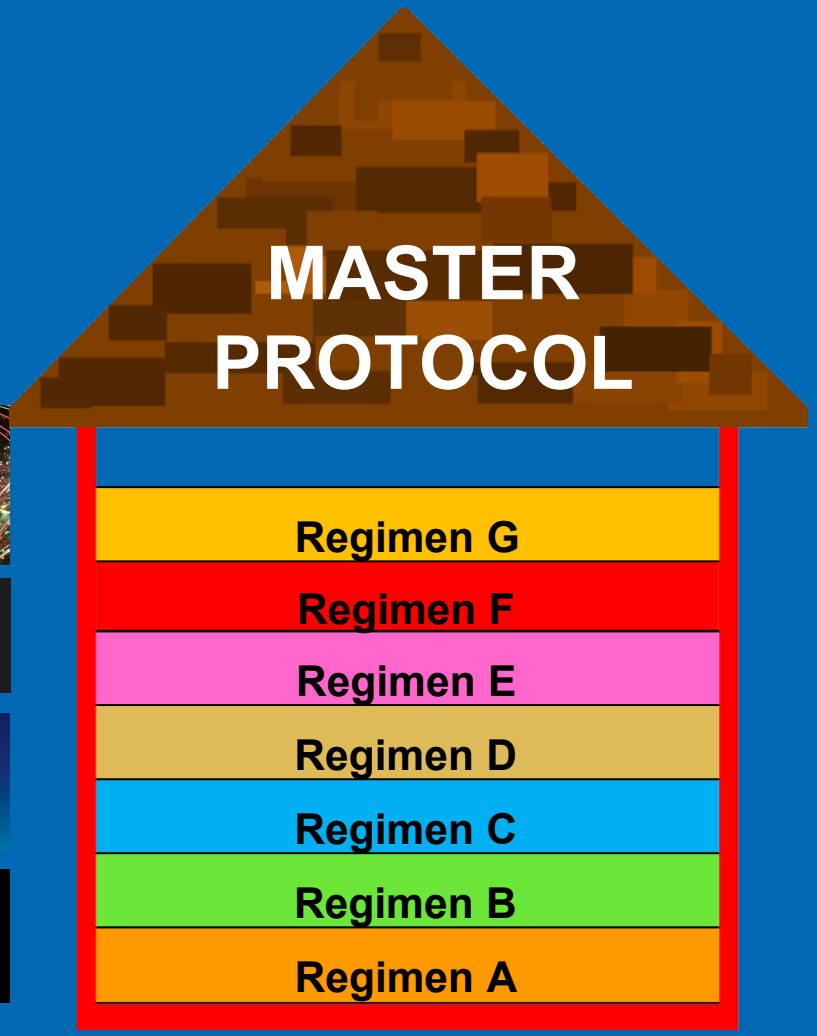
Common Protocol and Shared Infrastructure Allow for Operational and Scientific Efficiencies

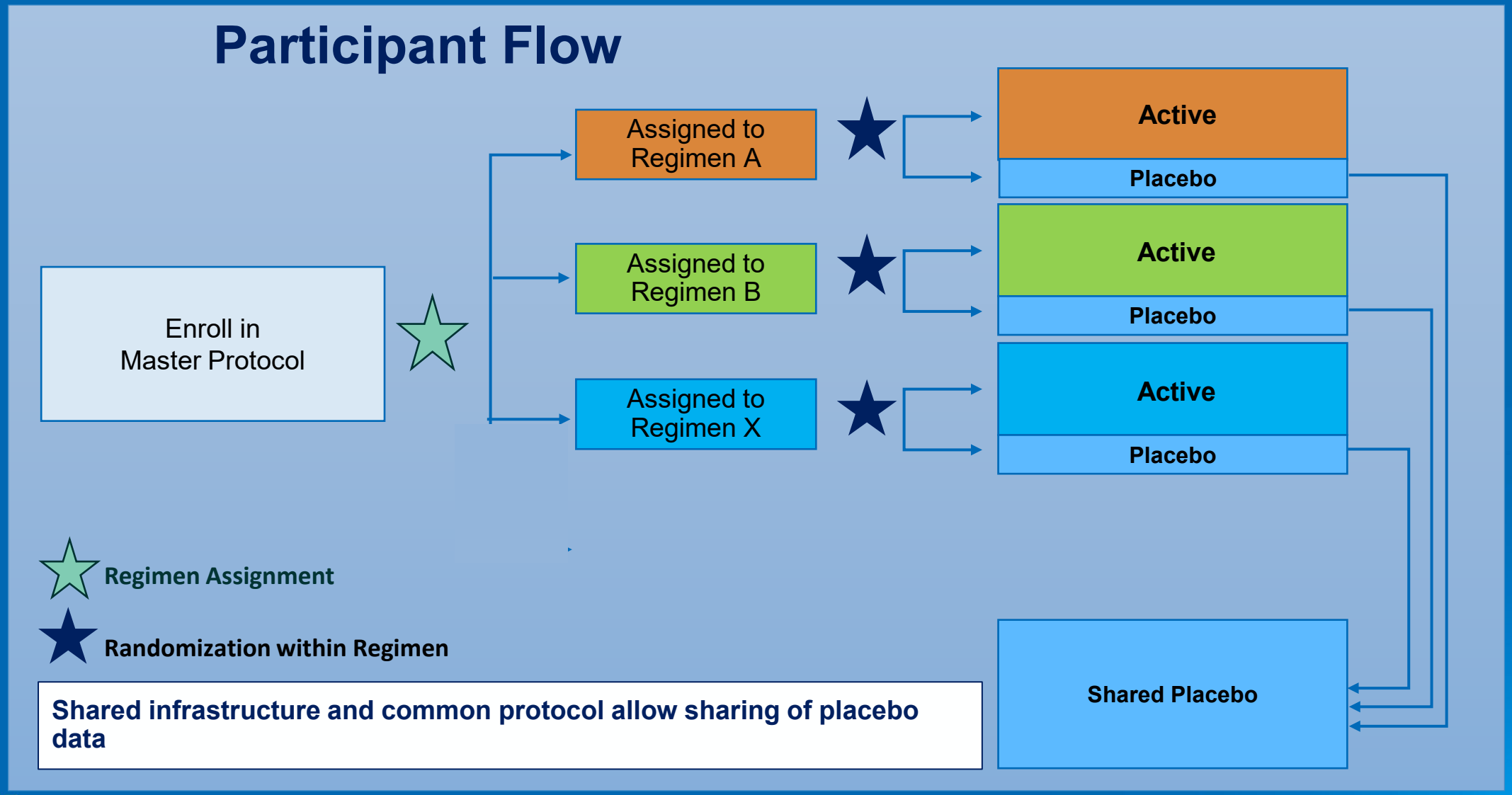


1 Protocol
1 single IRB
Central Governance

7 Regimens
70+ Enrolling Sites
>1300 Participants

Regimen: Active Study Drug + Matching Placebo

Master Protocol to Regimen Protocol (RSA)



Streamlined Regulatory Structure

- Healey team leads all FDA interactions
- 30-day review of each new Regimen Protocol

Single IND application

- Master Protocol
  - Each Regimen Protocol added as an Amendment
- Amendments
  - Safety Reports
  - Meeting Requests

Single IRB application

- Master Protocol
  - Each Regimen Protocol
- Each site added as an amendment

Mass General Brigham

- Each site has Reliance Agreement with MGH IRB
- IRB full board review for each new drug added
- Sites are added as an amendment

Database Structure

This database only includes data on Master Protocol Screening

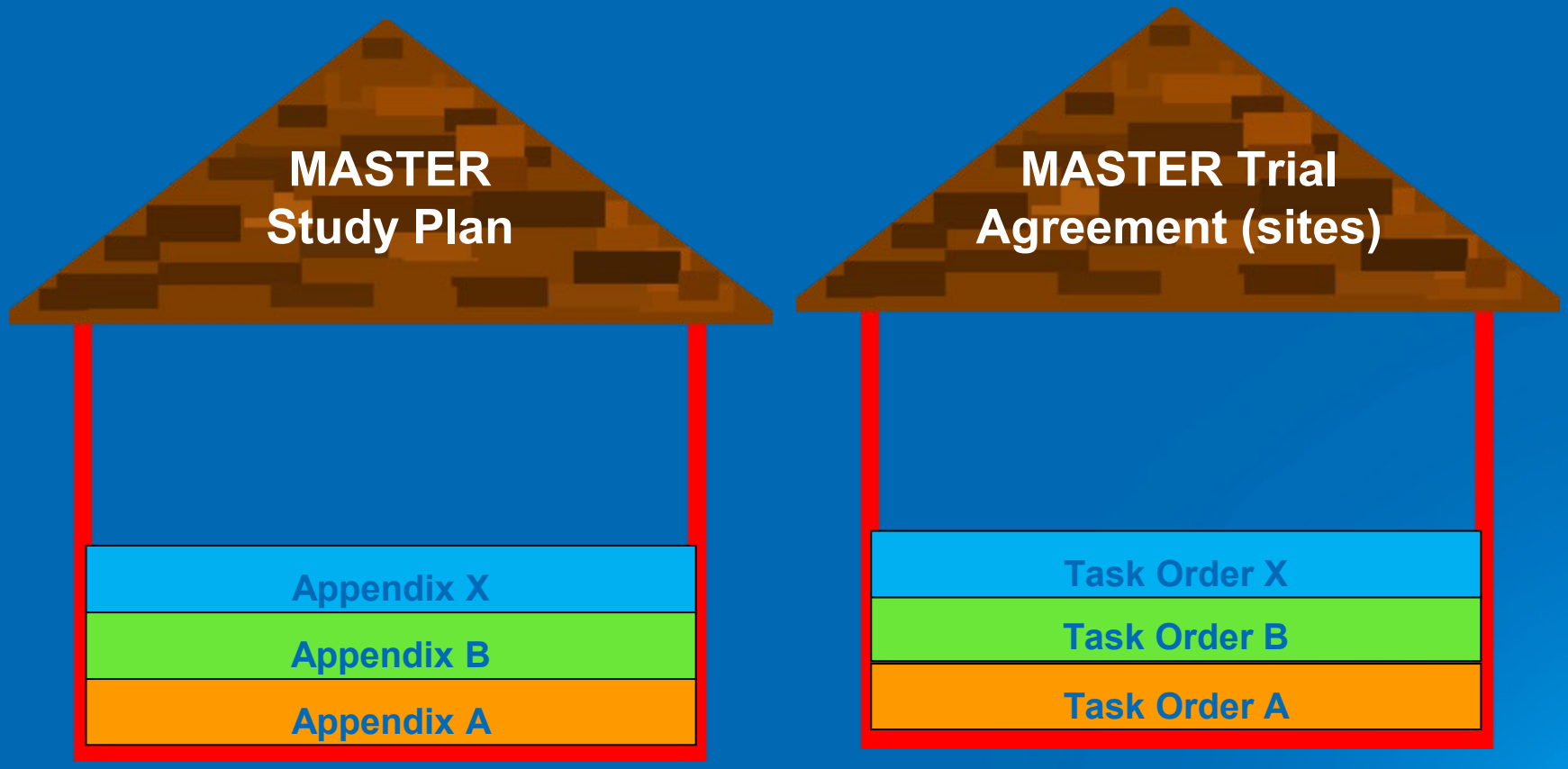
- Sites enter Master Protocol screening data
- If the participant meets eligibility, they are randomly allocated to 1 Regimen

Each Regimen database includes all data collected for that Regimen

- Sites enter Regimen-specific screening data
- Randomization occurs via IRT system
- Sites enter data from all study visits

Streamlined Operational Structure

- Statistical Analysis Plan
- Data Management Plan
- Safety Management Plan
- Monitoring Plan



THERAPY EVALUATION COMMITTEE

Goals

This group identifies the best therapeutic candidates from promising available drug candidates for inclusion in ALS Platform Trial. Therapies will be evaluated based on the following criteria:

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

Final therapy selection is determined in conjunction with the Executive Committee to include financial and operational considerations. The Therapy Evaluation Committee will meet monthly or ad hoc as needed for reviews.

Membership

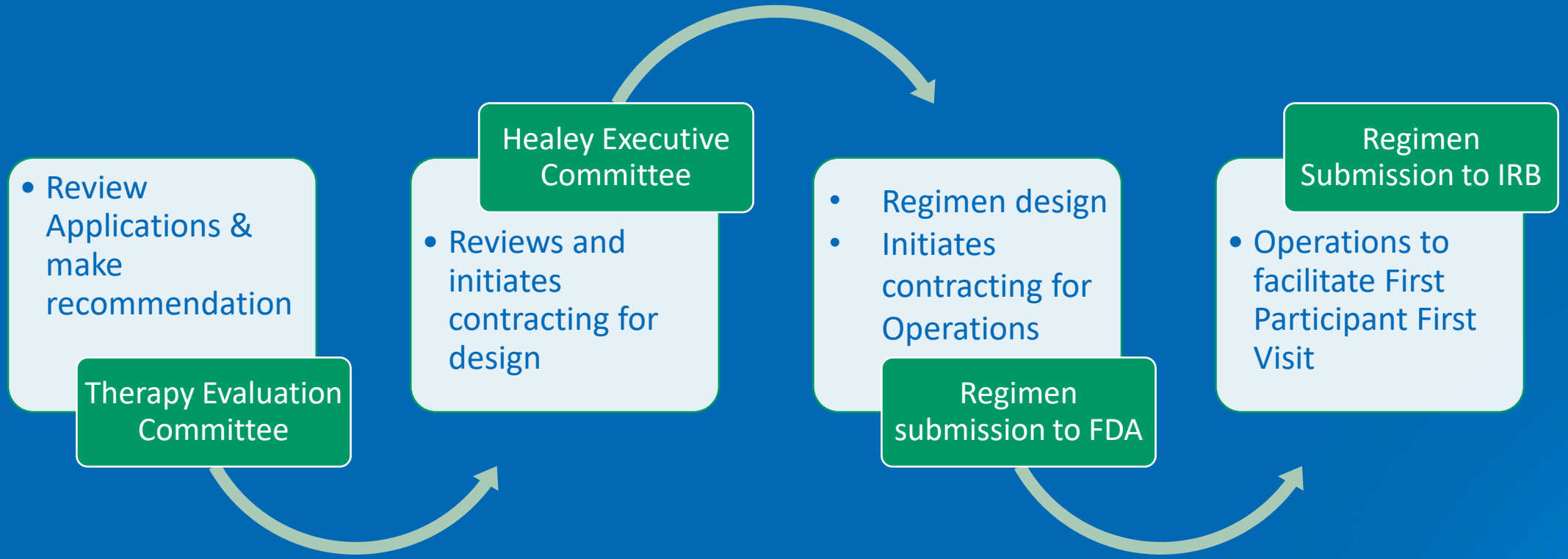
1. Timothy Miller, MD, PhD, Chair
2. Robert Brown, MD, PhD
3. Merit Cudkowicz, MD, MSc
4. Jonathan Katz, MD
5. Clotilde Lagier-Tourenne, MD PhD
6. Melanie Leitner, PhD
7. Ghazaleh Sadri-Vakili, PhD
8. Jeremy Shefner, MD, PhD

45 applications received and reviewed to date

Standing Monthly reviews Meetings

Anticipate adding up to 3 new companies every year

Efficient Process Application to Enrollment



Thank you!

The Evolution of Statistical Design within a Platform Trial

Melanie Quintana, PhD
Senior Statistical Scientist
Berry Consultants

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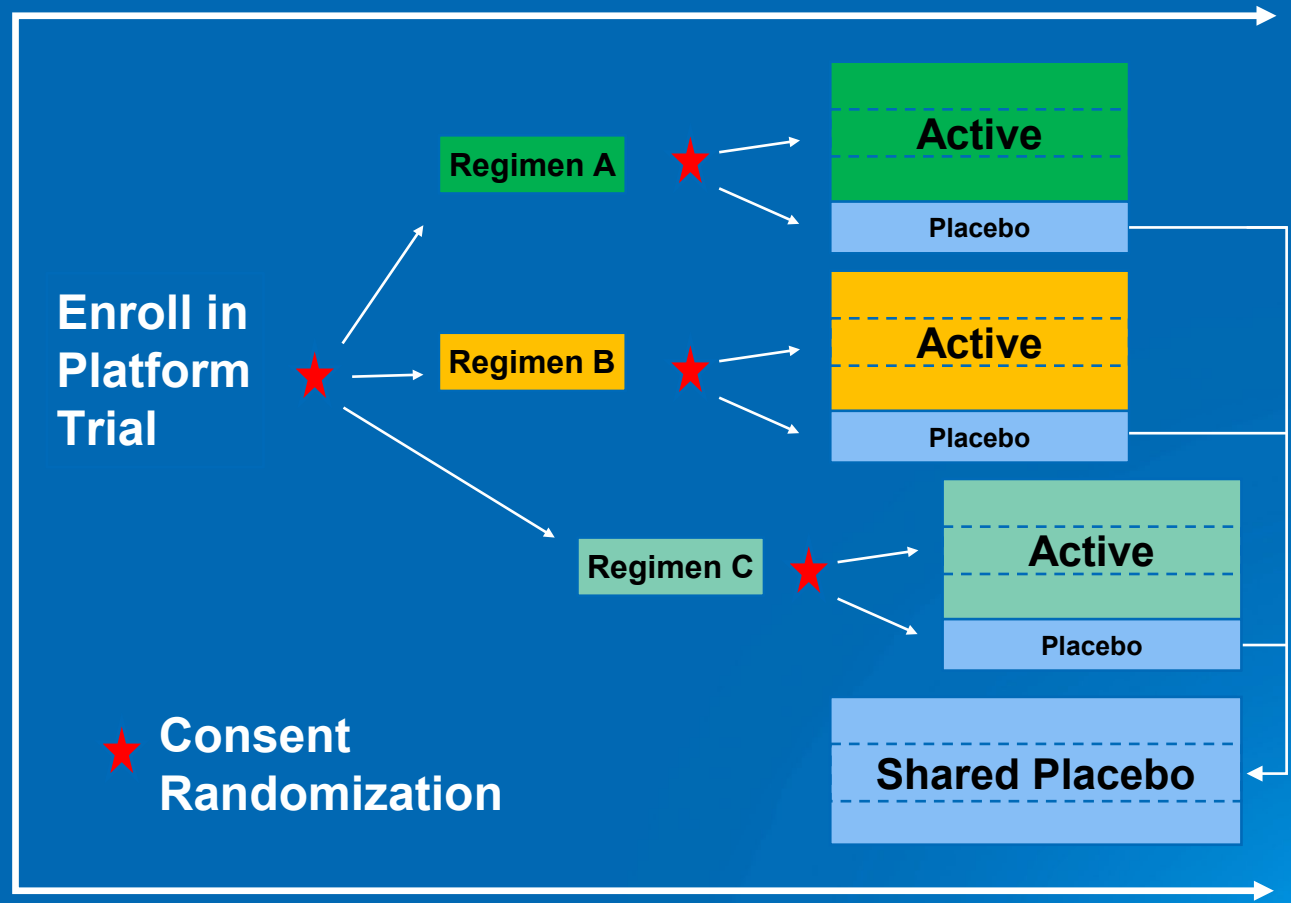
Platform Efficiencies

- Shared infrastructure means quicker time to start a new therapy
- Single consensus reached on optimal design across multiple partners
- *Statistical efficiency in terms of sample size from a shared/common control arm*
- *Fewer participants on control*
- *Ability to screen more agents faster and quickly reject ineffective therapies*

Example Master Protocol:
HEALEY ALS Platform Trial

- **Adaptive Platform Trial**
  - Perpetual trial that continuously tests interventions within ALS
  - Frequent platform-wide interims to stop regimens for early futility
- **N = 160 w/ 3:1 randomization** for each regimen, Active Treatment vs. Placebo
  - Shared placebo among all regimens
  - 80% power for 30% slowing
  - Type I error of 5%

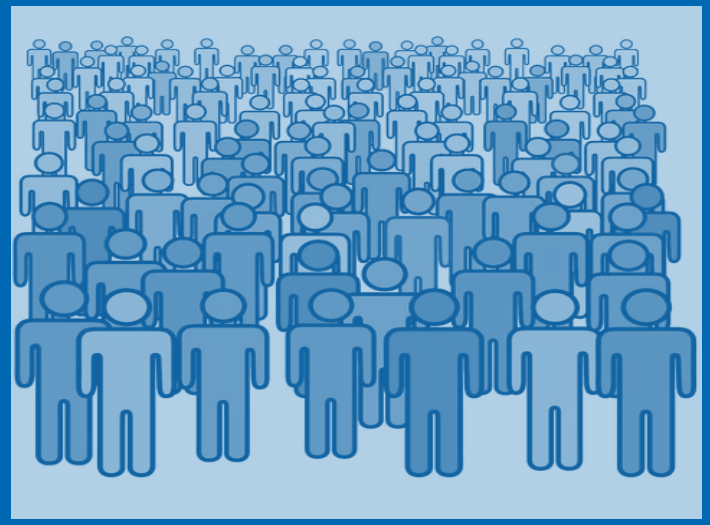


ALS Platform Efficiencies: Per Regimen

Traditional Drug Development

N=240 for 80% Power

120 Participants on Placebo



Adaptive Platform Trial w/ Shared Controls

N=160 for 80% Power

40 Participants on Placebo

N reduced by 1/3

 # PBO participants reduced by 2/3

ALS Platform Efficiencies: How quicky can we find the first effective therapy?

Traditional Drug Development

Sequence of fixed 1:1 trials

Lag of 3 months between trials

Adaptive Platform Trial w/ Shared Controls

Perpetually enrolling max. of 3 regimens

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**Assumes 10% of therapies tested are effective with a 30% slowing in rate of progression*

Platform Statistical Efficiencies + Complexities

Sharing of controls increases power and decreases the number of participants needed to go on placebo – backbone of the platform trial!

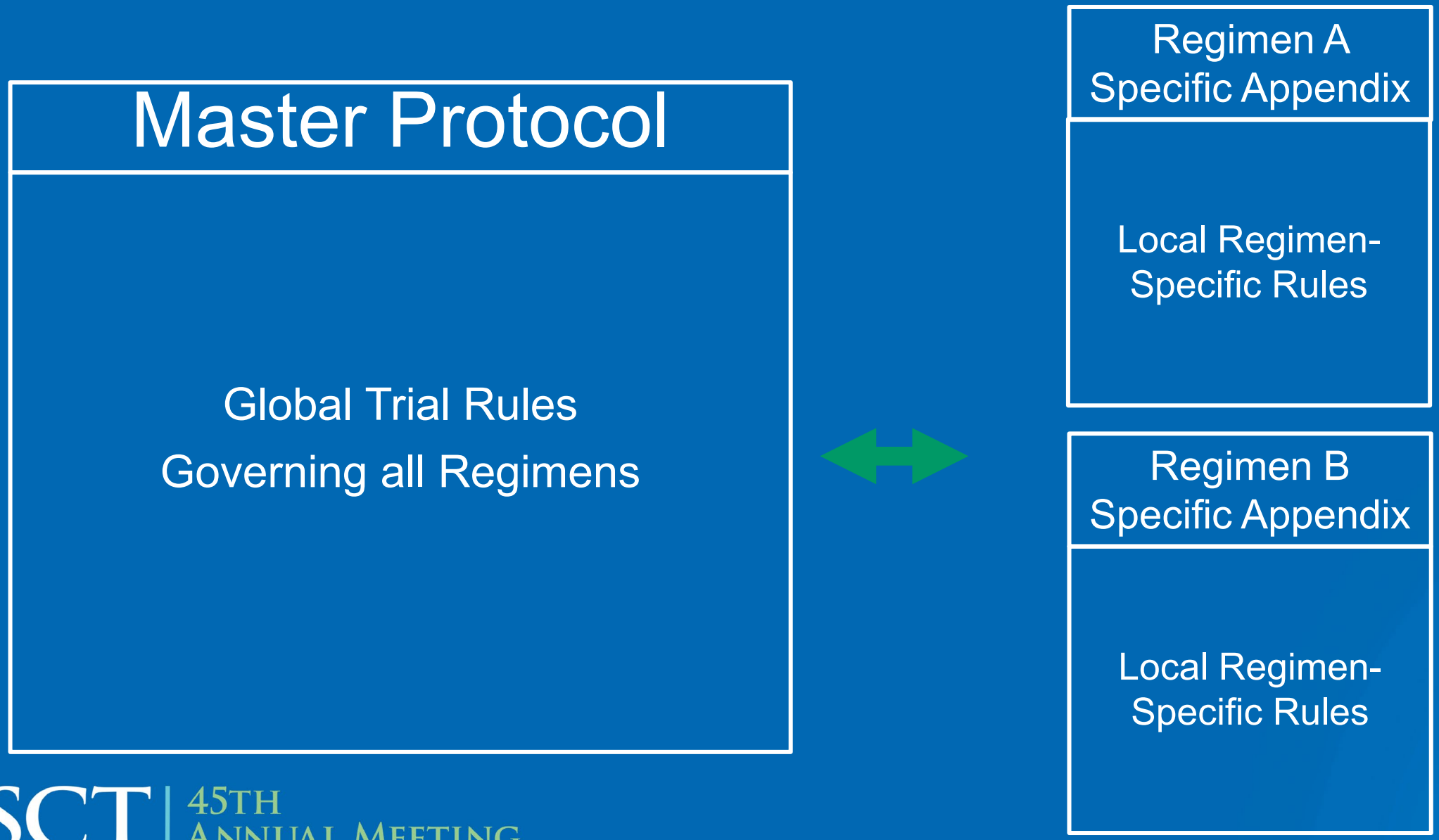
Careful considerations:

When developing a regimen-specific appendix, we need to be sure there is synergy with the other appendices

Comparing results across different populations could lead to bias.

Shared controls require ***similar patient populations*** *through careful design choices* & ***robust analysis methods*** that can adjust for potential differences across shared control

Master Protocol vs. Regimen Specific Appendix



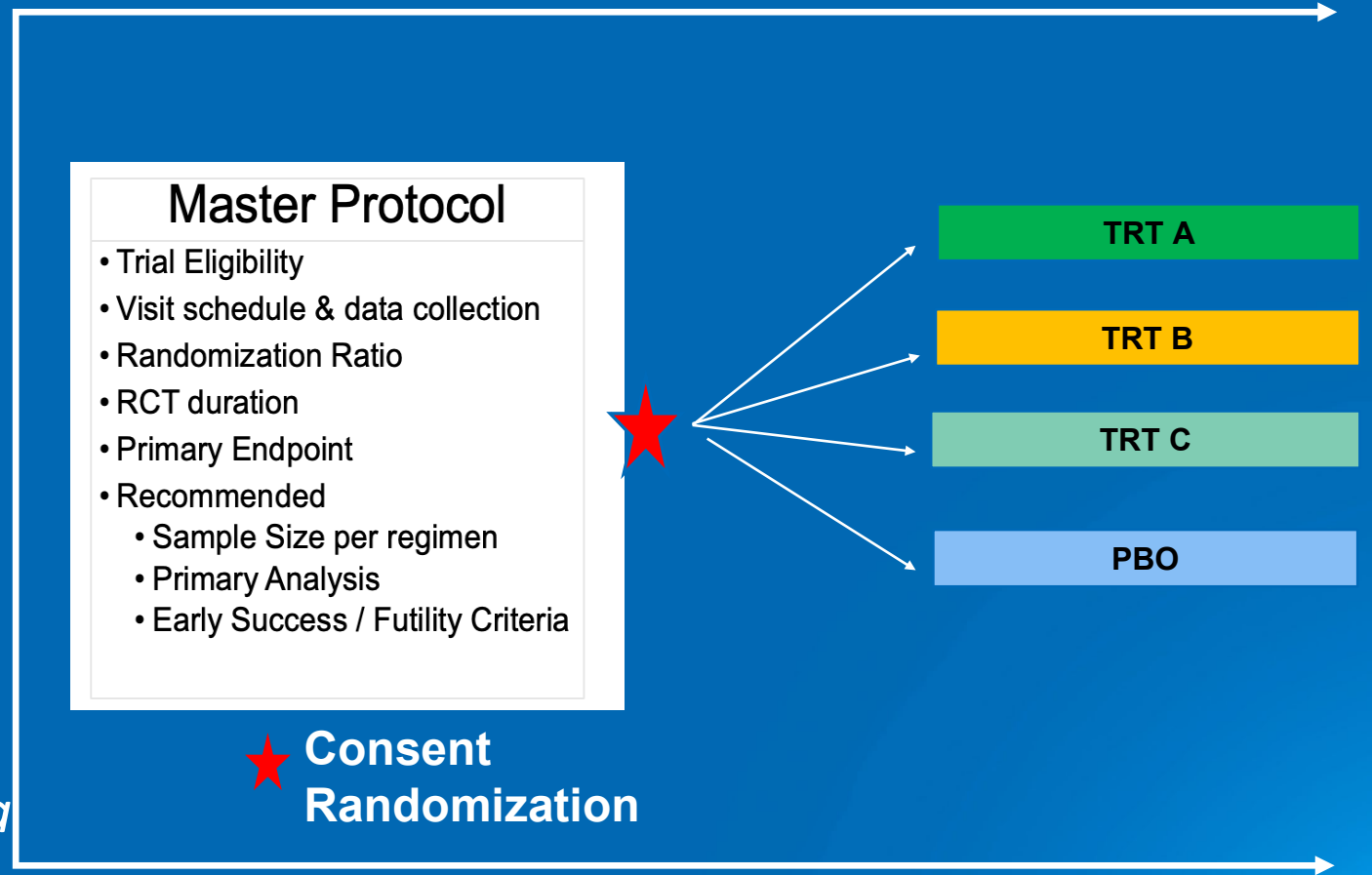
Platform Trial: Focus on Synergy

Master Protocol Driven Designs: Almost all design choices are specified in the MP.

Examples:

- All arms enroll under the same MP inclusion/exclusion at the same time
- Single consent process
- Single common control arm

Benefits: Same patient population in common control vs. each treatment arm
Risk: May not be able to accommodate a wide range of arms



Platform Trial: Focus on Flexibility

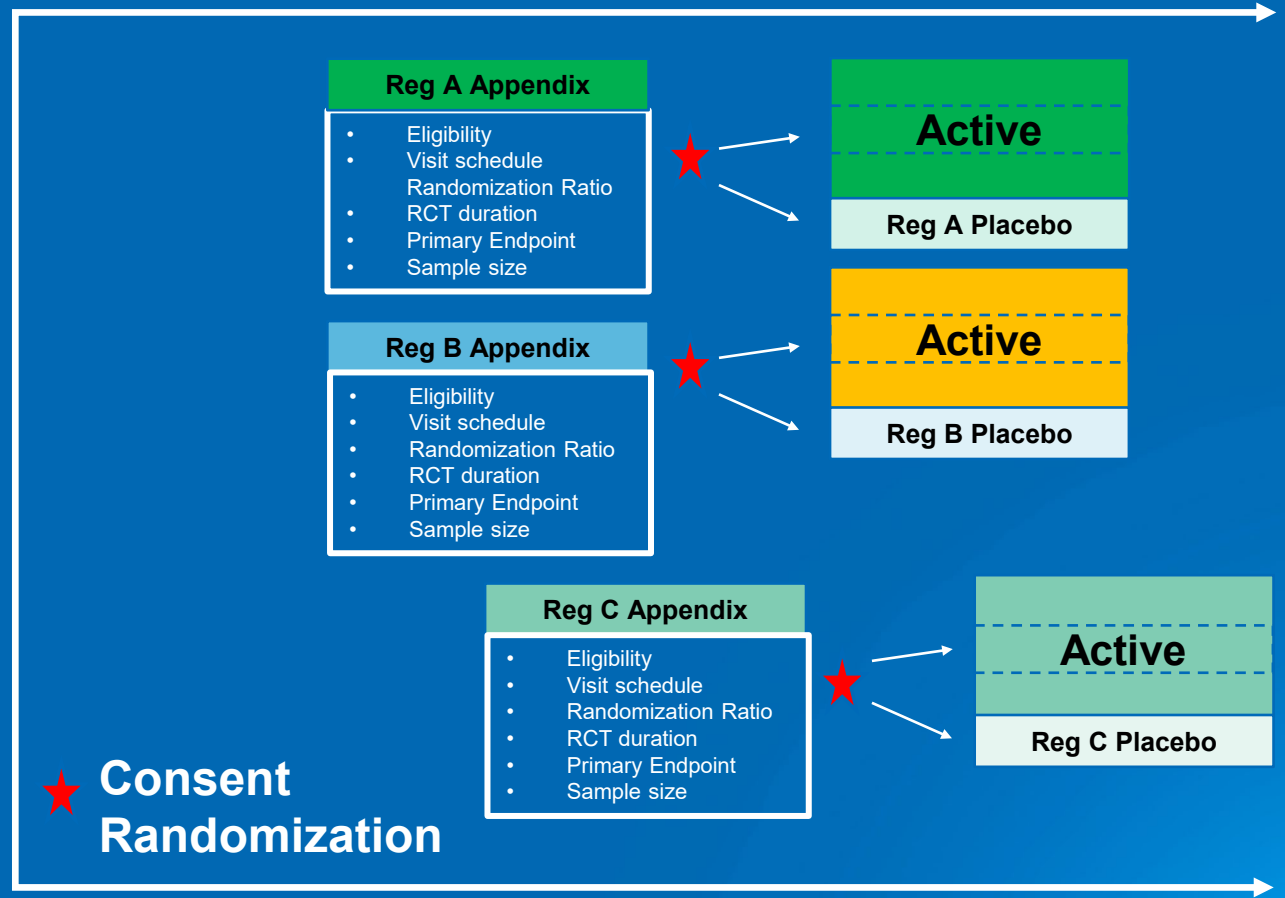
Appendix driven designs: Very little in MP and lots of flexibility in appendix

Examples:

- All arms choose their own population to enroll, their own endpoint, their own visit schedule, etc…
- Each arm may start at different times

Benefits: Extreme amount of flexibility for each arm

Risk: Lack of inferential synergy



Platform Trial: Balancing Synergy & Flexibility

Master Protocol

- Trial Eligibility
- Visit schedule & data collection
- Randomization Ratio
- RCT duration
- Primary Endpoint
- Recommended
  - Sample Size per regimen
  - Primary Analysis
  - Early Success / Futility Criteria

Regimen Specific Appendix

- Additional restrictions on Inclusion/exclusion
- Additional endpoints to be collected
- Study Stage / Goals
  - Success threshold / Type I error
  - Primary analysis
  - Bigger / smaller sample size
  - More aggressive futility

Example: Regimen Flexibility in Determining Inclusion/Exclusion

Concern with each regimen having their own inclusion/exclusion – lead to major differences in the populations

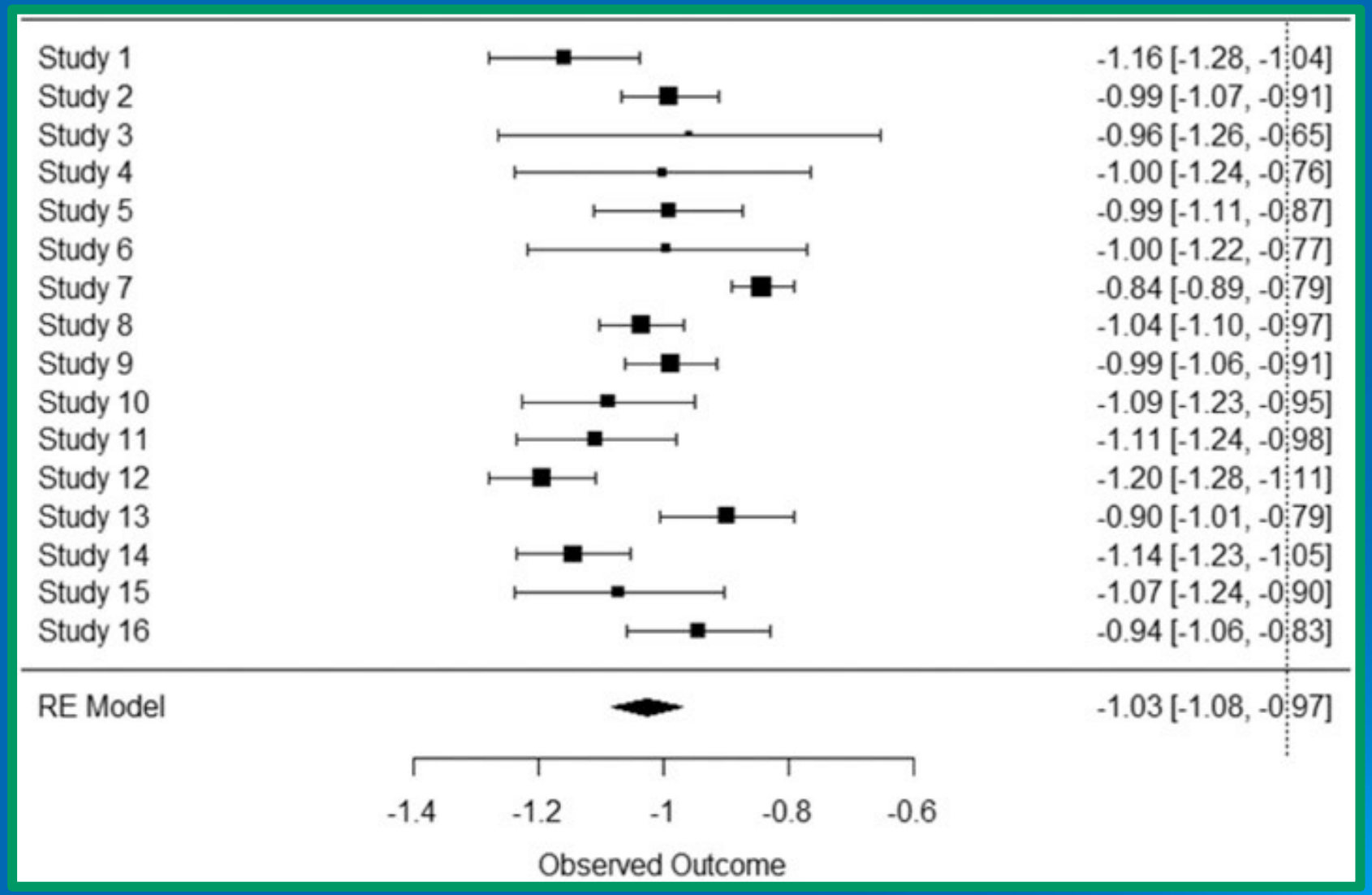
- Consider each proposed regimen-specific difference in inclusion/exclusion carefully – only allow necessary differences justified by safety or mechanism of action
- Judge if each difference is minor / major with respect to potential differences in primary outcome
- If judged to be a major difference limit shared control comparator to only those meeting this difference

Platform Trial: Balancing Synergy & Flexibility

- Within the platform we attempt to minimize differences across regimens by careful design choices.
- Some differences may still be present & unavoidable
- Example potential differences:
  - Enrollment time
  - Mode of administration
  - Minor differences in Inclusion / Exclusion
- *Can we quantify the likelihood that this would lead to meaningful differences in shared controls?*
- *Can we account for these potential differences with robust analysis methods?*

ALS Example: How likely are we to see differences in shared controls?

- Rates of progression across 16 different RCT in ALS from PRO-ACT database[1]
- Studies had different modes of administration, inclusion/exclusion criteria, enrolled at different sites and at different times.
- Mean estimate of -1.03 with SD = 0.11.



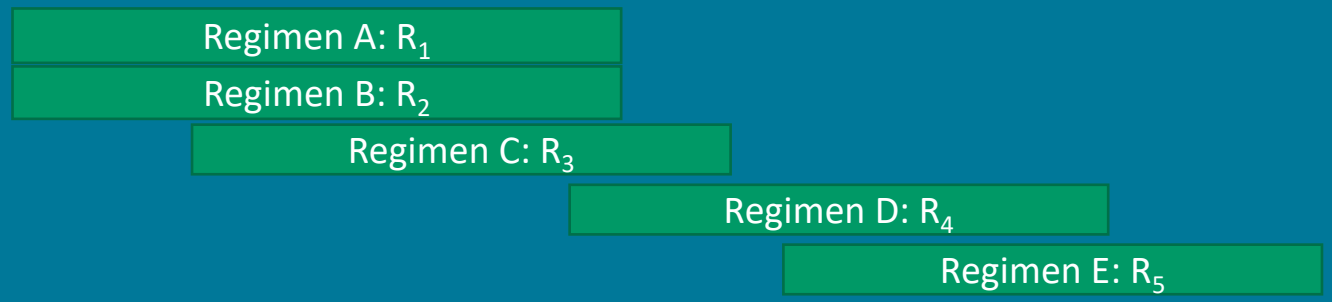
[1]Schoenfeld DA, F. D. M. E. e. a., 2019. Design and analysis of a clinical trial using previous trials as historical control. *Clinical Trials,* 16(5), pp. 531-538.

Account for differences using robust analysis methods

- *Primary analysis adjusts for potential differences in regimen-specific controls* ***across regimens*** *and across time*

Potential differences in controls across regimens (regimen-specific random effects)

- Hierarchical modeling of regimen-specific random effects
- More similar they are = more sharing of information



Example Hierarchical Model

$$R_i \sim N(\mu_R, \sigma_R^2); \mathrm{R} = 1{:}5$$

$$\mu_R \sim N(0, 10^2);$$

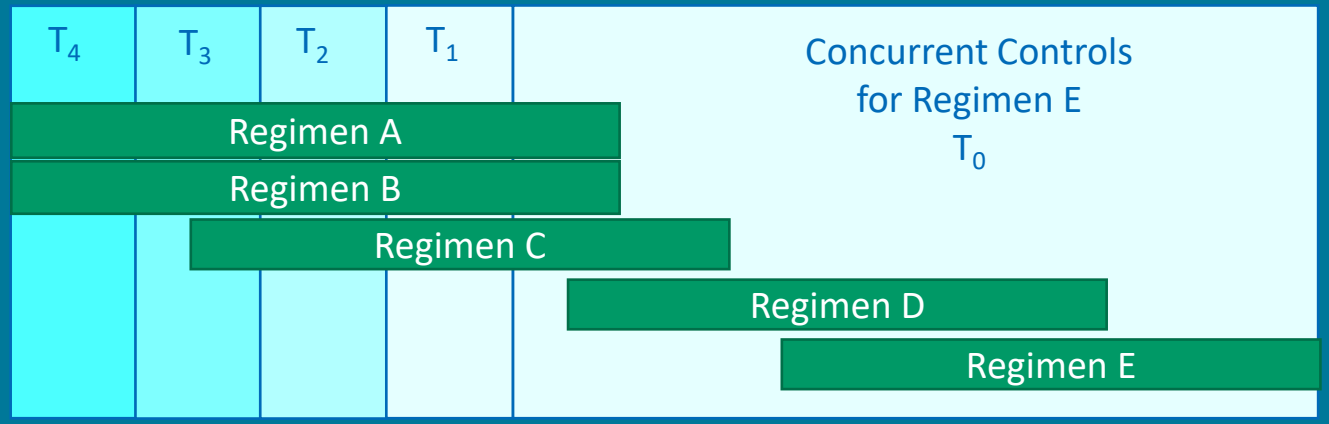
$$1/\sigma_R^2 \sim Gamma(a, b)$$

Account for differences using robust analysis methods

- *Primary analysis adjusts for potential differences in regimen-specific controls across regimens and* ***across time***

Differences in controls over time in analysis (time-trend effect)

- Concurrent vs. non-concurrently randomized controls
- All controls randomized within 24 weeks of regimen are considered concurrent.
- Model differences in the concurrent controls and each 12-week time bucket before



Example Simple NDLM

$$T_0 \sim N(0, 10^2);$$

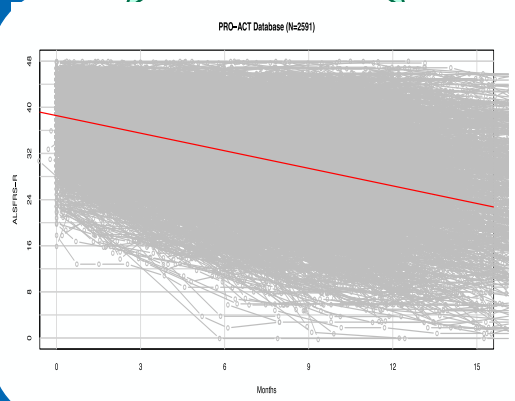
$$T_{n+1} \sim N(T_n, \sigma_t^2); \mathrm{n} = 2{:}4$$

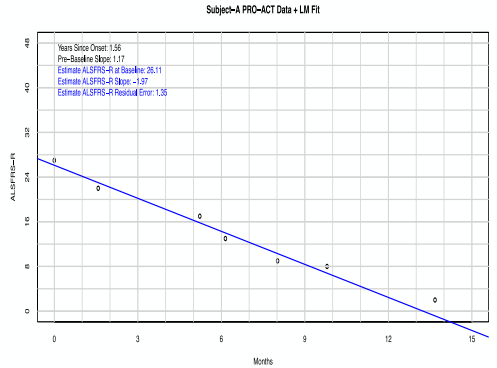
$$1/\sigma_t^2 \sim Gamma(a, b)$$

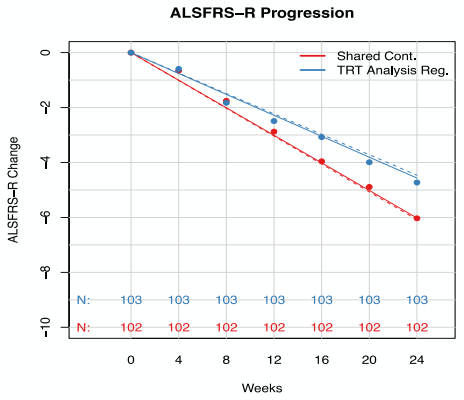
How do we customize each new RSA?
Clinical Trial Simulation

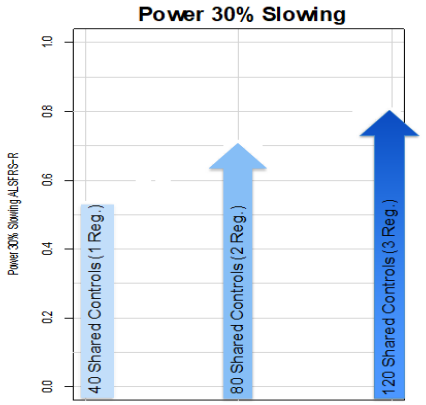
- Understand operating characteristics of proposed design / analysis method
- Optimize design/analysis under key trial parameters
- Understand robustness of results to modeling assumptions

Historical Data → Realistic Virtual Patient-level data → Proposed Design / Analysis → Power / Operating Char. of Design





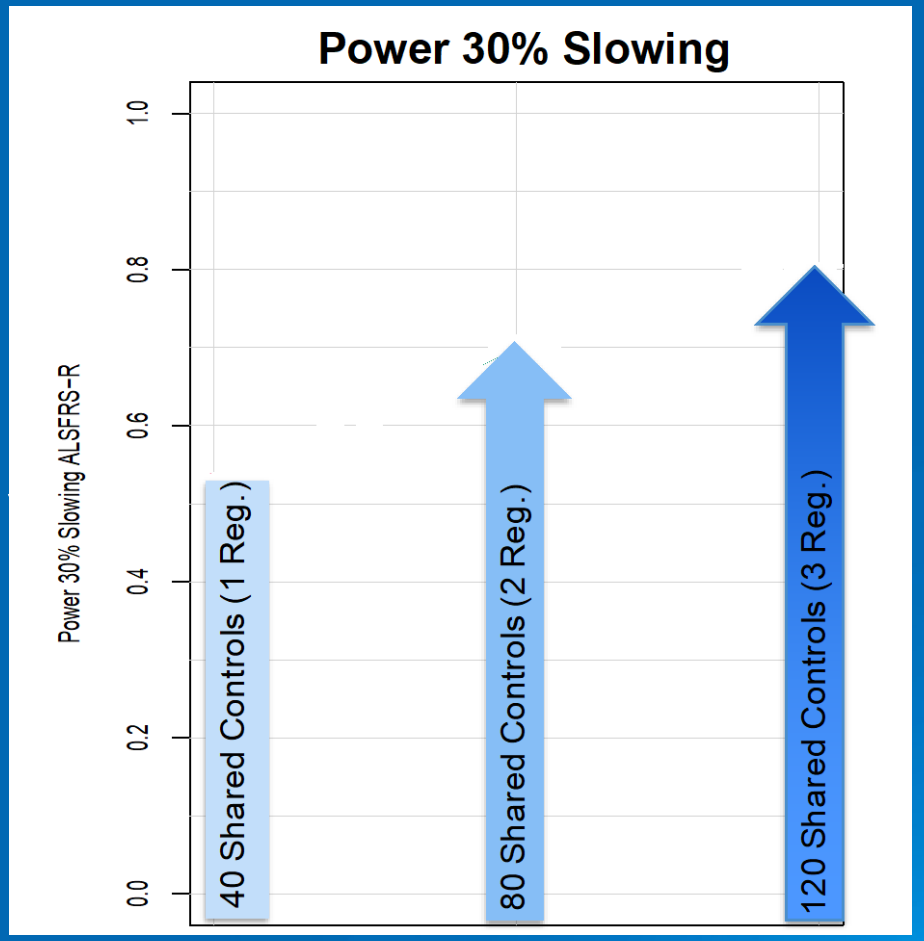




Clinical Trial Simulation: Power & Benefit of Shared Controls

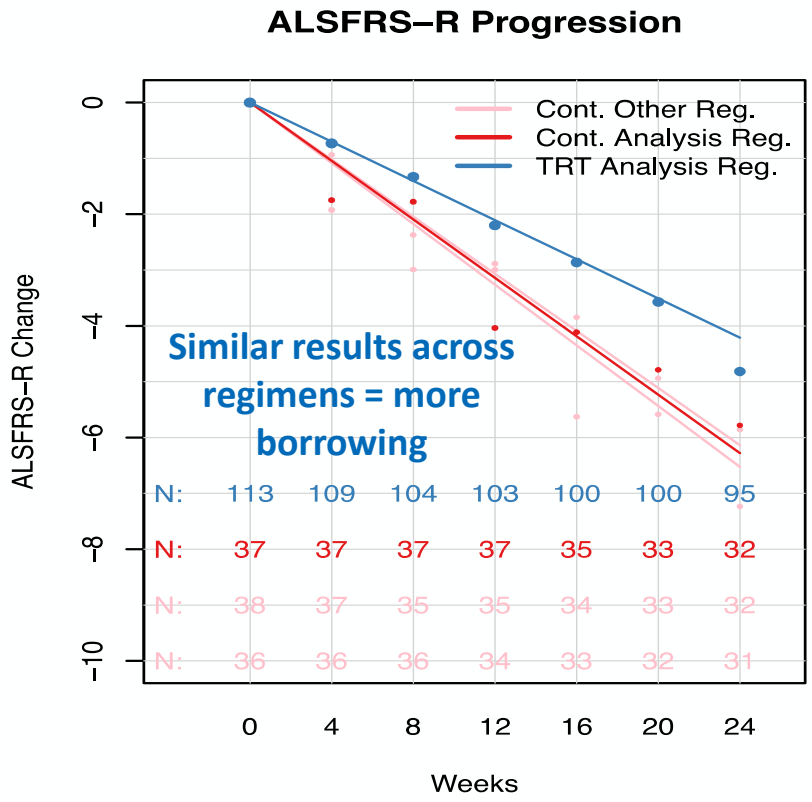
- *Example Operating Characteristics for first 3 regimens.*
- *Clinical trial simulations and operating characteristics customized based on future regimen's goals / needs*
- *Example: Mult. Doses, Different N, Sharing controls*

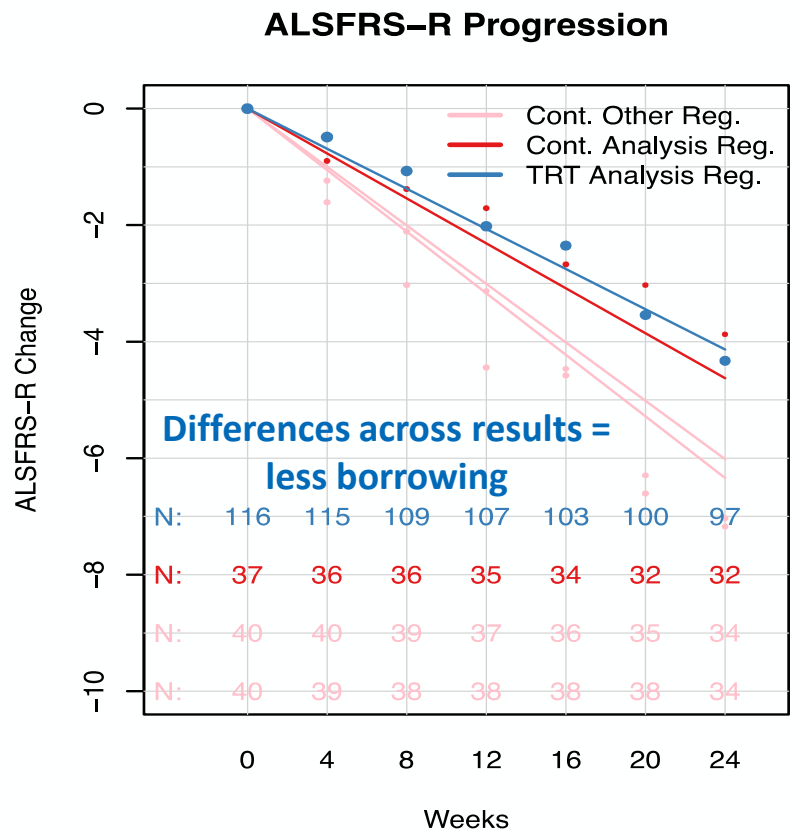
Operating Characteristics with Early stopping for Futility Assumes N=120 Treated and N=40 Controls + N=80 Shared controls from 2 other regimens				
Scenario (% Slowing ALSFRS-R)	**HR Mort.**	**Mean Duration (Months)**	**Prob. Success**	**Prob. Early Futility**
0%	1	14	0.024	0.28
25%	.75	15	0.61	0.01
30%	**.7**	**15**	**0.77**	**0.00**
35%	**.65**	**15**	**0.88**	**0.00**
30%	1	15	0.72	0.00
30%	1.3	15	0.68	0.01



Clinical Trial Simulation: Demonstration of Primary Analysis Method

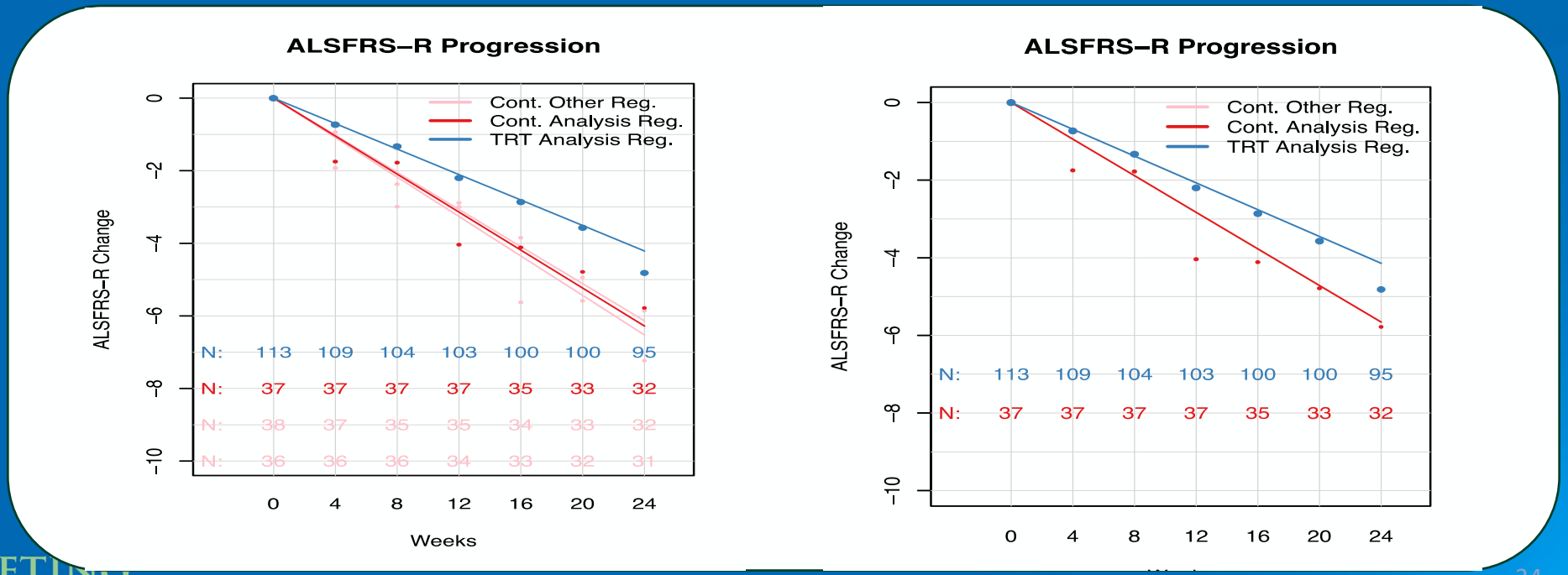
- *Primary analysis adjusts for potential differences in regimen-specific controls.*



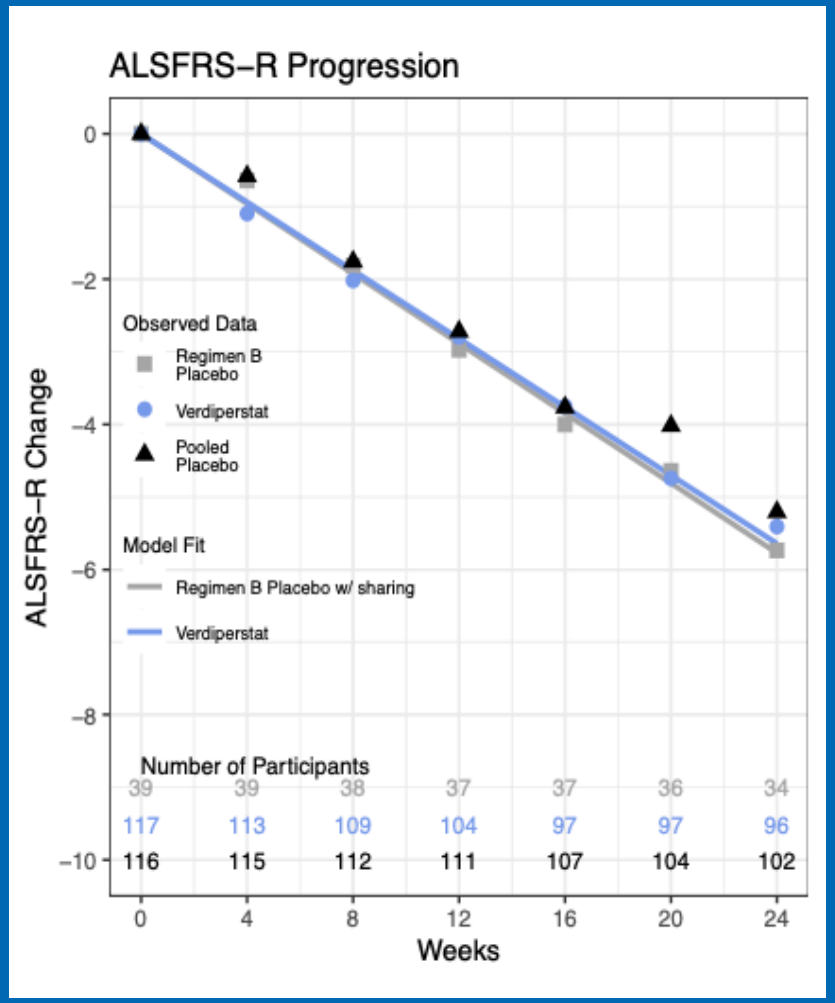


Clinical Trial Simulation: Demonstration of Sensitivity Analyses

- *Sensitivity analyses look at consistency of results across different assumptions in shared control*
  - *Regimen-only analysis: Using only regimen-specific controls*
  - *Common mode of administration analysis*
  - *Concurrent only control analysis*



ALS Platform: How have we done so far in practice?



Potential differences in shared controls:

- **Limit number of differences in inclusion/exclusion**
  - Very few participants who were eligible for the MP were ineligible for their assigned regimen
- **Overall similarities in outcomes across regimens**
  - Rate of progression per month on ALSFRS-R for first 5 regimen-specific control groups were consistent.
  - Primary analysis results with sharing across controls were all consistent with sensitivity analysis using regimen-only controls

Summary

- Backbone of platform trials = operational and inferential efficiencies brought about by synergy within the master protocol
- Need for regimen flexibility to accommodate needs of different types of investigational products
- Careful design + robust analysis methods can limit the potential for statistical bias due to potential differences in control populations
- Each platform must be considered individually – what is an appropriate justified assumption in one disease area my be completely inappropriate in another.

References

- Paganoni S, Berry JD, Quintana M, et al. **Adaptive Platform Trials to Transform Amyotrophic Lateral Sclerosis Therapy Development.** Ann Neurol. 2022 Feb;91(2):165-175.
- Quintana M, et al. **Design and Statistical Innovations in a Platform Trial for Amyotrophic Lateral Sclerosis.** Ann Neurol. 2023 Sept.; 94 (3): 547-560

Contracting Efficiencies Companies, Sites, and Vendors

Annette De Mattos, MPH
Administrative Manager, Research
Healey & AMG Center for ALS at Mass General

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Healey & AMG Center
Sean M. Healey & AMG Center for ALS
at Massachusetts General Hospital

HEALEY ALS Platform Trial

Traditional

	Intervention
Disease	Therapy A

Platform

	Intervention		
Disease	Therapy A	Therapy B	Therapy C

Outline

- Overview of HEALEY ALS Platform Trial infrastructure
- Scope of contracting
- Sites & Vendors: Selection and master agreements
- Industry Partners: Tiered contracting
- Sites & Vendors: Task Orders & Scope of Work Orders
- Summary: Key benefits and factors that contribute to efficiency

Healey & AMG Center
Sean M. Healey & AMG Center for ALS
at Massachusetts General Hospital

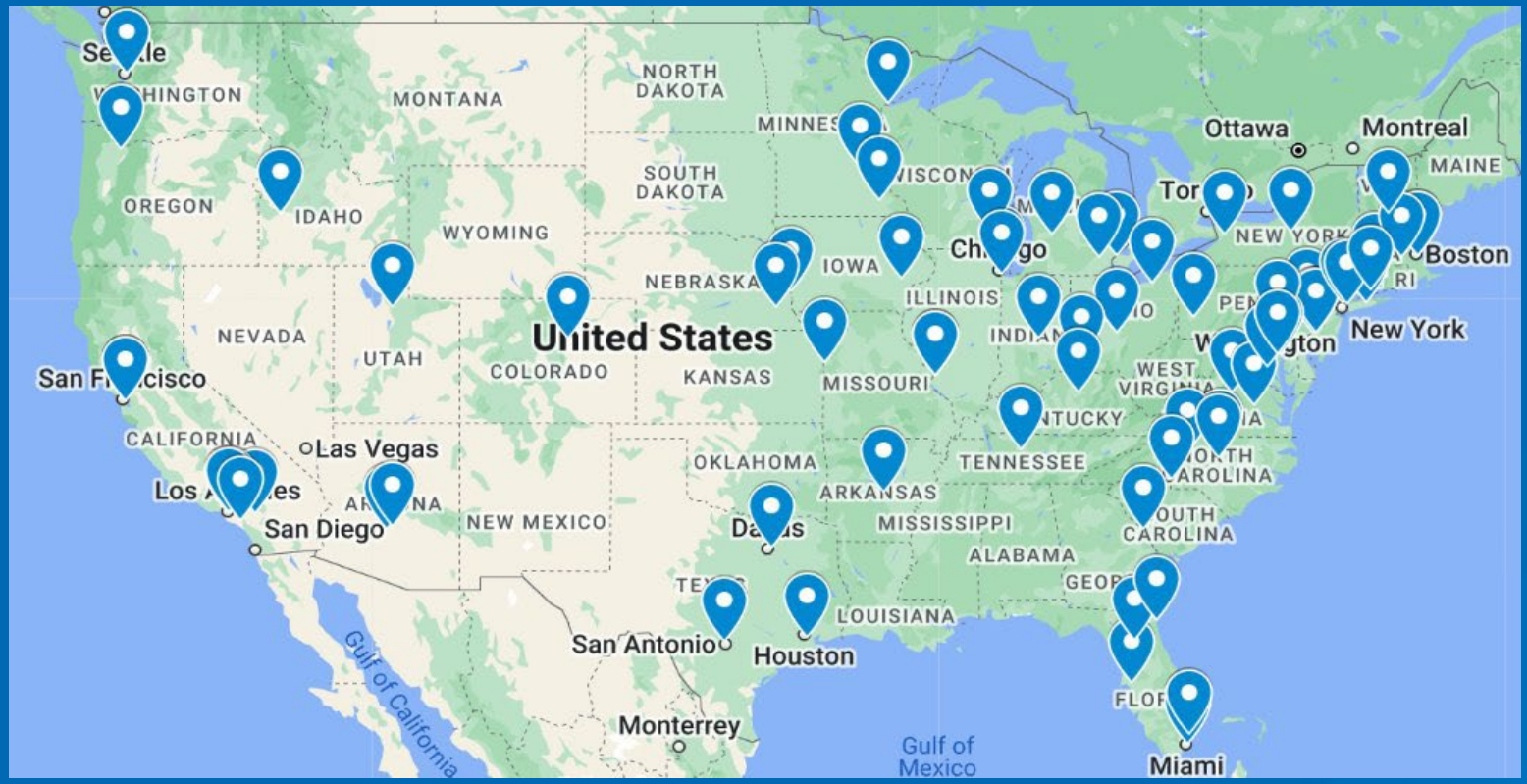
HEALEY ALS Platform Trial Infrastructure

MGH

CCC

DCC

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium



75+ Participating NEALS Sites!

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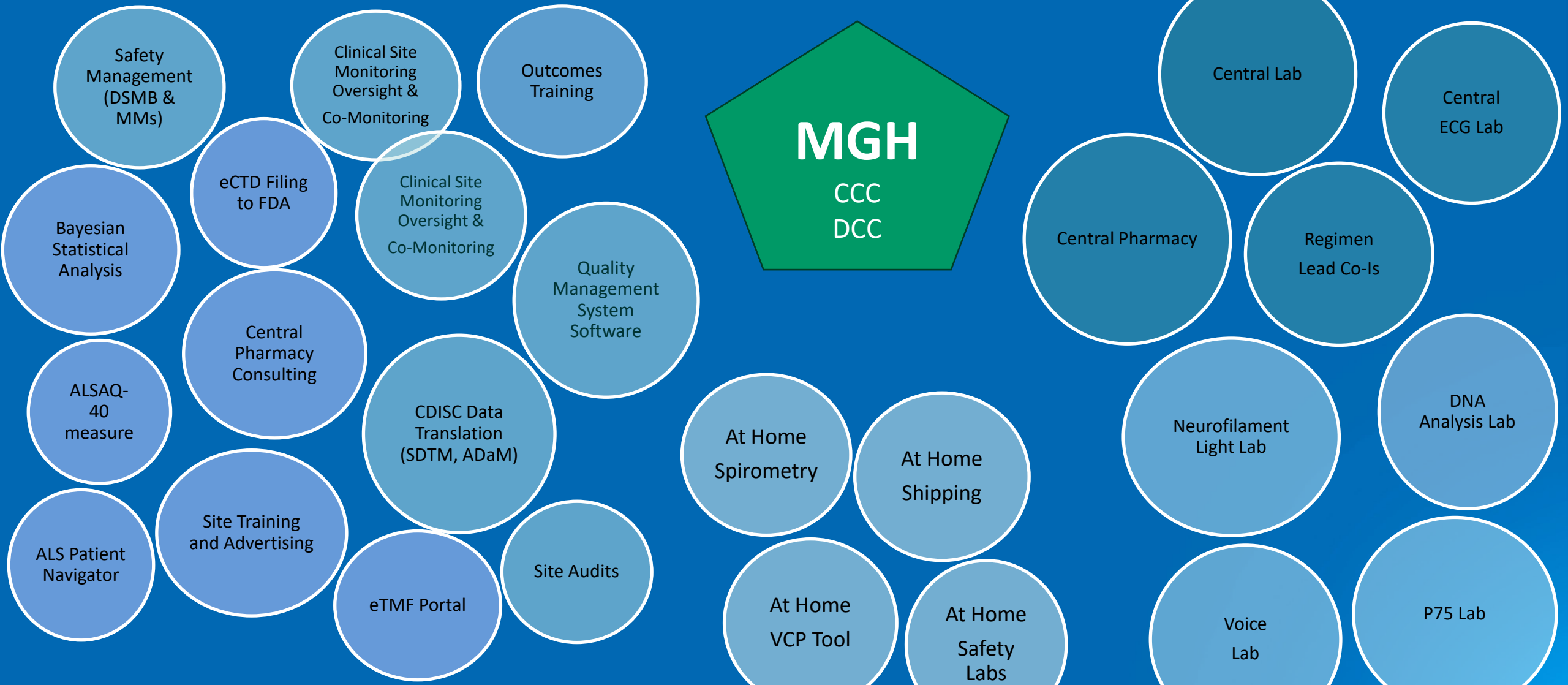
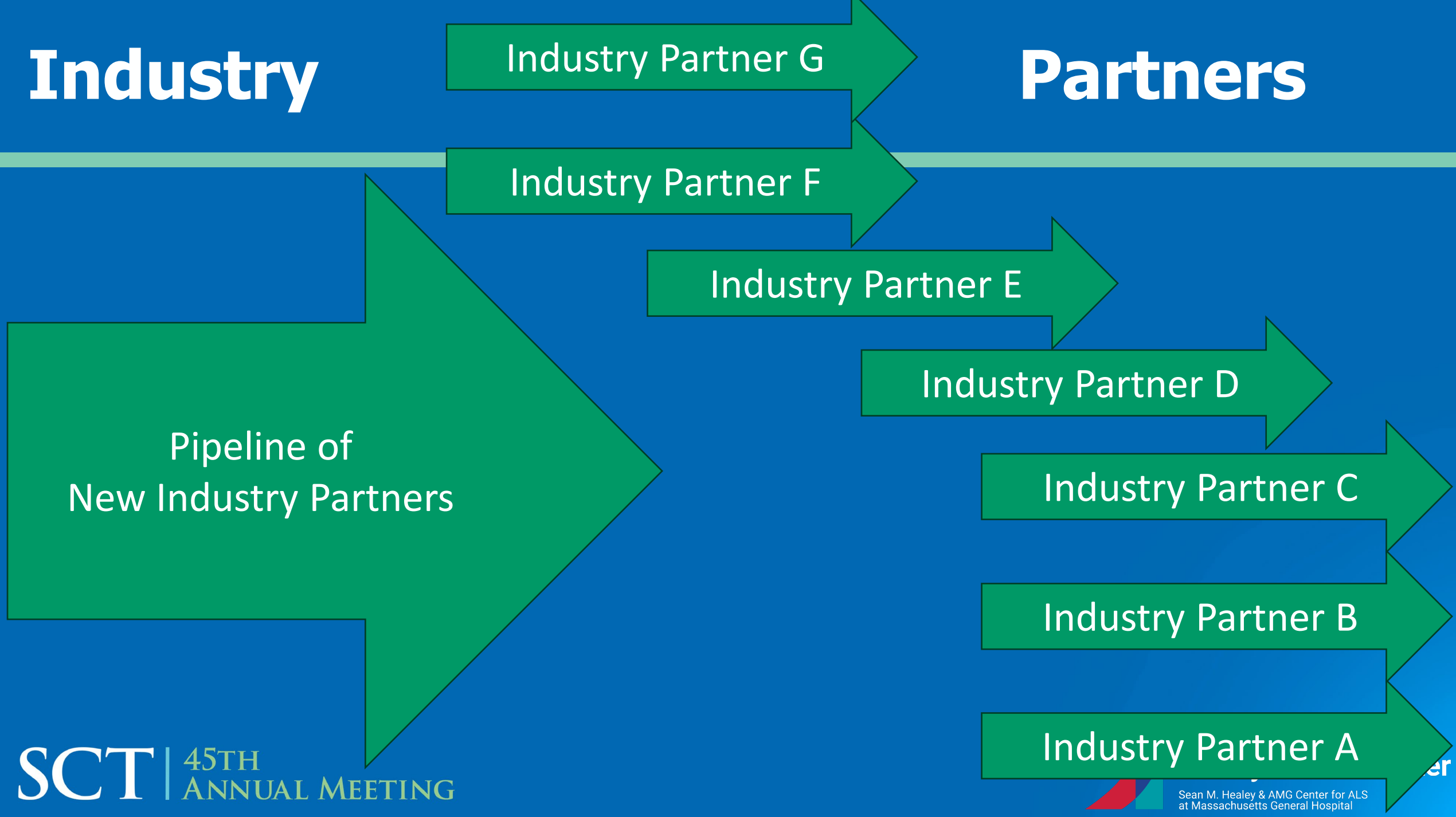
Vendors


Safety Management (DSMB & MMs)
Clinical Site Monitoring Oversight & Co-Monitoring
Outcomes Training
eCTD Filing to FDA
Clinical Site Monitoring Oversight & Co-Monitoring
Bayesian Statistical Analysis
Quality Management System Software
Central Pharmacy Consulting
ALSAQ-40 measure
CDISC Data Translation (SDTM, ADaM)
Site Training and Advertising
ALS Patient Navigator
eTMF Portal
Site Audits
MGH
CCC
DCC
At Home Spirometry
At Home Shipping
At Home VCP Tool
At Home Safety Labs
Central Lab
Central ECG Lab
Central Pharmacy
Regimen Lead Co-Is
Neurofilament Light Lab
DNA Analysis Lab
Voice Lab
P75 Lab

Industry Partners



Foundation of the
HEALEY ALS Platform Trial
Contract Infrastructure

Sites & Vendors: Selection & Master Agreements

2019 Infrastructure Build

Feasibility Questionnaire

Review & Selection

SITES

Site MCTA

Site Master Clinical Trial Agreement

Competitive Bidding

Review & Selection

VENDORS

Vendor MSA

Vendor Master Services Agreement

Master Clinical Trial Agreement (Site MCTA)

- Scope of Work
- Master Protocol
- Example Regimen Task Order

Who will do what and how?

- Terms and Conditions
  - Human Data & Materials
  - Publication
  - Intellectual Property
  - Liability and Subject Injury

What are the rules of the game?

2019 Infrastructure Build

Feasibility Questionnaire

Review & Selection

SITES

Site MCTA

Site Master Clinical Trial Agreement

Competitive Bidding

Review & Selection

VENDORS

Vendor MSA

Vendor Master Services Agreement

Introducing New Regimens to the HEALEY ALS Platform Trial

Industry Partner Agreements

Industry Partners: A Tiered Approach

DESIGN CONTRACT

Scope of Work

Terms & Conditions

Budget & Payment: Design Only

Design Period
Develop RSA & Budget

Establish Key Cost Drivers of the Operations Period:

Sample Size
Duration of Trial
Additional Participant Assessments

OPERATIONS AMENDMENT

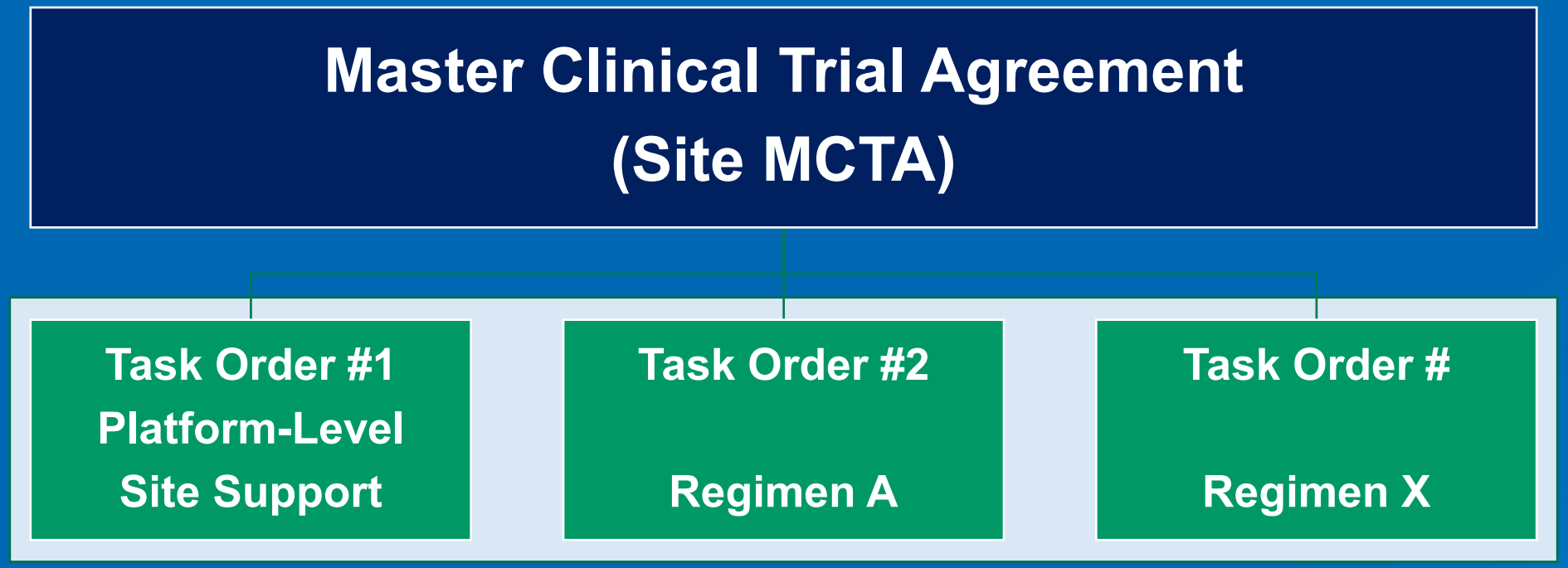
Amendment Adds Tailored Budget for the Operations Period

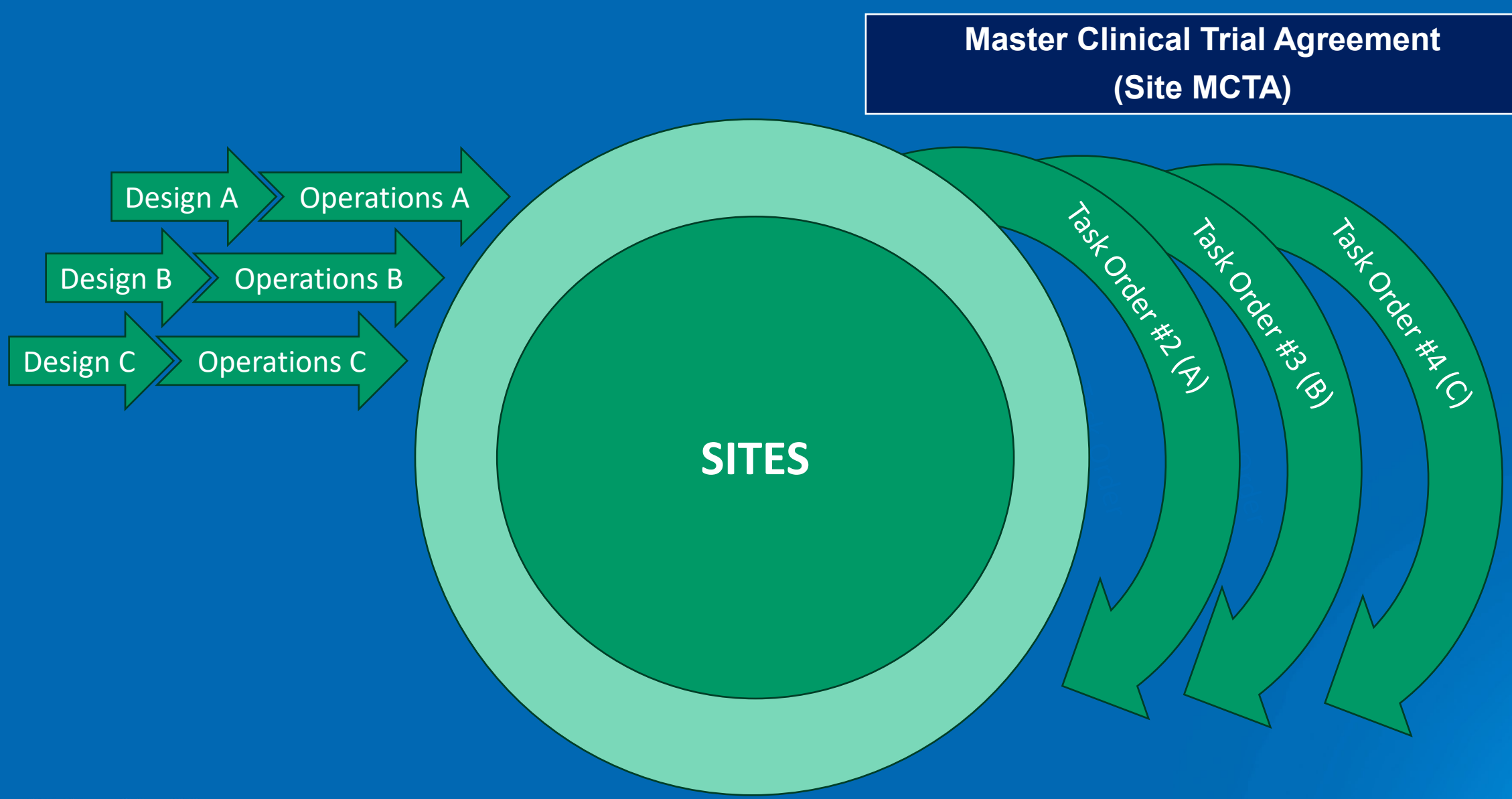
Operations Period

Introducing New Regimens
to the
HEALEY ALS Platform Trial

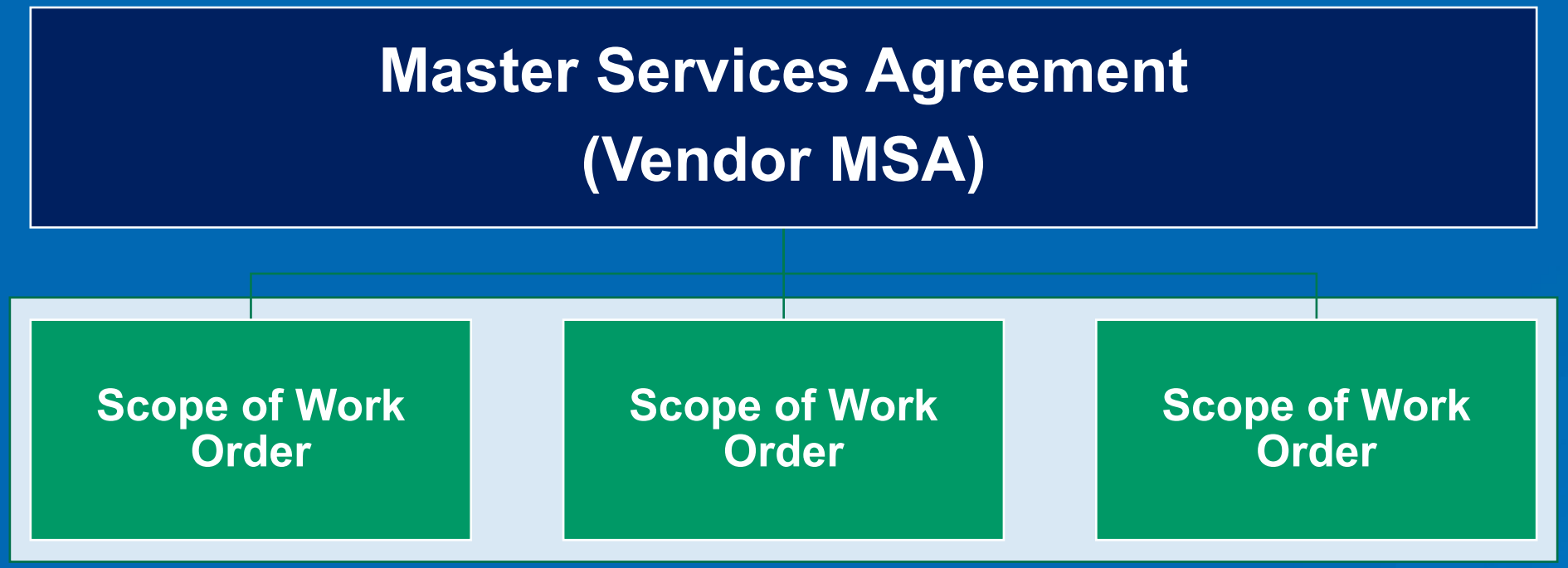
Sites & Vendors: Regimen Task/Work Orders

Site Agreement Structure

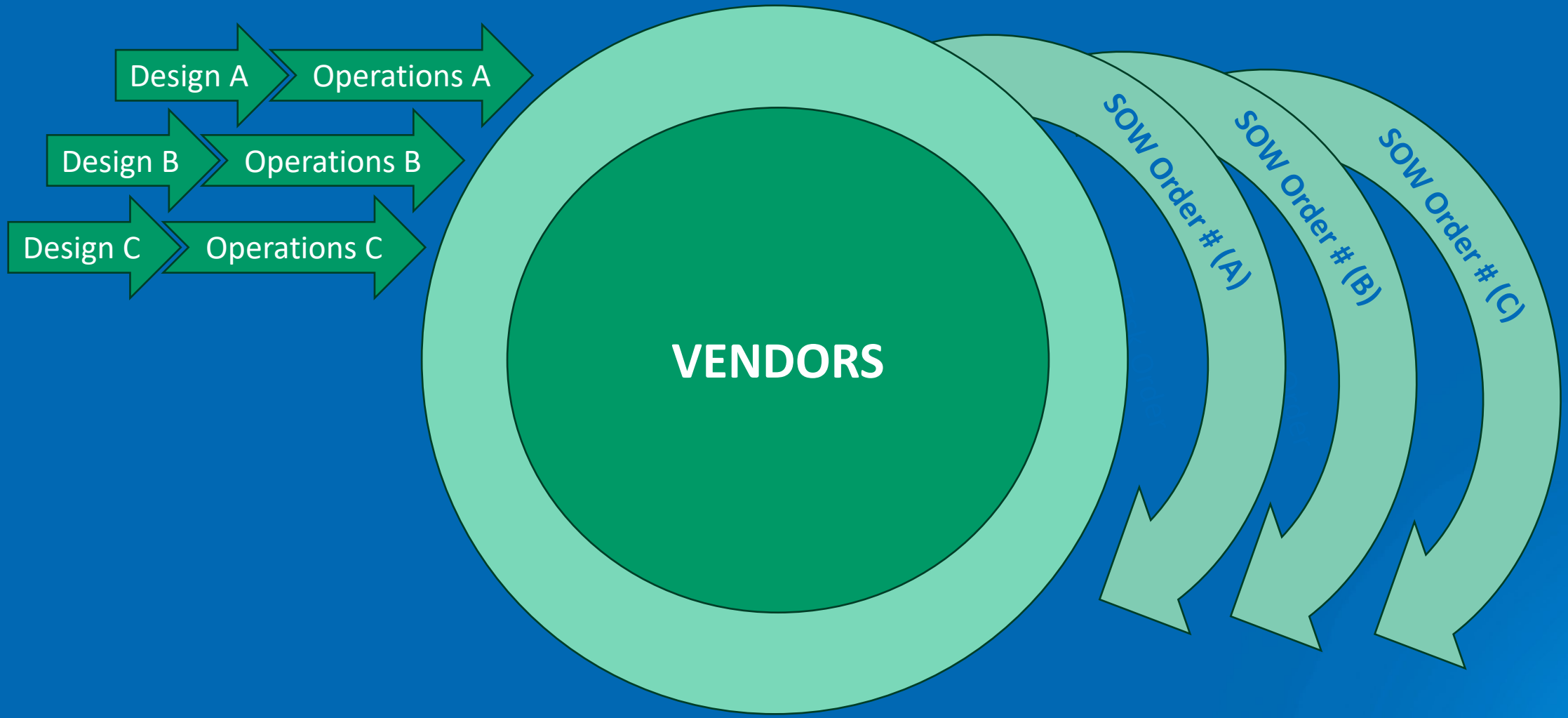



Master Clinical Trial Agreement
(Site MCTA)
Design A
Operations A
Design B
Operations B
Design C
Operations C
SITES
Task Order #2 (A)
Task Order #3 (B)
Task Order #4 (C)

Vendor Agreement Structure



Master Services Agreement
(Vendor MSA)



Summary

Summary

- Pre-contract selection process is largely complete and does not need to be repeated w/ new regimens
- Pre-existing master contracts reduce negotiation time when new regimens are introduced
- Tiered contracting allows for tailored regimen budgeting and industry partner involvement
- Real-time cost information throughout the design period helps to facilitate design decisions.
- Overlapping the operations budget development with the design period enables industry partners to negotiate budget in parallel.

Thank you!

Characteristics of Efficient Regimen Design

Brittney Harkey, PhD
Senior Clinical Trial Project Manager
Healey & AMG Center for ALS at Mass General

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Regimen Start-Up Overview

- What is the goal of the start-up phase for any clinical trial?
  - Design, operationalize and implement a protocol as efficiently as possible
  - Initiate enrollment quickly
- Reduced time to FPFV = Reduced start-up **costs**
- How do we leverage the platform infrastructure to efficiently design regimens and initiate enrollment?

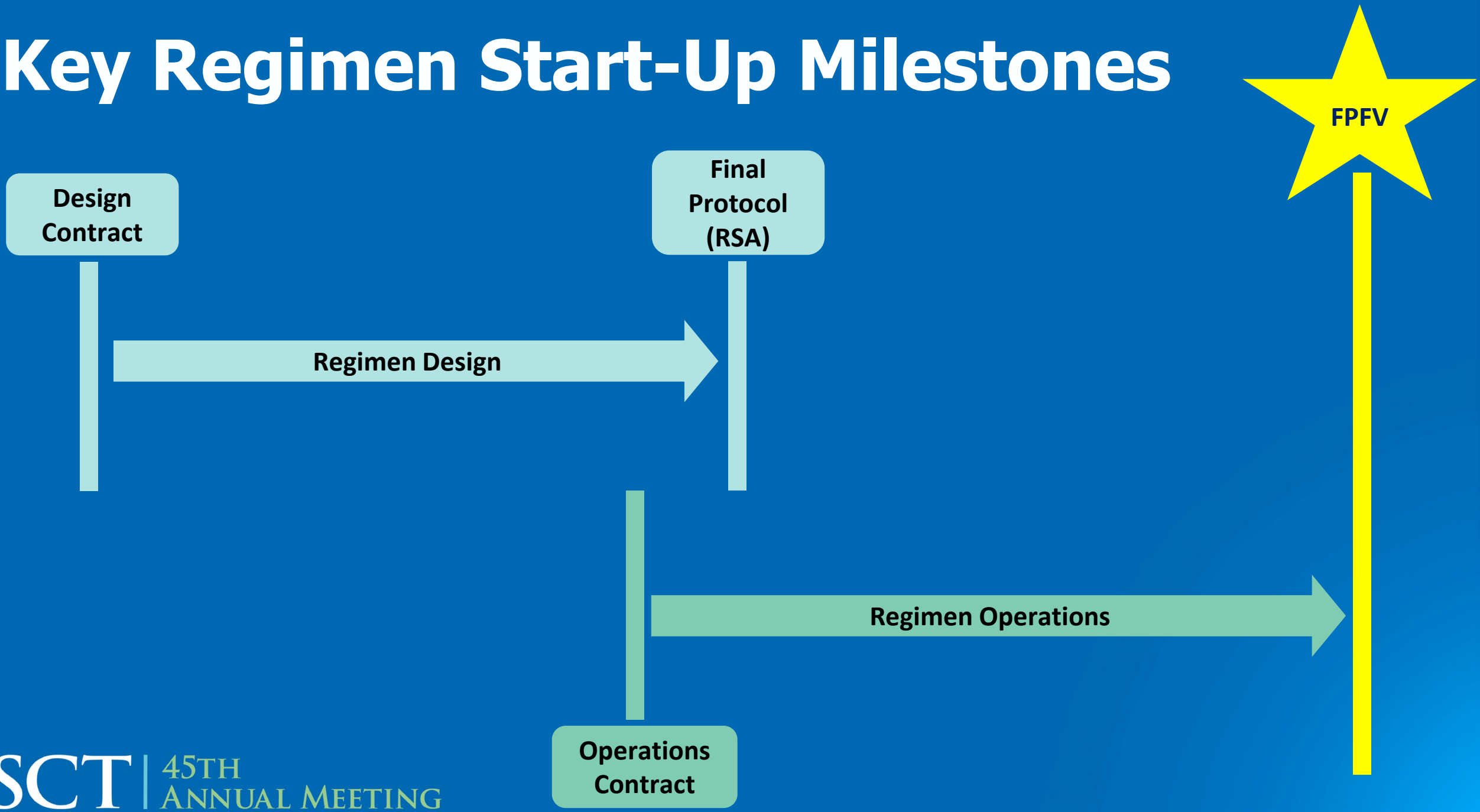
Regimen Start-Up Phases

Regimen Design → **Regimen Operations**

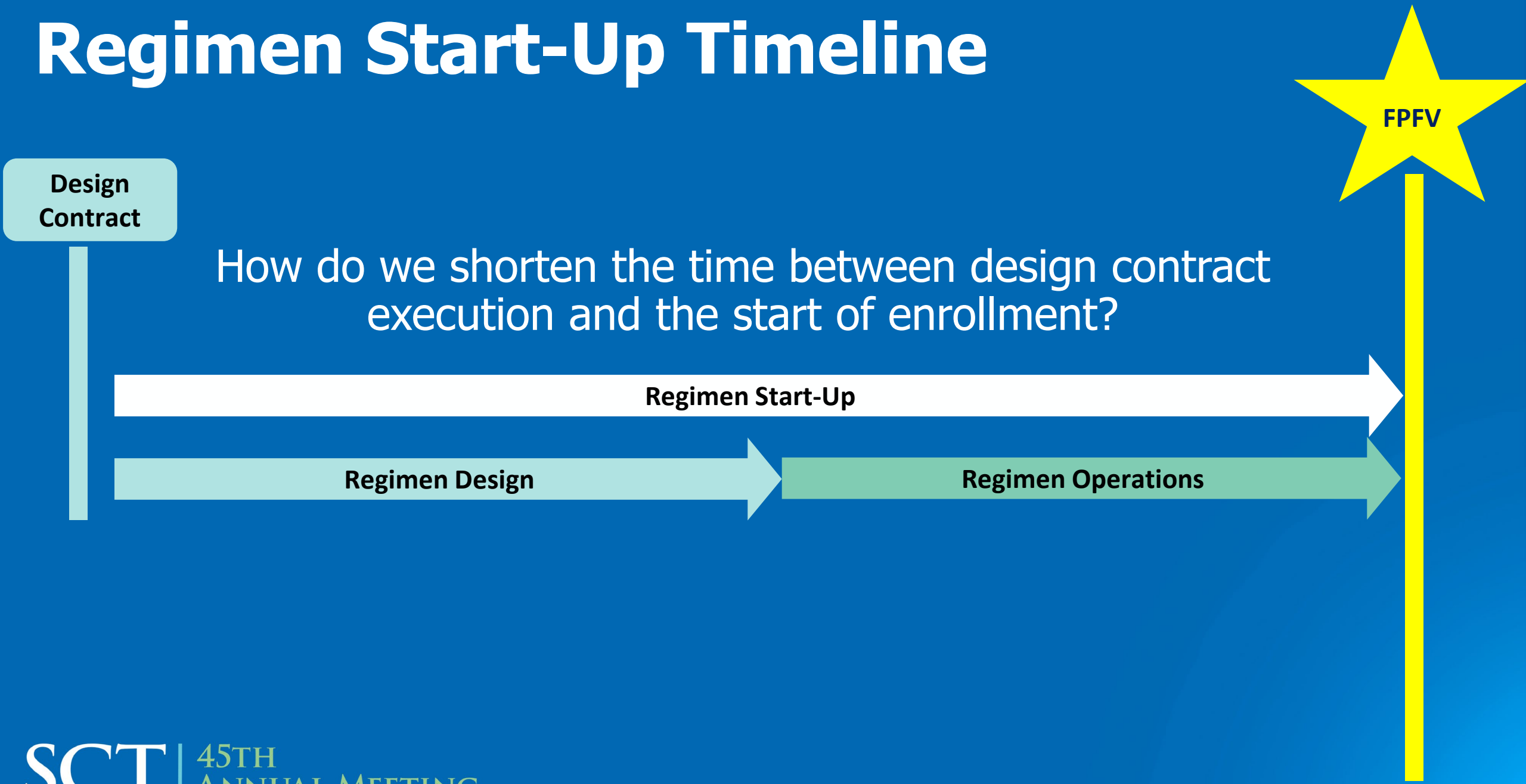
- Goal = develop and finalize a Regimen Specific Appendix (RSA), the regimen's protocol
  - Aligns with the Master Protocol
  - Customized to the Investigational Product
  - Informs full regimen budgeting

- Goal = integrate final RSA into existing trial infrastructure
  - Regulatory Approvals
  - Regimen Contracting
  - Electronic data capture (EDC) / Interactive Response Technology (IRT) build
  - Site Regulatory Requirements

Key Regimen Start-Up Milestones

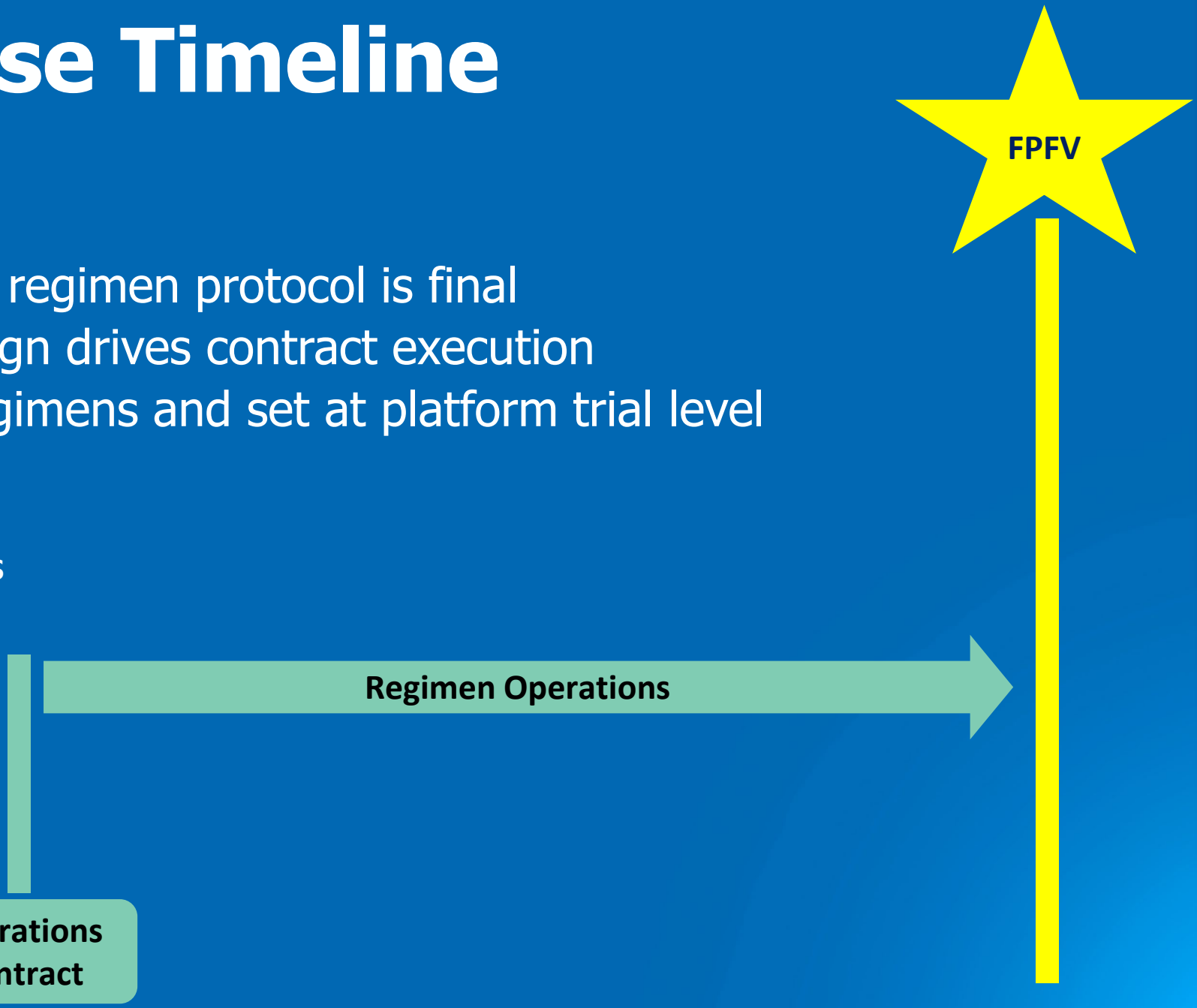


Regimen Start-Up Timeline

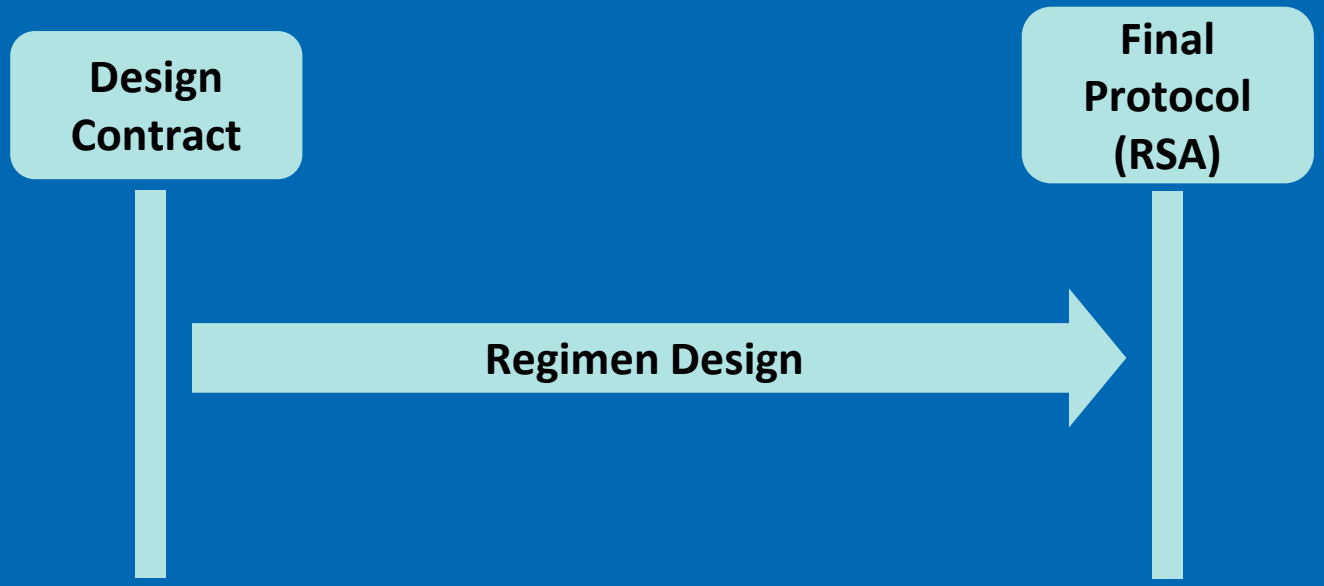


Operations Phase Timeline

- Largely fixed
  - Cannot begin until after the regimen protocol is final
  - Budget development in design drives contract execution
  - Timelines based on prior regimens and set at platform trial level
    - New Regimen sIRB Approval
      - RSA – average of 17.5 days
      - Sites – average of 5.87 days
    - Vendor SOWs for regimens
      - 30 – 90 days
    - EDC/IRT build time
      - 6 weeks

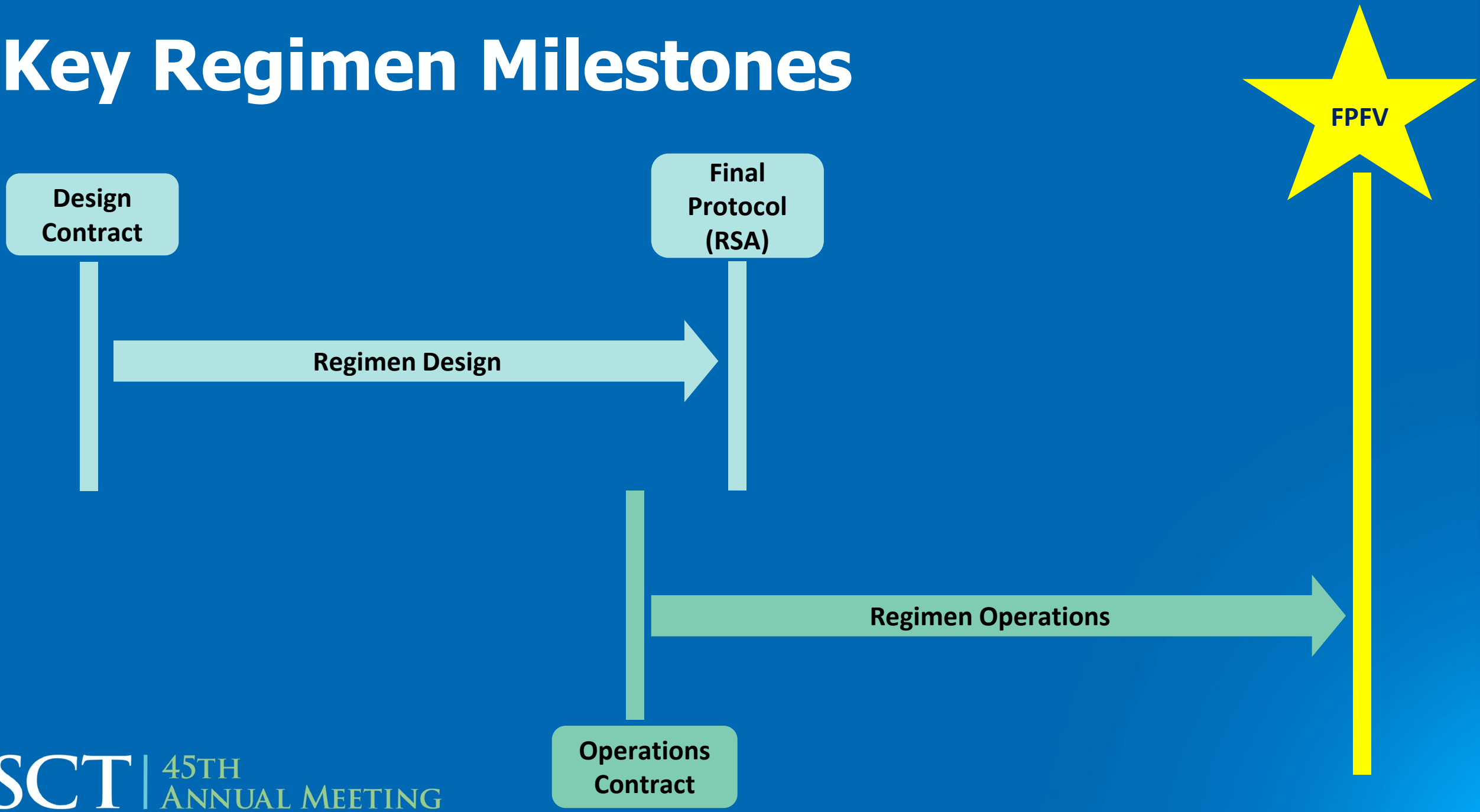


Design Phase Timeline

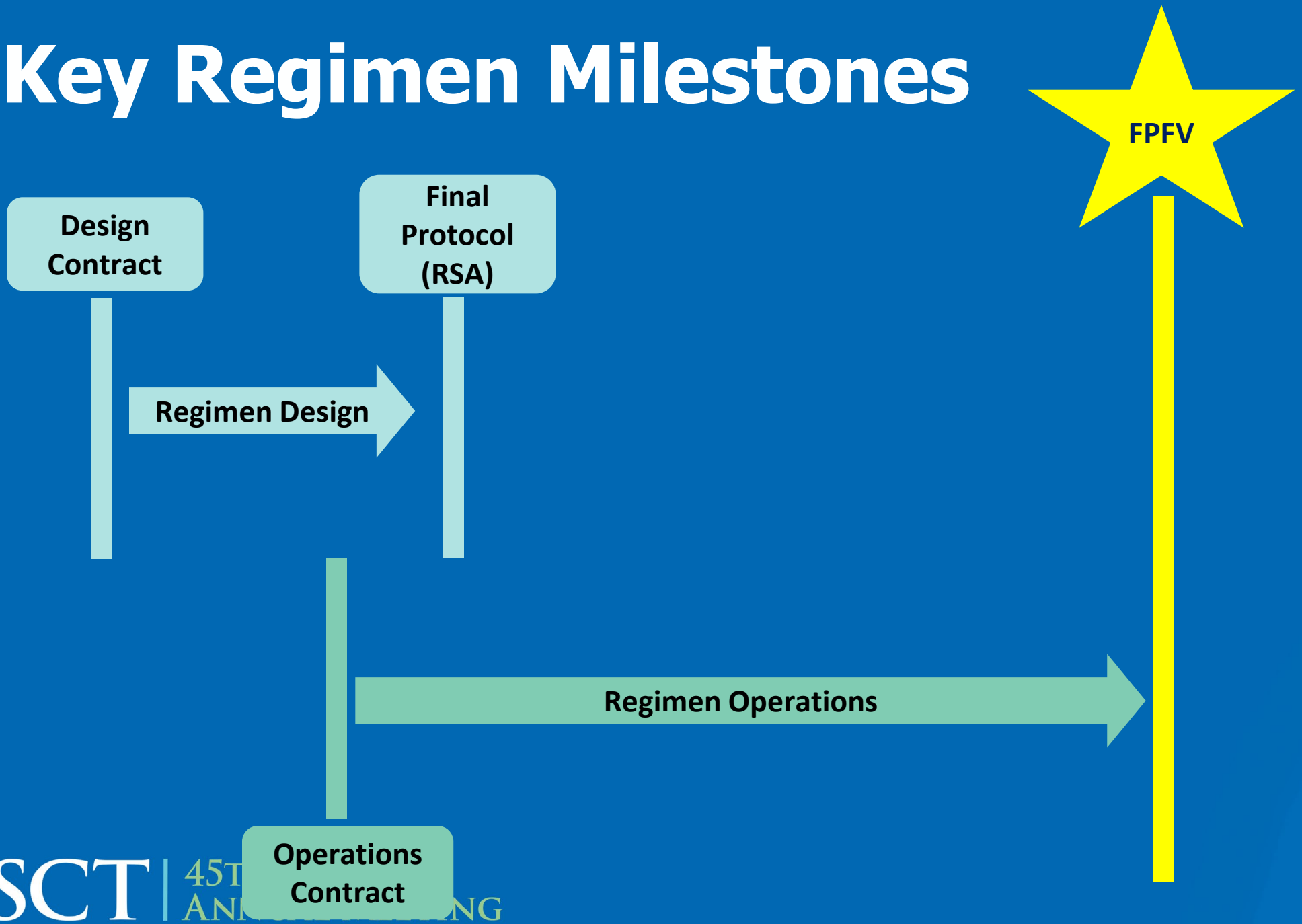


- Design and statistical decisions needed for the regimen are known in advance
- Dependent on standard process, and how efficiently key design decisions can be made

Key Regimen Milestones



Key Regimen Milestones



How do we shorten the regimen design phase?

- Expedited regimen protocol development/efficient decision making
- Early determination of operational budget drivers
- Strategic regulatory meeting planning

Regimen Design Committee

- Governs the regimen design and approves final regimen protocol

- Members
  - Core MGH Members
    - Sponsor, Regimen Leads, Biostatisticians, Project Management
  - Industry Partner Members

- Weekly Design Committee Meetings
  - Decisions on critical path to finalizing the regimen protocol (RSA) are frontloaded
    - Sample Size, Eligibility Criteria, Objectives and Endpoints, Schedule of Activities
  - Operational and statistical discussions occur in parallel

Expedited Regimen Protocol Development

- Regimen Protocol Template
  - Pre-populated sections align with the current version of Master Protocol
  - Regimen-specific sections customized by Industry Partner
- Operational sections complete offline, questions brought to meetings as needed

- Prioritization of discussions on sections on critical path to final version of the regimen protocol (RSA)
  - ❑ Inclusion/Exclusion Criteria
  - ❑ Sample Size
  - ❑ Outcomes and Endpoints
  - ❑ Schedule of Activities
  - ❑ Safety Monitoring/Management
  - ❑ Investigational Product

Design Meeting Discussion Roadmap

- ❑ Inclusion/Exclusion Criteria
- ❑ Sample Size
- ❑ Objectives and Endpoints
- ❑ Schedule of Activities
- ❑ Safety Monitoring/Management
- ❑ Investigational Product

Determine need for regimen-specific simulations

Regimen Protocol (RSA) Development

Set Regimen Inclusion/Exclusion Criteria

Statistical Discussion
Operational Discussion

Design Meeting Discussion Roadmap

- ✓ Inclusion/Exclusion Criteria
- ❑ Sample Size
- ❑ Objectives and Endpoints
- ❑ Schedule of Activities
- ❑ Safety Monitoring/Management
- ❑ Investigational Product

Determine need for regimen-specific simulations

Set Regimen Inclusion/Exclusion Criteria

Statistical Discussion
Operational Discussion

Design Meeting Discussion Roadmap

- ✓ Inclusion/Exclusion Criteria
- ❑ Sample Size
- ❑ Objectives and Endpoints
- ❑ Schedule of Activities
- ❑ Safety Monitoring/Management
- ❑ Investigational Product

Determine need for regimen-specific simulations

Review regimen-specific simulations and set sample size

Regimen Protocol (RSA) Development

Set Regimen Inclusion/Exclusion Criteria

Statistical Discussion
Operational Discussion

Design Meeting Discussion Roadmap

- ✓ Inclusion/Exclusion Criteria
- ✓ Sample Size
- ❑ Objectives and Endpoints
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Regimen Protocol (RSA) Development

Set Regimen Inclusion/Exclusion Criteria

Statistical Discussion
Operational Discussion

Design Meeting Discussion Roadmap

- ✓ Inclusion/Exclusion Criteria
- ✓ Sample Size
- ❑ Objectives and Endpoints
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- ❑ Investigational Product

Determine need for regimen-specific simulations

Review regimen-specific simulations and set sample size

Regimen Protocol (RSA) Development

Set Regimen Inclusion/Exclusion Criteria

Initial SOA Review

Statistical Discussion
Operational Discussion

Design Meeting Discussion Roadmap

- ✓ Inclusion/Exclusion Criteria
- ✓ Sample Size
- ❑ Objectives and Endpoints
- ❑ Schedule of Activities
- ❑ Safety Monitoring/Management
- ❑ Investigational Product

Determine need for regimen-specific simulations

Review regimen-specific simulations and set sample size

Review Endpoint hierarchy

Regimen Protocol (RSA) Development

Set Regimen Inclusion/Exclusion Criteria

Initial SOA Review

Review Objectives and Endpoints

Set Objectives and Endpoints

Statistical Discussion
Operational Discussion

Design Meeting Discussion Roadmap

- ✓ Inclusion/Exclusion Criteria
- ✓ Sample Size
- ✓ Objectives and Endpoints
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- ❑ Investigational Product

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Regimen Protocol (RSA) Development

Set Regimen Inclusion/Exclusion Criteria

Initial SOA Review

Review Objectives and Endpoints

Set Objectives and Endpoints

Statistical Discussion
Operational Discussion

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- ✓ Inclusion/Exclusion Criteria
- ✓ Sample Size
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Regimen Protocol (RSA) Development

Set Regimen Inclusion/Exclusion Criteria

Initial SOA Review

Review Objectives and Endpoints

Set Objectives and Endpoints

Set SOA

Statistical Discussion
Operational Discussion

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Set Regimen Inclusion/Exclusion Criteria

Initial SOA Review

Review Objectives and Endpoints

Set Objectives and Endpoints

Set SOA

Statistical Discussion
Operational Discussion

Design Meeting Discussion Roadmap

- ✓ Inclusion/Exclusion Criteria
- ✓ Sample Size
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- ✓ Investigational Product

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Review Endpoint hierarchy

Regimen Protocol (RSA) Development

Set Regimen Inclusion/Exclusion Criteria

Initial SOA Review

Review Objectives and Endpoints

Set Objectives and Endpoints

Set SOA

Final Review of Protocol

Operational sections completed offline

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Statistical Discussion
Operational Discussion

Strategic Regulatory Meeting Planning

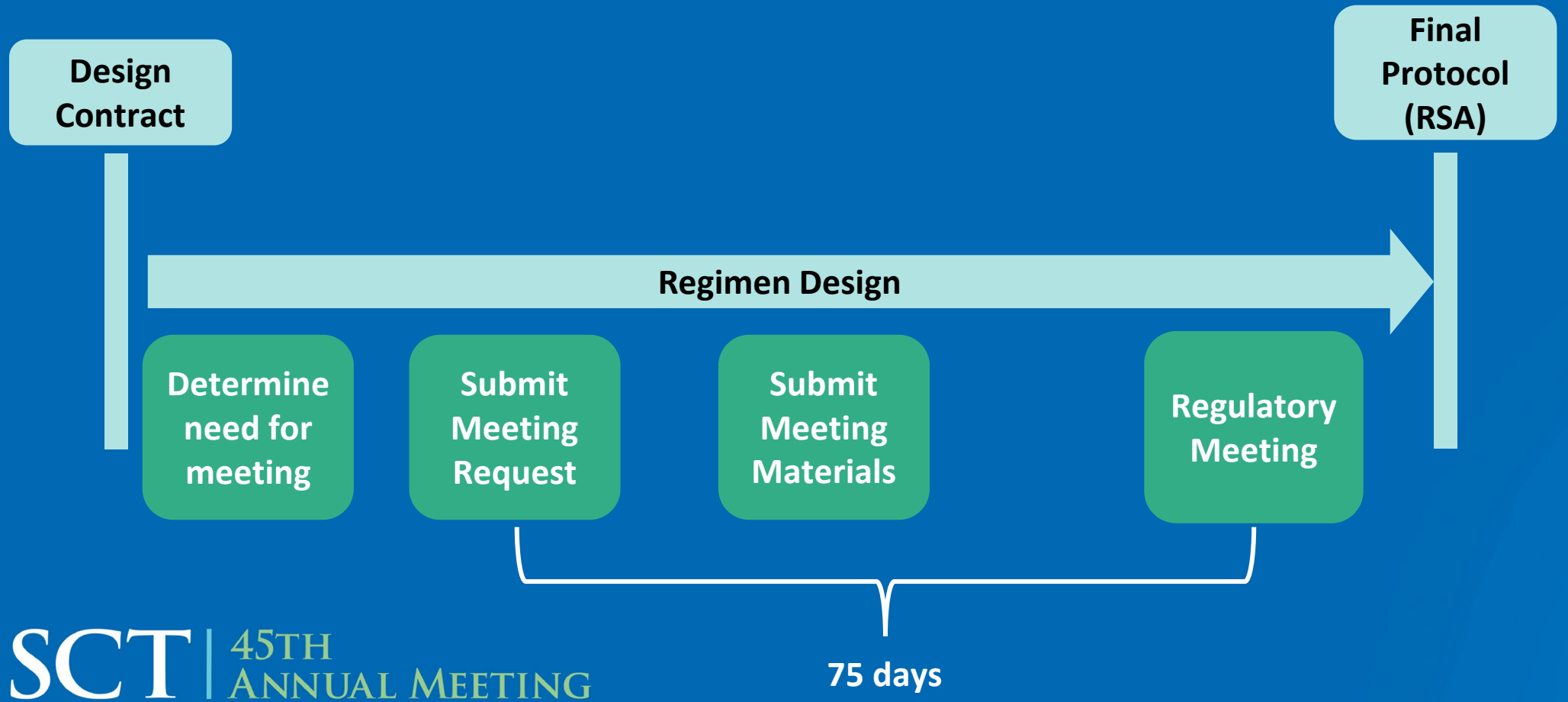
- Each new regimen has an opportunity to meet with FDA during a Type C meeting for guidance prior to finalizing the regimen protocol (RSA)

- Requesting a meeting is optional, and questions are limited to regimen investigational product and safety
  - Inclusion/Exclusion Criteria
  - Dose selection
  - Safety monitoring

- RSA cannot be finalized until *after* Type C meeting

Strategic Type C Meeting Planning

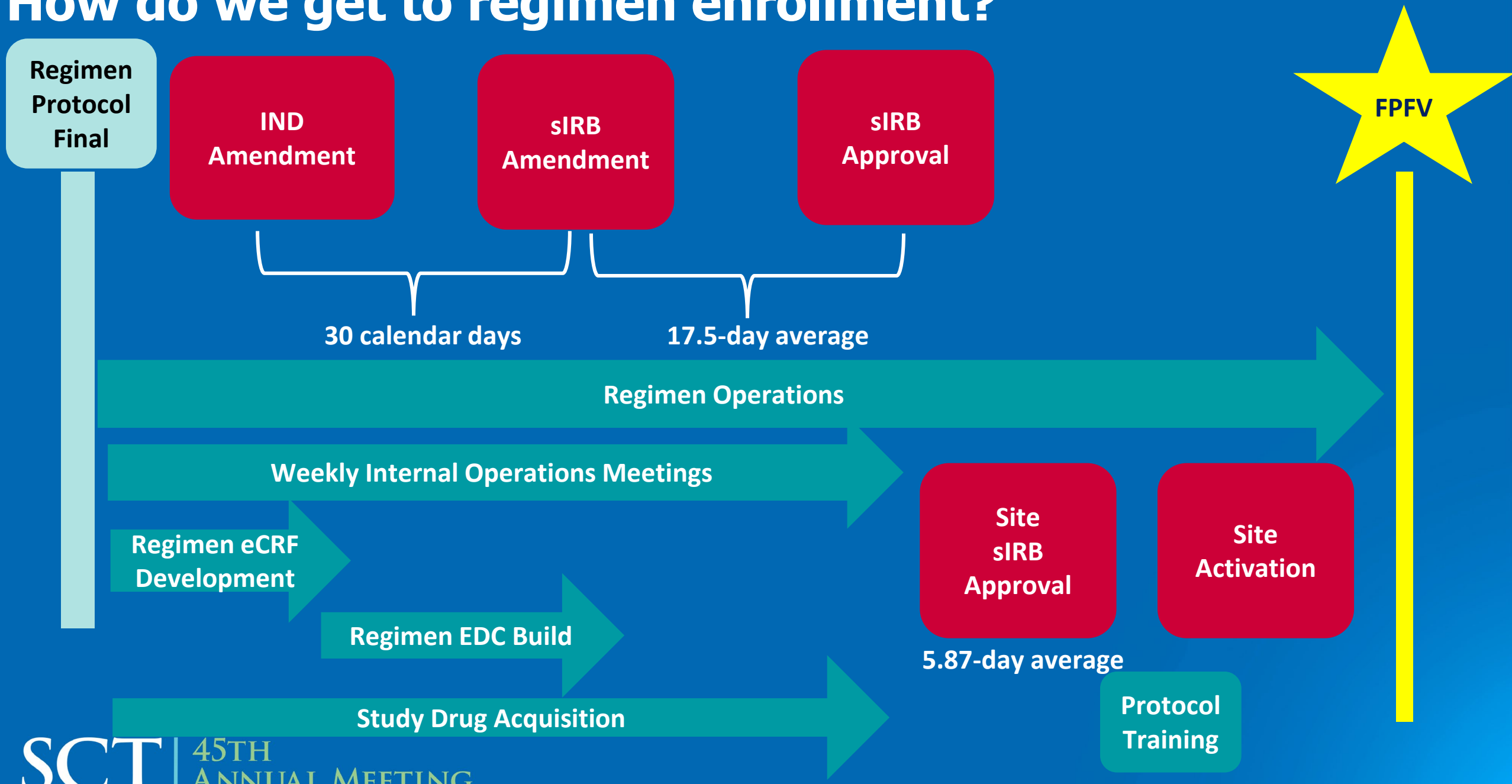
- Meeting planning runs in parallel with ongoing regimen protocol development



Regimen Design Summary

- Expedited regimen protocol development/efficient decision making
- Early determination of operational budget drivers
- Strategic regulatory meeting planning

How do we get to regimen enrollment?



Thank You