Invited Session 21

From Integration to Dissemination: Data and Statistical Management in a Perpetual ALS Platform Trial

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Hong Yu: Optimizing Data Integration and Quality through Multidisciplinary Collaboration and Vendor Management

Lori Chibnik, PhD: Standardization and Statistical Frameworks for Regimen-Level Analyses and Data Sharing in a Shared Placebo Platform Trial

Brittney Harkey, PhD: Operationalizing Data Integrity: Blinding, Timelines, and Results Management in a Perpetual Platform Trial

Lindsay Heyd: Enabling Re-Use of Trial Data to Inform Design, Build a Culture of Responsible Sharing, and Support Scientific Collaboration through Post-Regimen Data and Sample Sharing

Healey & AMG Center for ALS at Mass General
Boston, MA

Disclosures

- No authors have disclosures to report

Platform Trial Efficiencies

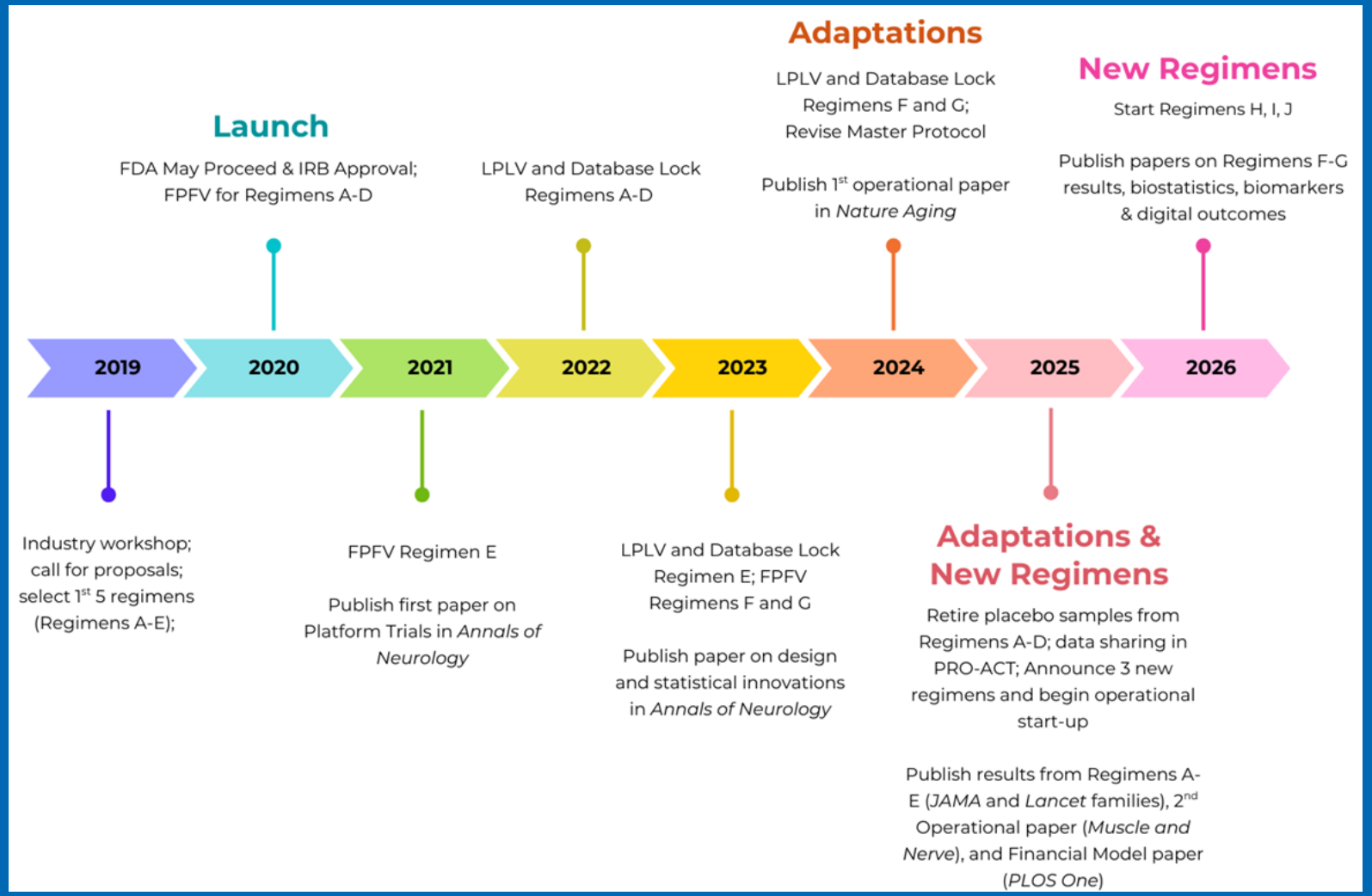
Traditional

	Intervention
Disease	Therapy A

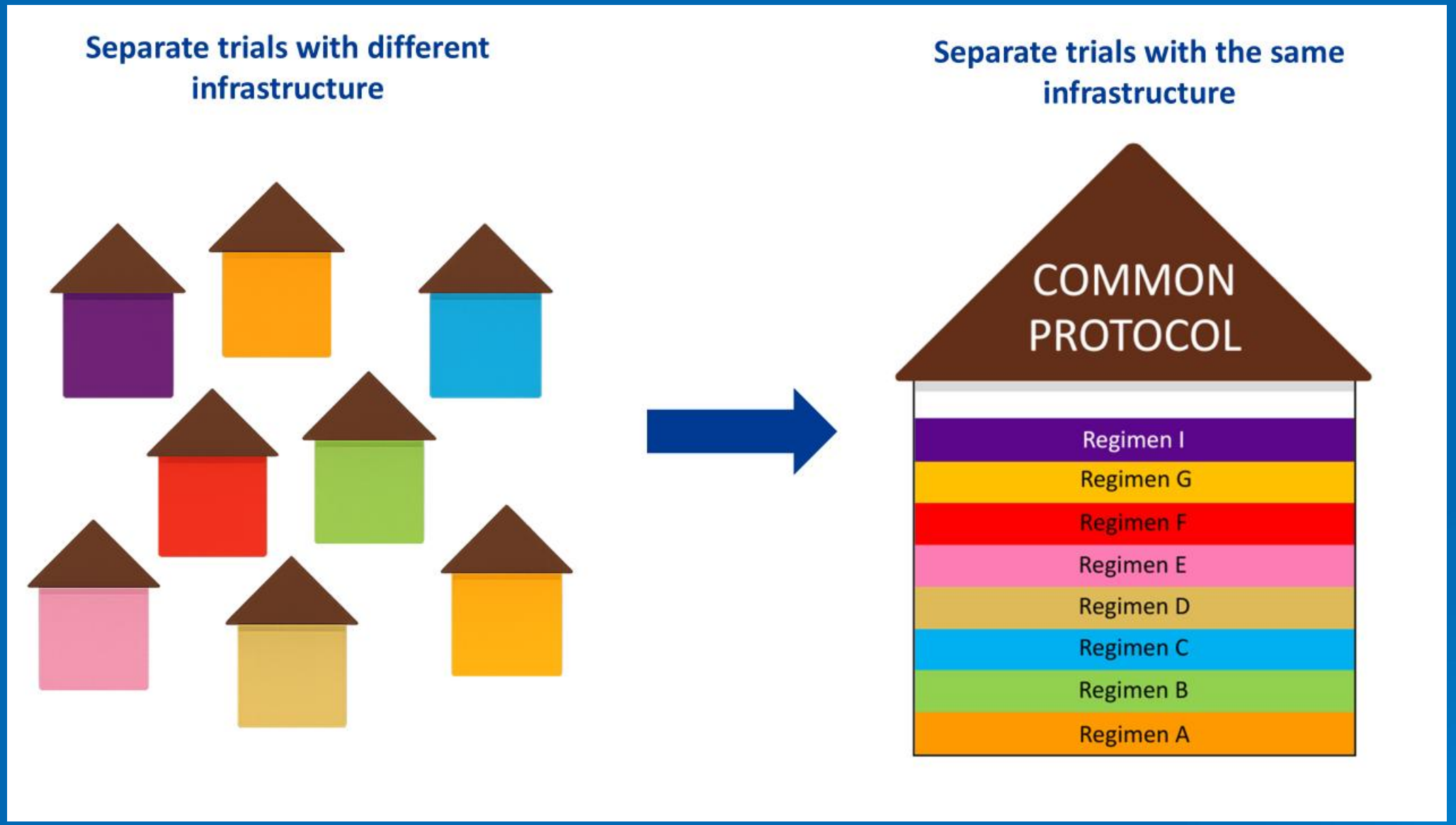
Platform

	Intervention		
Disease	Therapy A	Therapy B	Therapy C

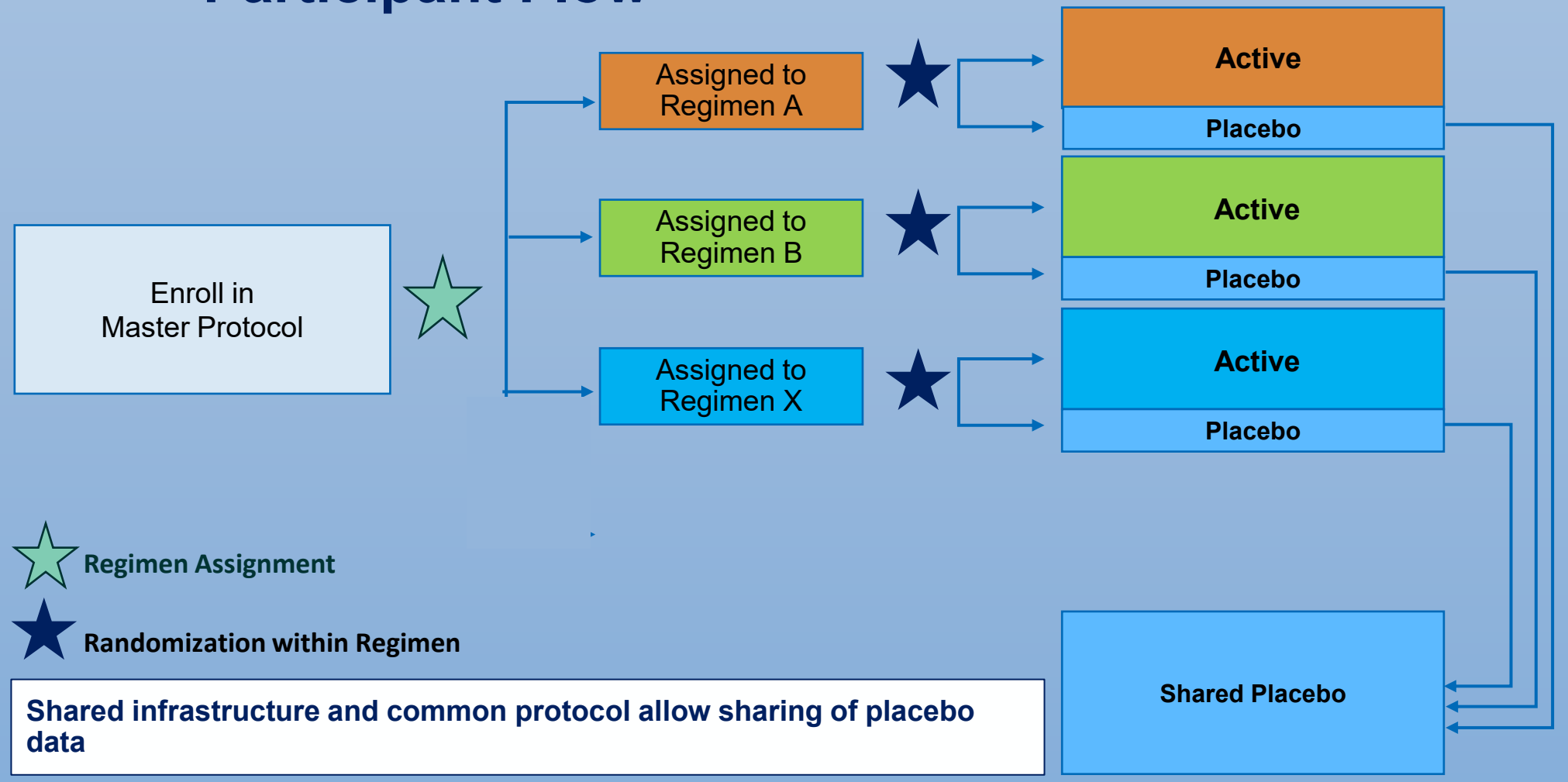
HEALEY ALS Platform Trial



- **75+ Trial sites**
- **1 Protocol**
- **1 single IRB**
- **Central Governance**
- **1,700+** participants consented at the Master Protocol
- **1,300+** participants randomized within a regimen
- **7** regimens tested to date


Separate trials with different infrastructure
Separate trials with the same infrastructure
COMMON PROTOCOL
Regimen I
Regimen G
Regimen F
Regimen E
Regimen D
Regimen C
Regimen B
Regimen A

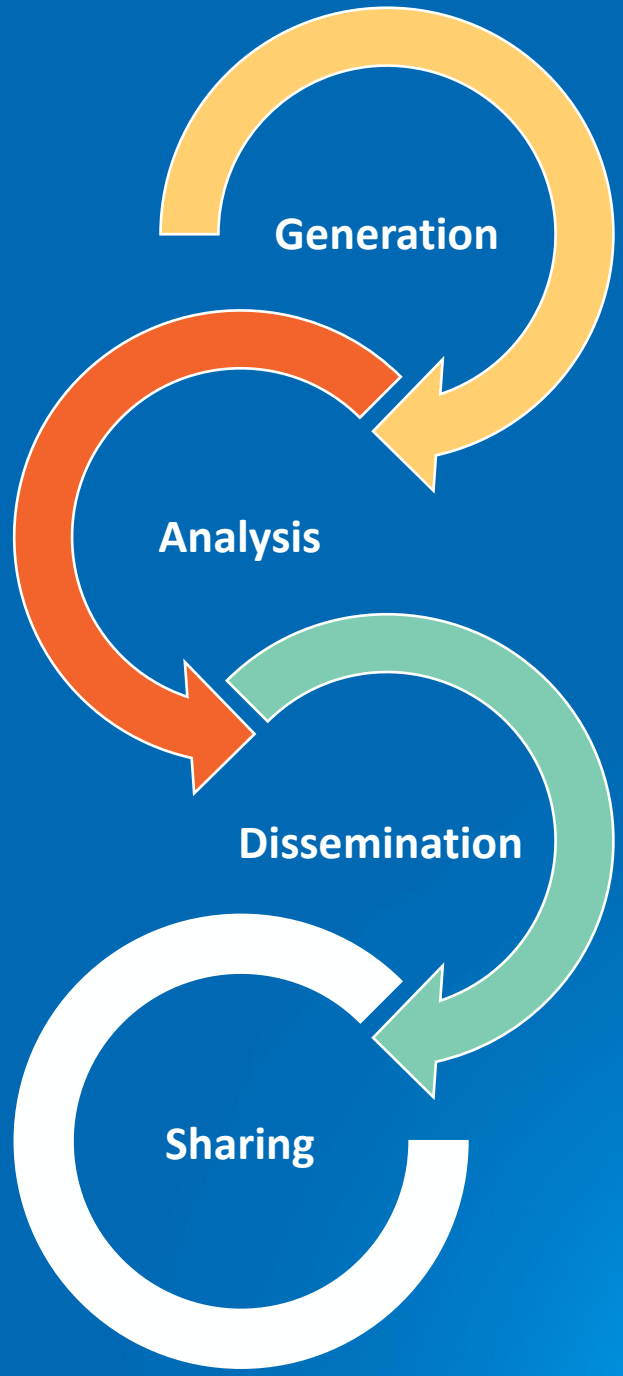
Participant Flow



Shared infrastructure and common protocol allow sharing of placebo data

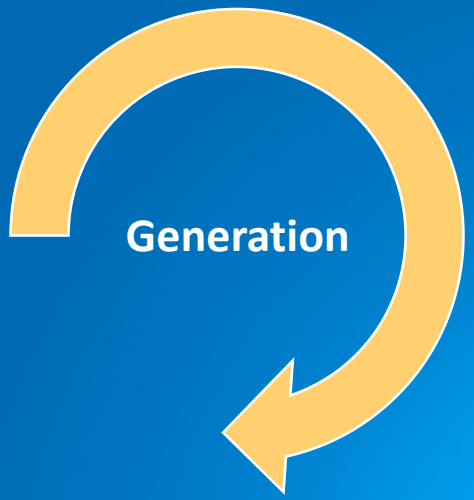
Session Objectives

- Provide an integrated overview of the data, statistical, and operational methodologies of the HEALEY ALS Platform Trial
- Describe the end-to-end data lifecycle per regimen
- Highlight lessons learned and best practices for data integrity, transparency, and collaboration in perpetual platform trials



Optimizing Data Integration and Quality through Multidisciplinary Collaboration and Vendor Management

Hong Yu
Director, Data Management
Healey & AMG Center for ALS at Mass General
Boston, MA



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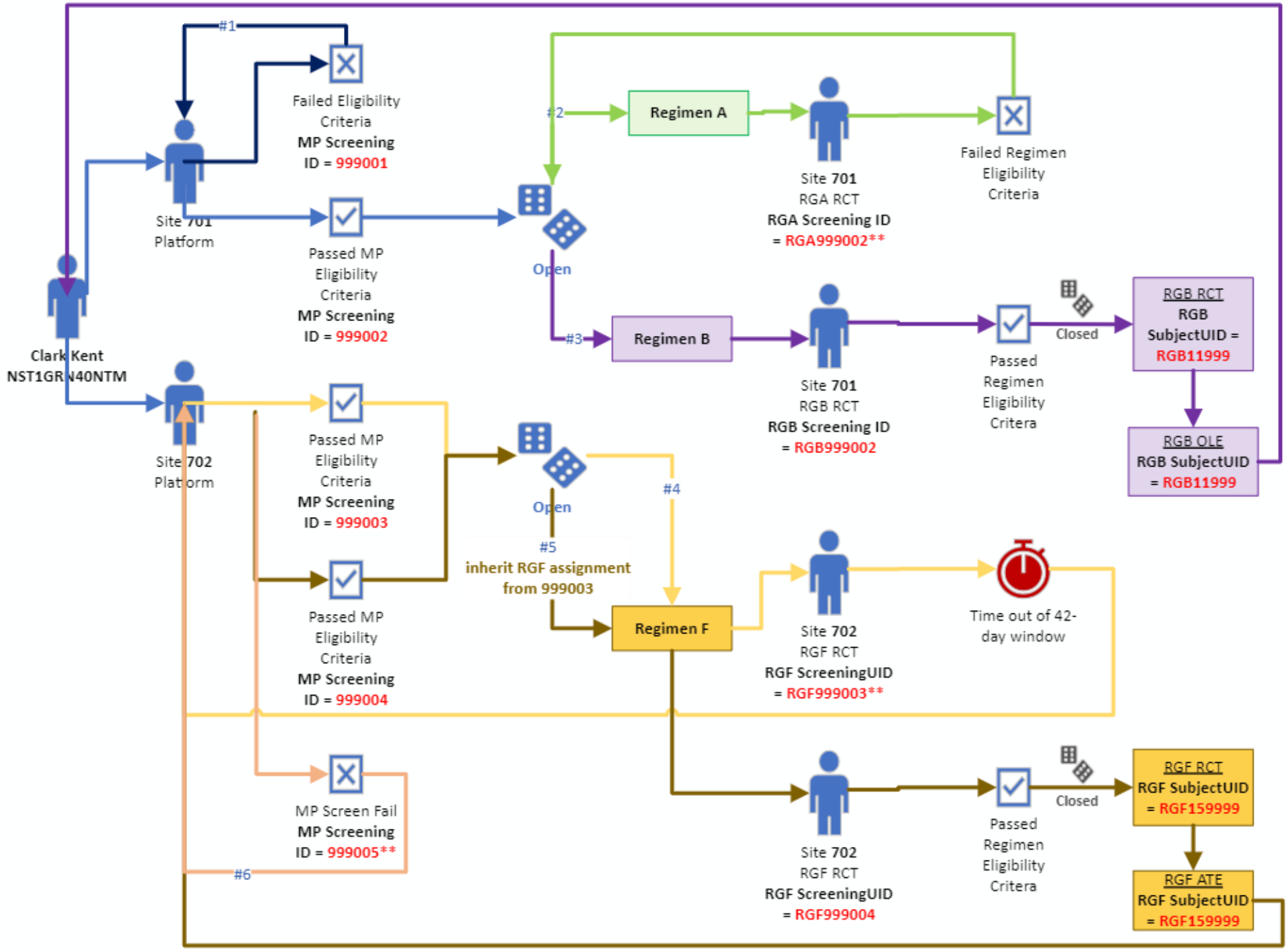
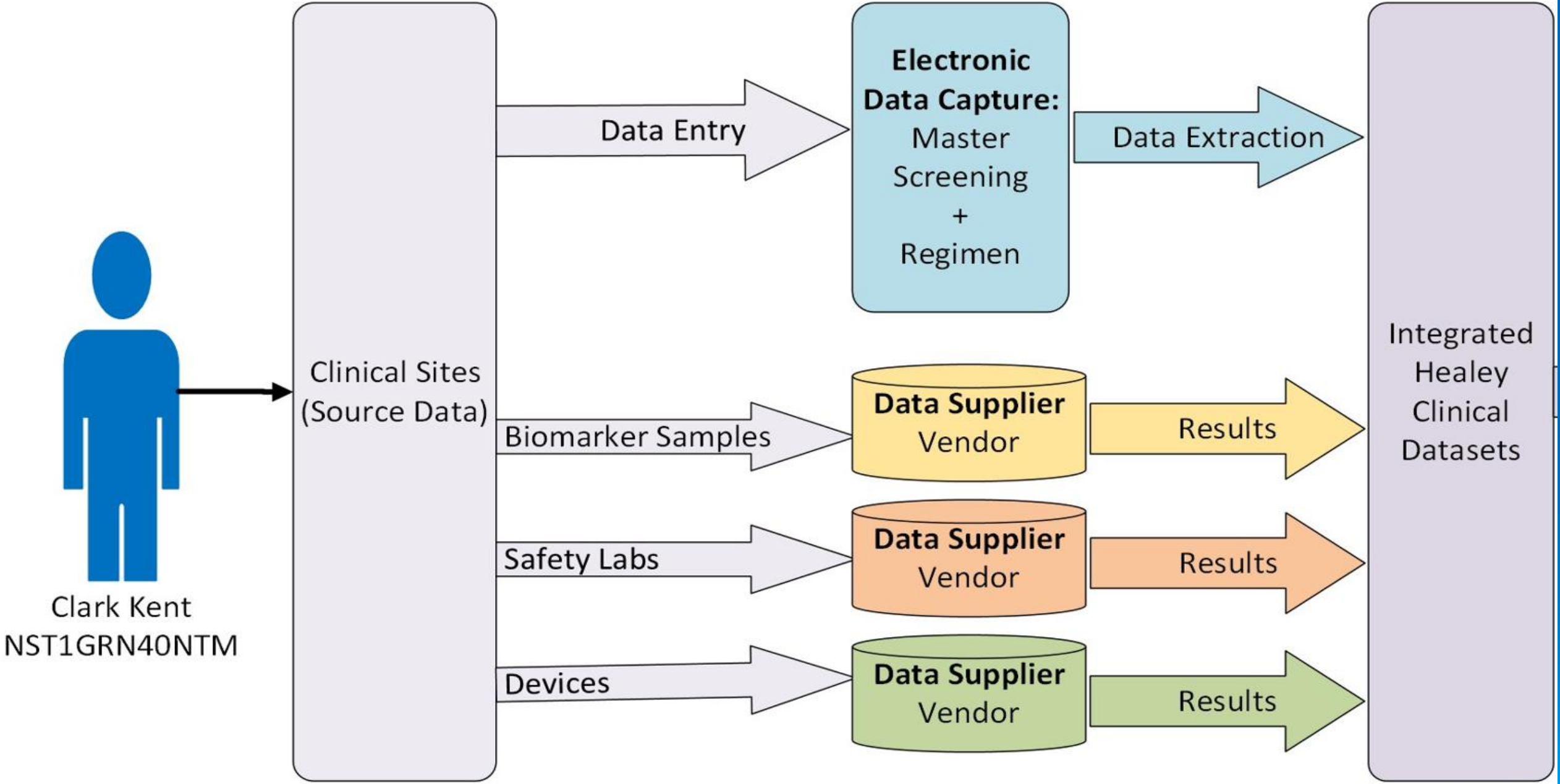
Introduction

- Multiple Sources of Data
  - Clinical, Safety and Vendor data
  - Master Protocol Screening vs. Regimen level data
  - Perpetual platform design allows for sequential enrollment across different regimens
- Data Integration and Quality Control Strategy
  - Clinical, Operational and Statistical teams conduct multidisciplinary review
  - Standardized vendor processes, timelines, and communication pathways
- Final Data Packaging
  - High-quality final data package delivered to the CDISC vendor

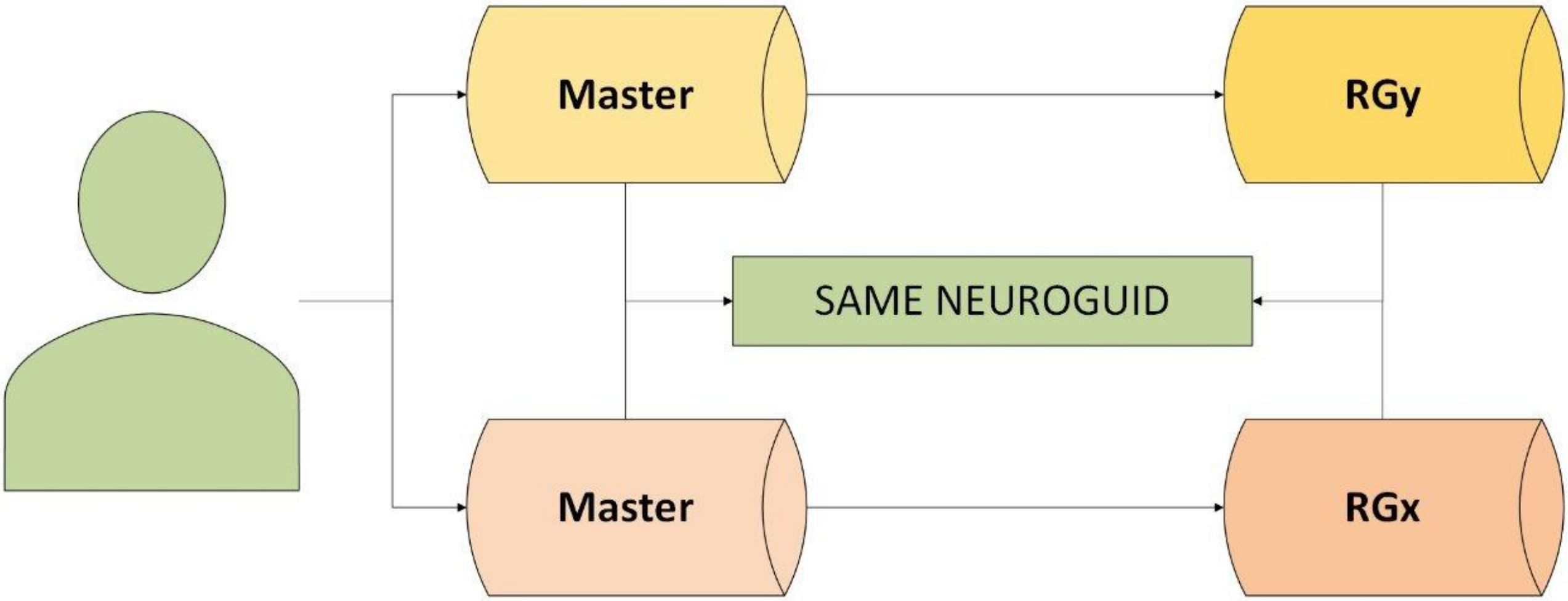

#1
Failed Eligibility Criteria
MP Screening ID = 999001
Site 701 Platform
Passed MP Eligibility Criteria
MP Screening ID = 999002
Clark Kent
NST1GR N40NTM
#2
Regimen A
Site 701
RGA RCT
RGA Screening ID = RGA999002**
Failed Regimen Eligibility Criteria
Open
#3
Regimen B
Site 701
RGB RCT
RGB Screening ID = RGB999002
Passed Regimen Eligibility Critera
Closed
RGB RCT
RGB SubjectUID = RGB11999
RGB OLE
RGB SubjectUID = RGB11999
Site 702 Platform
Passed MP Eligibility Criteria
MP Screening ID = 999003
Passed MP Eligibility Criteria
MP Screening ID = 999004
Open
#4
#5
inherit RGF assignment from 999003
Regimen F
Site 702
RGF RCT
RGF ScreeningUID = RGF999003**
Time out of 42-day window
MP Screen Fail
MP Screening ID = 999005**
#6
Site 702
RGF RCT
RGF ScreeningUID = RGF999004
Passed Regimen Eligibility Critera
Closed
RGF RCT
RGF SubjectUID = RGF159999
RGF ATE
RGF SubjectUID = RGF159999


Clark Kent
NST1GRN40NTM
Clinical Sites
(Source Data)
Data Entry
Electronic
Data Capture:
Master
Screening
+
Regimen
Data Extraction
Biomarker Samples
Data Supplier
Vendor
Results
Safety Labs
Data Supplier
Vendor
Results
Devices
Data Supplier
Vendor
Results
Integrated
Healey
Clinical
Datasets

Platform Data Structure

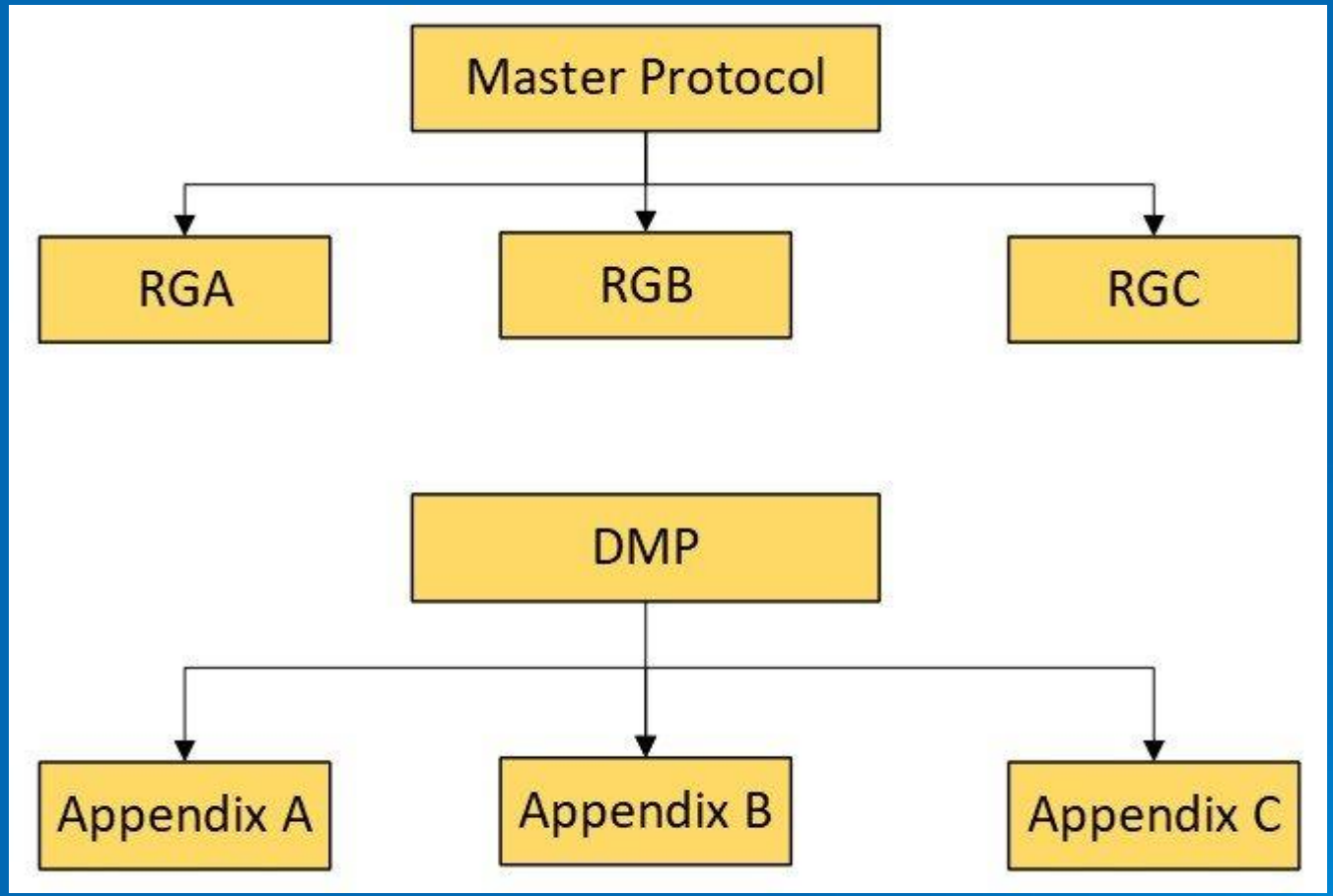
- Master Protocol screening links to multiple Regimens
- Each Regimen has a standalone database to support efficient start-up and close-out
- NeuroGUID is a unique alphanumeric identifier generated from participant information
- NeuroGUID enables secure linkage of data across Regimens without directly identifying the participant
- Linking data across Regimens supports a more complete understanding of disease progression and outcomes, enabling more meaningful analyses

NeuroGUID in Platform Trial



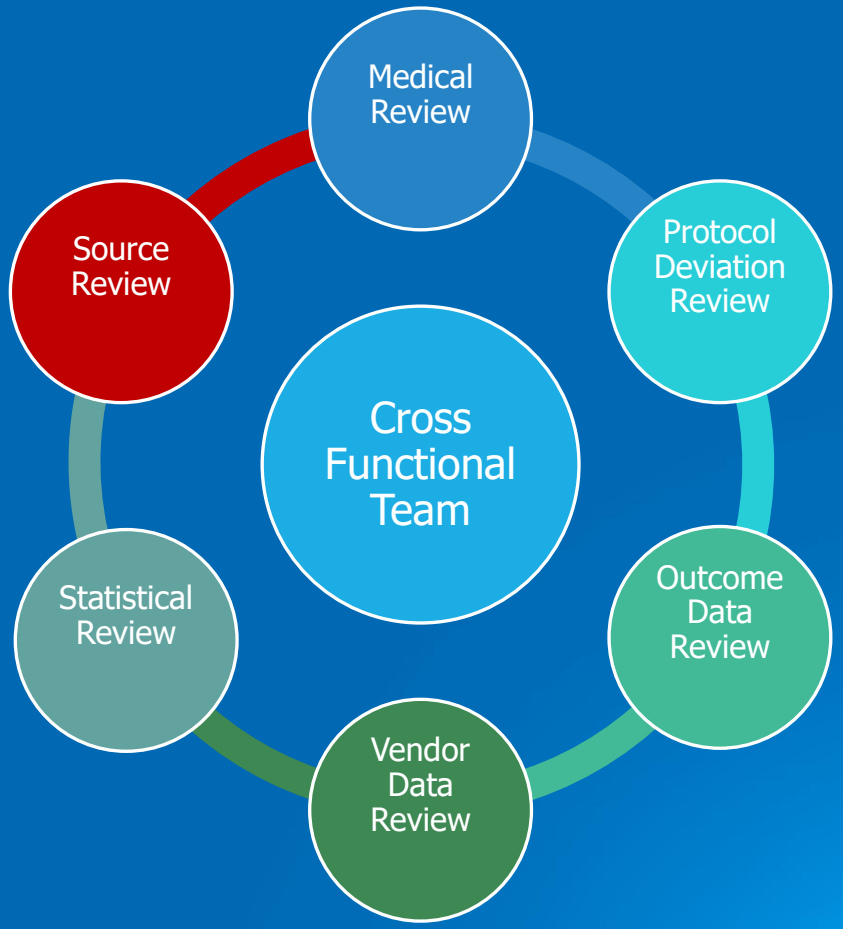
Operational Blueprints

- Master Protocol
  - Regimen Specific Appendices:
    - RSA A (regimen A "RGA")
    - RSA B RGB (regimen B "RGB")
    - RSA C RGC (regimen C "RGC")
- Master Data Management Plan
  - Regimen Specific Appendices:
    - Appendix A (RGA DMP)
    - Appendix B (RGB DMP)
    - Appendix C (RGC DMP)
- Similar structure is used for
    - Project Management Plan (PMP)
    - Clinical Monitoring Plan (CMP)
    - Safety Management Plan (SMP)
    - Statistical Analysis Plan (SAP)



Scalable Collaborative Model

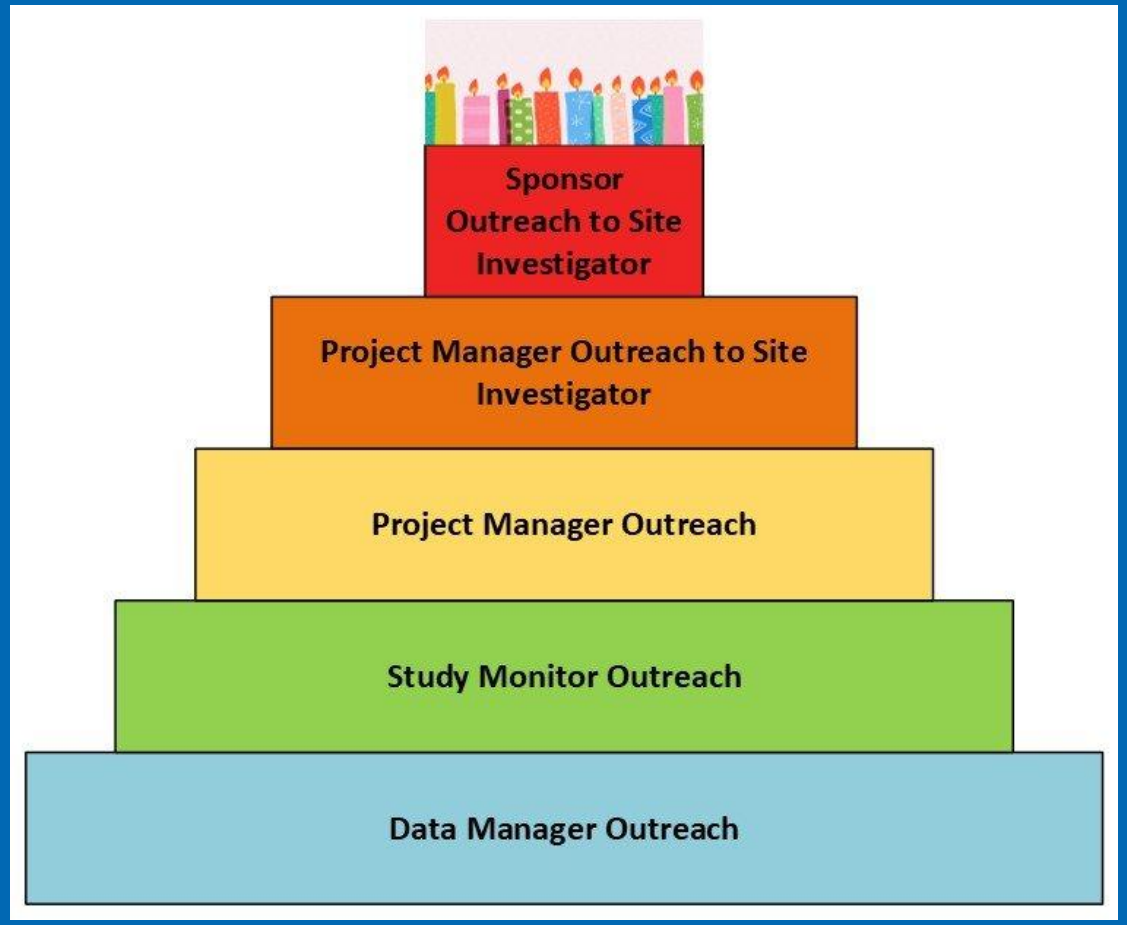
- Integrated, cross-functional team with shared ownership across clinical, operational, and statistical domains
- Source Review supporting site–level data quality and protocol adherence
- Medical Review providing ongoing clinical oversight and safety governance
- Collaborative review model with continuous communication to support data quality, participant safety, and operational efficiency



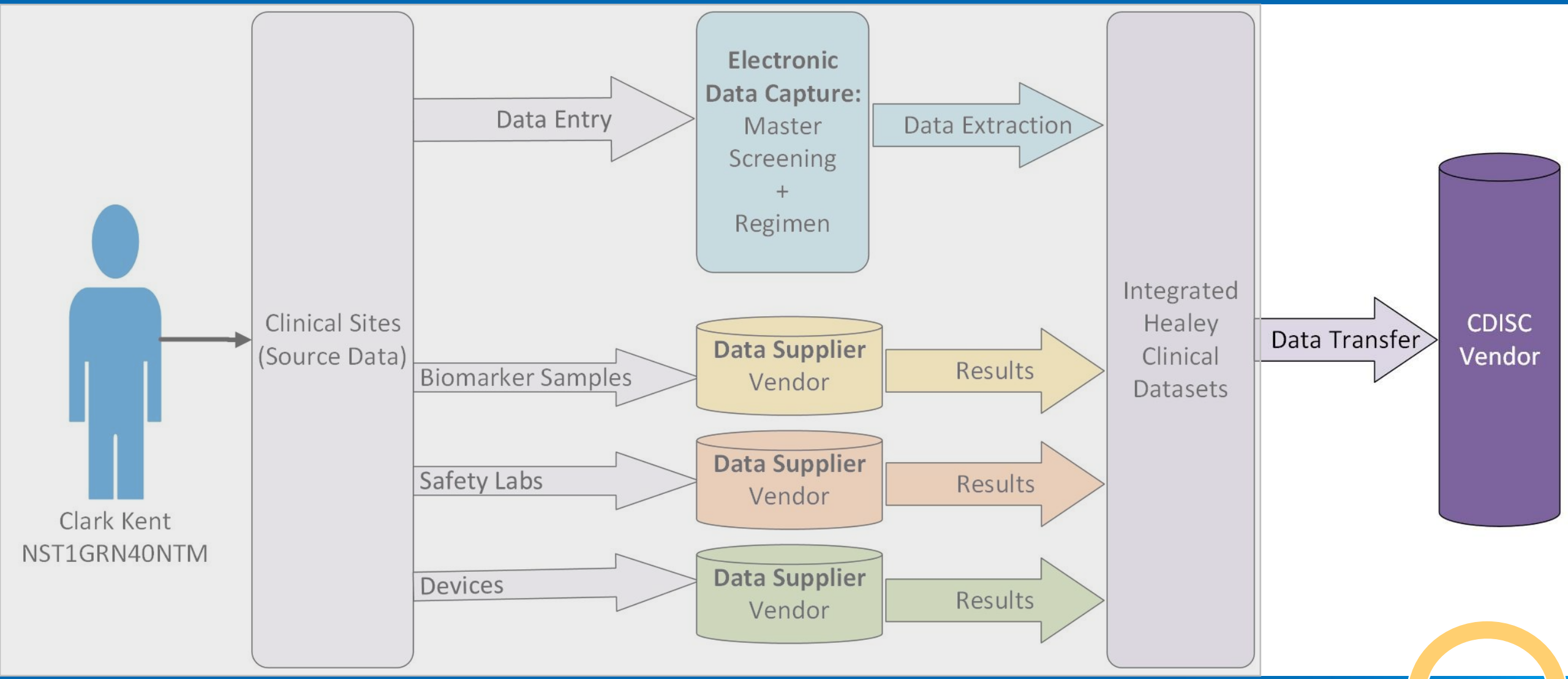
Vendor Management

- Align on evolving scope and complexity of Platform trial
- Establish robust DTS for data quality and integrity
- Plan for staff turnover risks
- Frequent meetings for vendor engagement
  - - Ensure visibility into upcoming pipeline
  - - Bi-weekly meetings for study updates
  - - Ad-hoc meetings for prompt escalation

Escalation Pathway



- Clear escalation tiers and ownership at each level
- Defined triggers for escalation
- Cross-functional alignment during escalation
- Rapid resolution with proper visibility


Clark Kent
NST1GRN40NTM
Clinical Sites
(Source Data)
Data Entry
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Results
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Vendor
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Integrated
Healey
Clinical
Datasets
Data Transfer
CDISC
Vendor

Standardization and Statistical Frameworks for Regimen-Level Analyses and Data Sharing in a Shared Placebo Platform Trial

Lori B. Chibnik, PhD, MPH
Associate Professor, Department of Neurology
Sean M. Healey & AMG Center for ALS at MGH
Boston, MA

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Prioritizing Alignment

- Master SAP
- CDISC structure

Allowing for Flexibility

- Regimen SAP
- Statistical Modeling
- Within CDISC

Expecting the Unexpected

- Validating data with shared placebos
- Results sharing

Master Protocol & M-SAP

Prioritizing Alignment

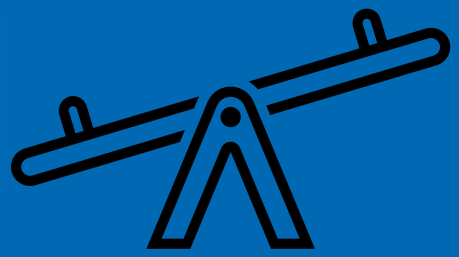
- Covers the entire trial structure including Double Blind Period and Active Treatment Extension (ATE)
- Keeps consistency while allowing for flexibility
- Elements that do not differ by Regimen – but more can be added
  - Primary Endpoint & model
  - Endpoints and other variables collected – including definitions
  - Core schedule of assessments
  - Analysis sets

Writing the M-SAP

Prioritizing Alignment

- Need consistency across Regimens
  - What is the bare minimum we need to share placebos with other regimens?
  - Over the course of the Platform Trial we have added and subtracted from the M-SAP (on v4.0)
  - Any changes limits if historical placebos can be used

It's often a balancing act



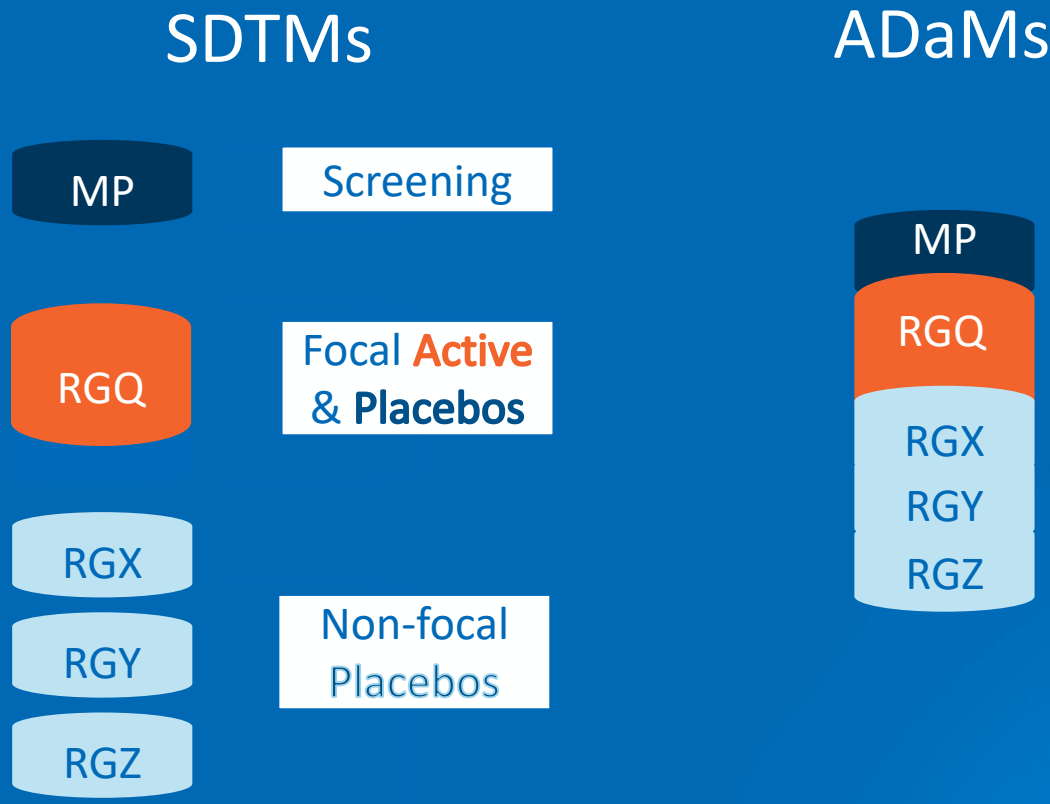
A very complicated balancing act

CDISC data structure

Prioritizing Alignment

- **MP** = Master Protocol Screening
- **Focal** = regimen with active drug (RGQ)
- **Non-focal** = regimens sharing placebos
- (RGX, RGY, RGZ as placeholders)
- Includes both RCT and ATE period

To stack or not to stack, that is the question



Final data package includes multiple SDTM packages (as shown) and a single ADaM package including all data

Allowing for Flexibility

- Regimen SAP
- Statistical Modeling
- Within CDISC

Regimen SAPs

Allowing for Flexibility

- Start with the M-SAP and modify as needed
- Some changes & additions are simple, some cause problems
- Most common differences

Simple

- Secondary and exploratory endpoints
- Endpoint hierarchy
- Sub-groups
- Statistical models for secondary and exploratory

Causes Issues

- Inclusion / Exclusion Criteria

Seems Simple but Causes Issues

- Small changes to model specifications

Statistical Modeling

Allowing for Flexibility

- Primary Model
  - Bayesian Shared Parameter Model of Function and Mortality
  - Allows for dynamic sharing of placebos
  - Sensitivity analyses to assess assumptions of shared placebos
    - Limited to regimen only
    - Comparison of placebo groups

Ann Neurol. 2023 Sep;94(3):547-560. doi: 10.1002/ana.26714. Epub 2023 Jun 22.

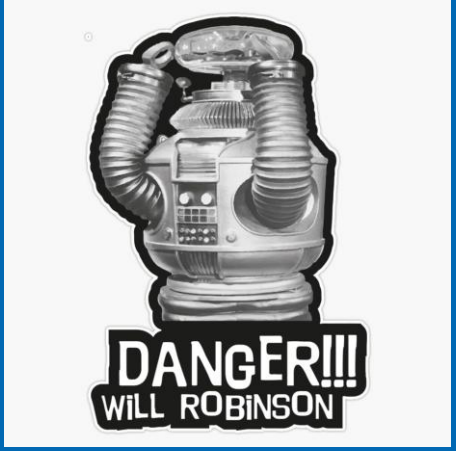
Design and Statistical Innovations in a Platform Trial for Amyotrophic Lateral Sclerosis

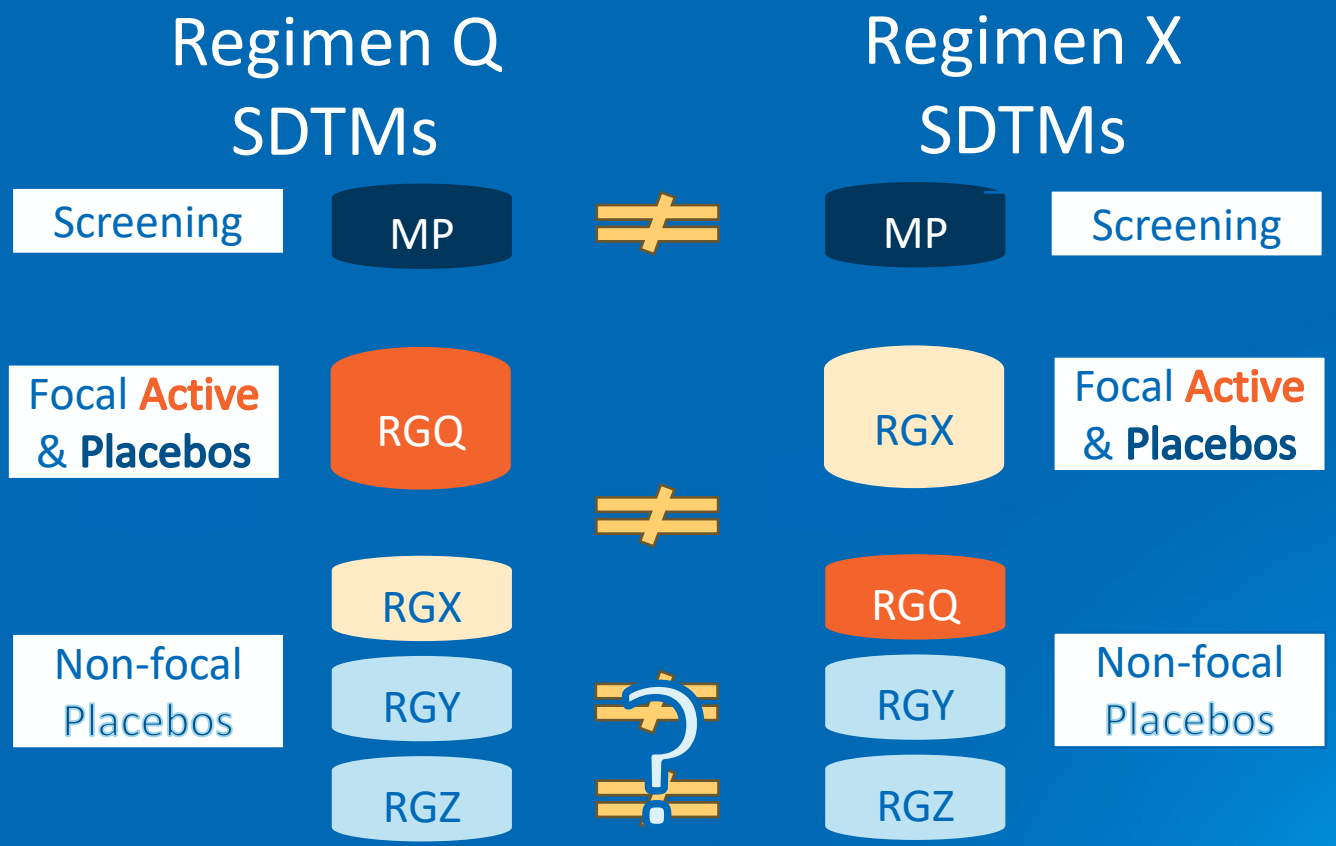
Melanie Quintana [1], Benjamin R Saville [1 2], Matteo Vestrucci [1], Michelle A Detry [1], Lori Chibnik [3 4], Jeremy Shefner [5], James D Berry [6 7], Marianne Chase [6 7], Jinsy Andrews [8],

CDISC data

Allowing for Flexibility

- Be careful
- The contents of the data packages – with same label, same name, same perceived contents might be different





Expecting the Unexpected

- Validating data with shared placebos
- Results sharing

Data & results validation

Expecting the Unexpected

- Our blinded team is large-ish, our unblinded team is not
- We outsource creation of CDISC package to a CRO, but we prioritize validation of all
  - Primary, secondary and exploratory endpoints and covariates in models
  - Top line results
- Blinded team can assist for regimen only analysis but when shared placebos come in it causes issues
- Dummy randomization will bring in the wrong people as shared placebos – once you run with real randomization you have different people

Small differences in model specifications can cause large increases in work and risks of human error

Sharing of results

Expecting the Unexpected

- Regimens will use shared placebos from other regimens still ongoing
- Sharing full results can risk unblind placebos (or results) in other regimens
- We show results for Regimen placebo group & shared placebo group
  - Any differences in events between regimen placebo and shared placebo is, by definition, a placebo in another regimen
  - All categories with events <10 are displayed as <10 until other regimen is unblinded

Sharing of results - example

- Cartoon example

TEAE	Active (n=100)	Combined Placebo* (n=100)	Regimen Placebo (n=50)
Angina	30 (30%)	16 (16%)	10 (20%)
MI	3 (3%)	<10	2 (4%)

* Includes regimen placebo

Sharing of results - example

Expecting the Unexpected

- Cartoon example

TEAE	Active (n=100)	Combined Placebo* (n=100)	Regimen Placebo (n=50)
Angina	30 (30%)	16 (16%)	10 (20%)
MI	3 (3%)	<10	2 (4%)
MI (actual)	1 (1%)	2 (2%)	0 (0%)

* Includes regimen placebo

	52-week change from baseline		
Endpoint	Active (n=100)	Combined Placebo* (n=100)	Regimen Placebo (n=50)
Functional score	-10.0 (2.0)	-7.2 (2.5)	-9.8 (2.7)
Strength Score	-22.2 (8.5)	-25.2 (9.0)	-24.9 (9.5)
Biomarker	0.22 (0.10)	0.23 (0.09)	0.21 (1.4)

* Includes regimen placebo

Prioritizing Alignment

- Master SAP
- CDISC structure

Allowing for Flexibility

- Regimen SAP
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Expecting the Unexpected

- Validating data with shared placebos
- Results sharing

Operationalizing Data Integrity: Blinding, Timelines, and Results Management in a Perpetual Platform Trial

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

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Introduction

- Prompt sharing of research results accelerates scientific progress and benefits patient care

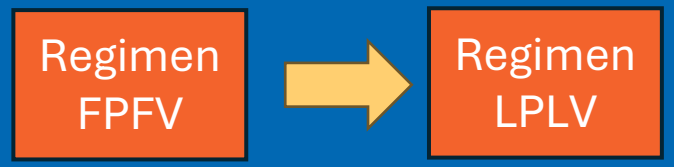
- If a platform trial is perpetual, how can we ensure results are disseminated timely for each regimen?

- Each regimen has a pre-specified process for results dissemination
  1. **Topline Results**
  2. **Full Data Delivery**
  3. **Primary Manuscript & ClinicalTrials.gov**

- Platform level governance plans ensure regimen-level and trial-level data integrity over time

Topline Results

- Topline results planning begins before enrollment ends



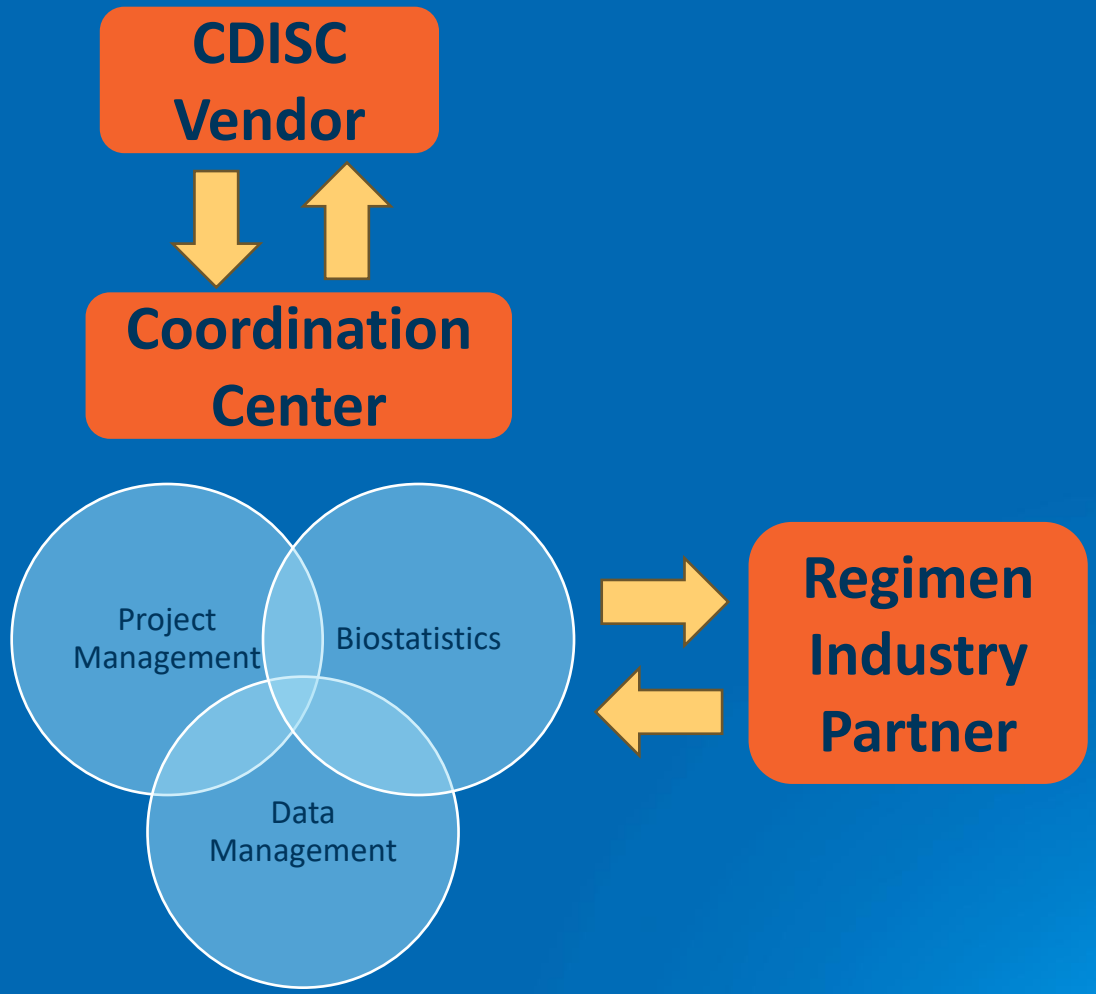
- Regimen milestones and deliverables are mapped as soon as first participant is enrolled into regimen

- Governing platform-level plans are critical for ensuring data integrity
  - Blinding and Unblinding Plan
  - Data Sharing Policy
  - CDISC Vendor Management Plan

Activity	Target completion date	Actual completion date	Dependency
Execute regimen contract			
Lead statistician reviews & provides comments on draft eCRFs			
Lead statistician reviews and provides comments on draft aCRFs			
Initiate statistical programming			
Review test data transfer from vendors			

Topline Results

- Pre-database lock dry-runs are critical
  - Ensure stakeholder alignment
  - Support rapid release of topline results following database lock
- Blinded SDTMs, ADaMs, and TLFs
  - Safety and participant disposition
  - No efficacy shared
- Initiated 12 weeks prior to anticipated database lock



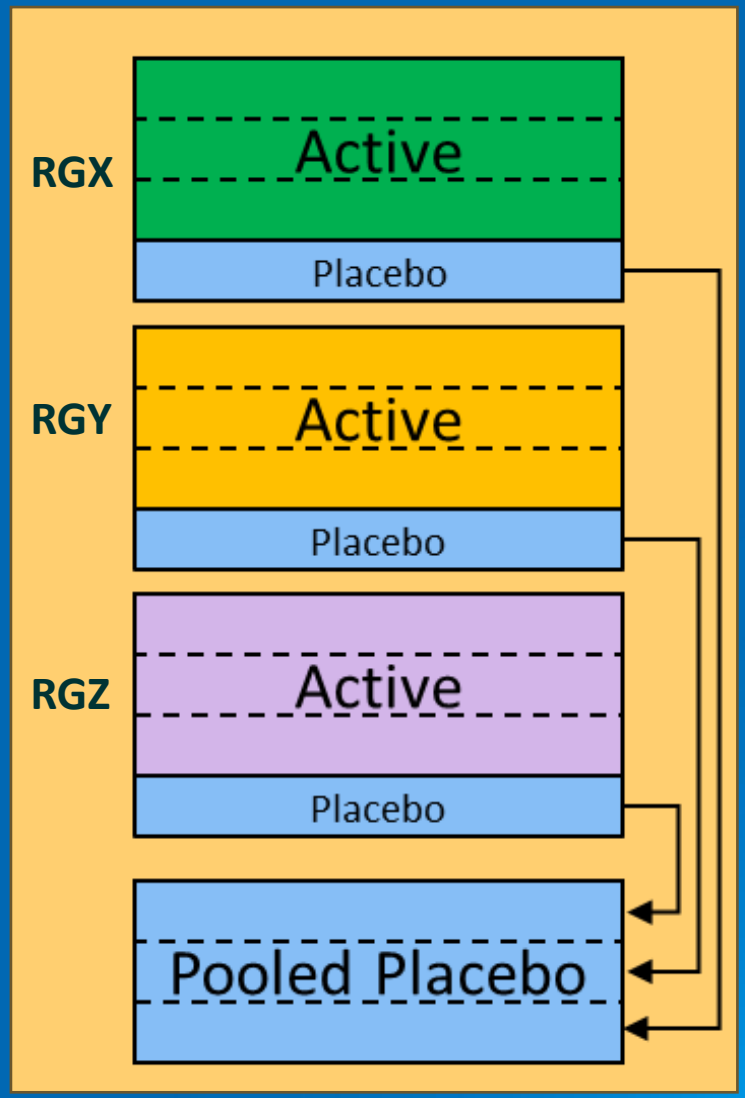
Topline Results

Each regimen follows an identical timeline and process for topline results

1. **Last Participant Last Visit**
   - RCT Final Vendor Data Transfers Complete
   - RCT EDC Data Complete
   - Full Data Package Delivered to CDISC Vendor
2. **Full Database Lock**
   - TLR TLFs Produced
3. **TLF Delivery to Sponsor**
   - Initial results sharing meeting between Sponsor and Industry Partner
4. **Initial Public Dissemination**
   - Coordinated Press Release
   - Regimen Participant Webinars
   - Public Webinars

Full Data Delivery

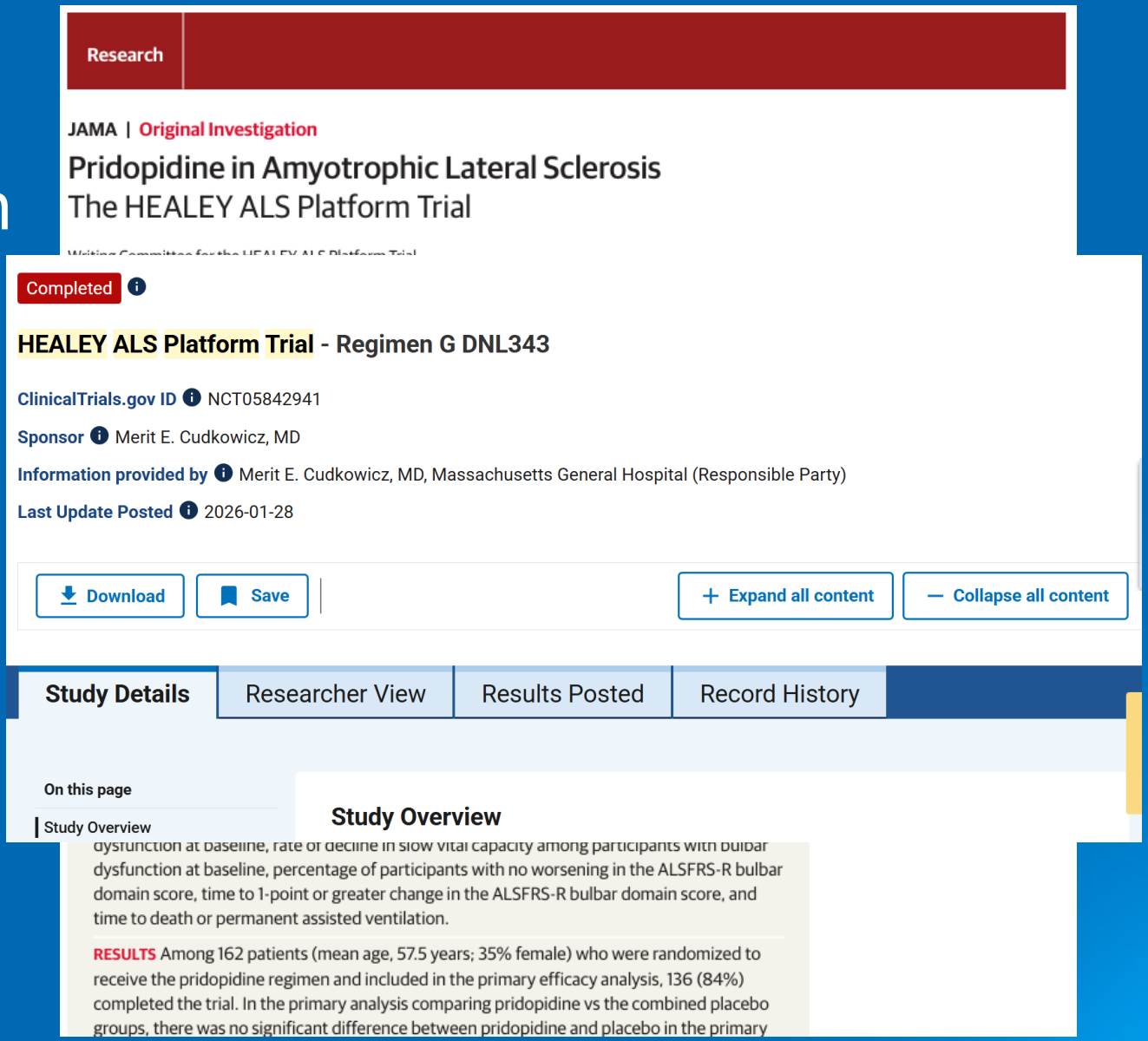
- Full data delivery includes all unblinded datasets with all analysis populations
- Per *Data Sharing Policy,* SDTM data cannot be shared with an industry partner until all contributing regimens have been locked
- Dedicated unblinded teams manage data sets and delivery per *Blinding and Unblinding Plan*
  - CDISC Vendor
  - Coordination Center Biostats and Data Management
  - Regimen Industry Partner Biostats



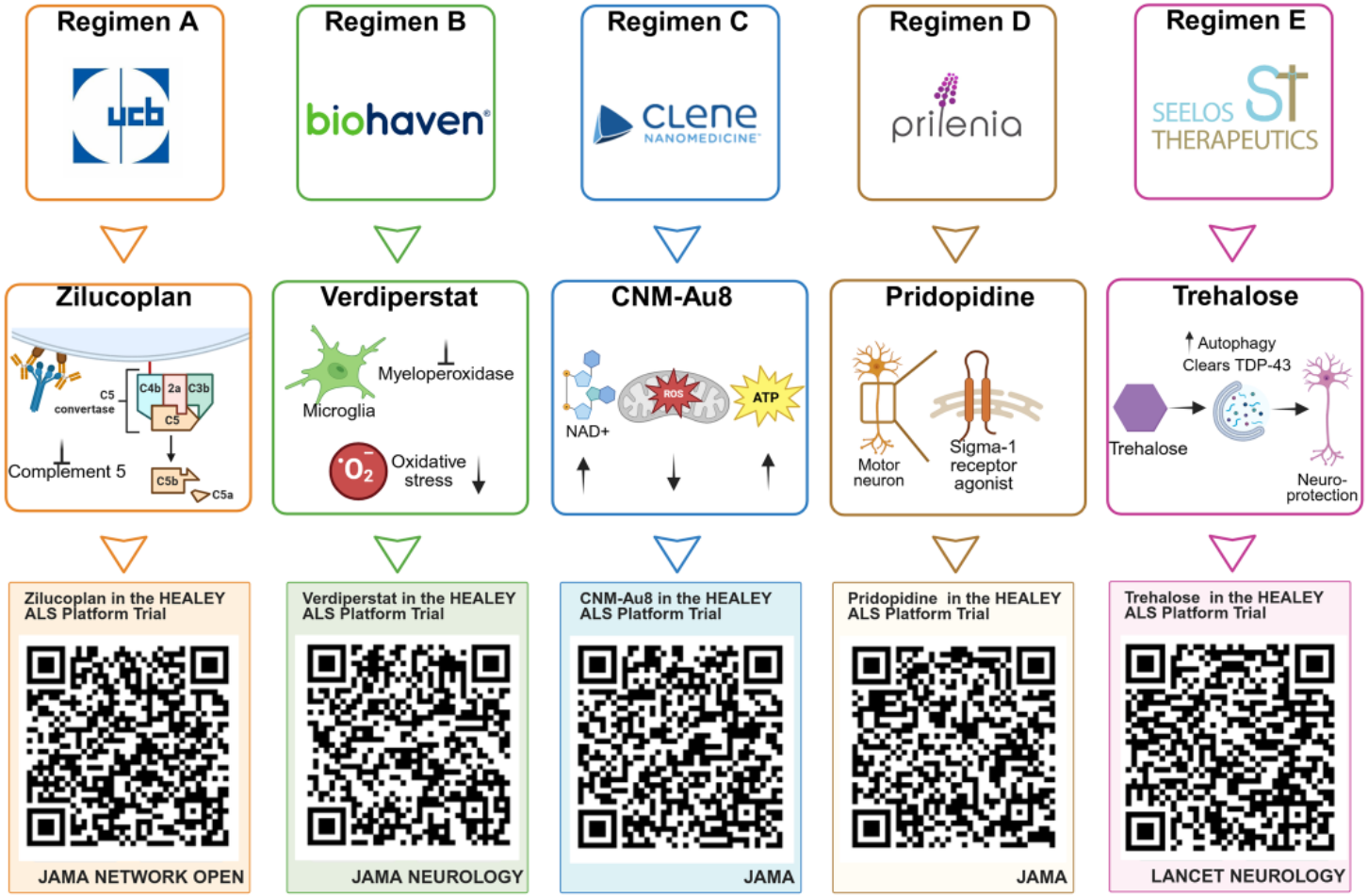
Primary Manuscript

ClinicalTrials.gov

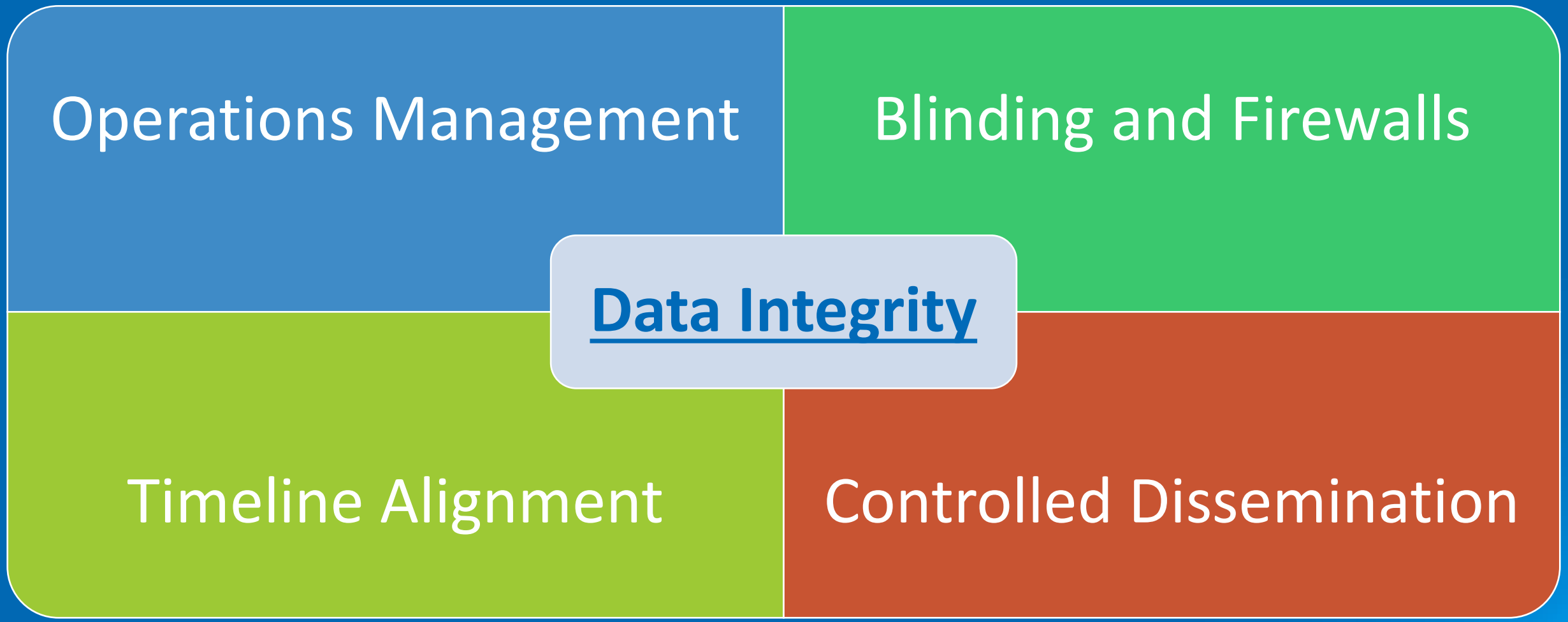
- Manuscript drafting is led by Sponsor team in collaboration with the Regimen Industry Partner
- Based on the regimen SAP and available regimen-specific biomarker data as applicable
- Author listing governed by the *Publication Policy*
  - HEALEY ALS Platform Trial Study Group



Publications from Regimens A-E



Summary


Operations Management
Blinding and Firewalls
Data Integrity
Timeline Alignment
Controlled Dissemination

Enabling Re-Use of Trial Data to Inform Design, Build a Culture of Responsible Sharing, and Support Scientific Collaboration through Post-Regimen Data and Sample Sharing

Lindsay Heyd
Clinical Trial Project Director
Healey & AMG Center for ALS at Mass General
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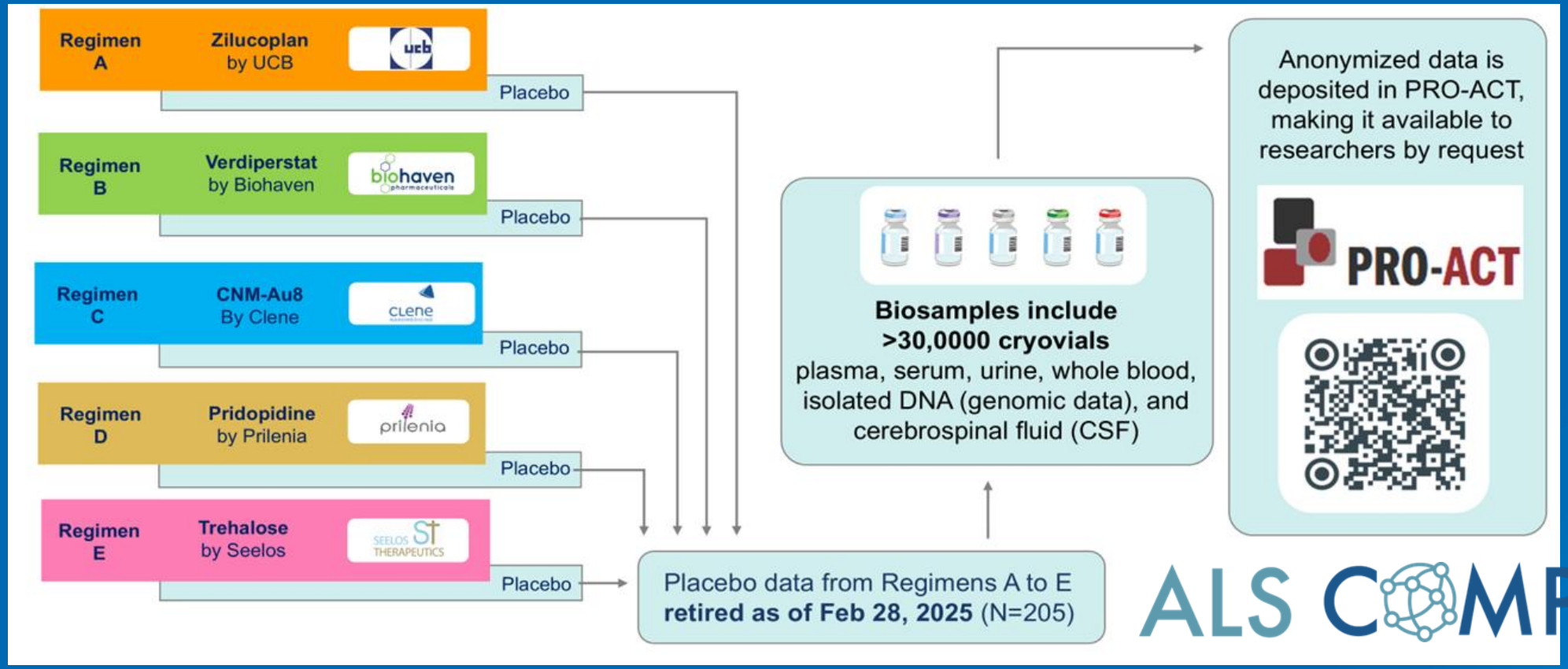
Aim: to accelerate drug development and advance ALS science through structured data sharing



Definition of retirement:

Placebo group no longer in use for analyses in an active regimen

Primary publication published

Governing study documents

Clinical Trial Agreements

Share **de-identified** study data and tangible materials with non-profit institutions for further research and educational research purposes outside of the Study

…applicable law and pursuant to a written agreement with the recipient that contains appropriate terms and conditions regarding the **privacy and security of human subjects derived data and materials**

ICF – Samples and Data

Samples and data will be stored in biorepository for **neurological clinical research**

All data will be de-identified for sharing with other researchers for **any medical research purpose**

ICF - DNA

Individual genomic data and health information may be put in a **controlled access database**

May share sample and genetic de-identified clinical data with **collaborators for medical research** in academic, not-for-profit, or commercial institutions

Public information

- HEALEY ALS Platform Trial Data and Report Sharing Policy

- HEALEY ALS Platform Trial Data and Sample Request Form

HEALEY ALS Platform Trial Research Partners

https://www.massgeneral.org/neurology/als/research/research-partners

Investigator Resources

Create de-identified datasets

- **Sources of data: EDC/IRT, vendors, coded, genetic/genomic**

- **Study Dataset(s)**
- **Repository dataset(s)**
- **Limited dataset(s)**

- **Considerations:** contractual due diligence, size, for-profit vs not-for-profit, perpetual scalability

Create operations

- **Reconciliation of material/samples**
- **Ship samples and associated dataset to repository**

- **Workflow: Requestor → review → data sharing → material shipment → tracking**

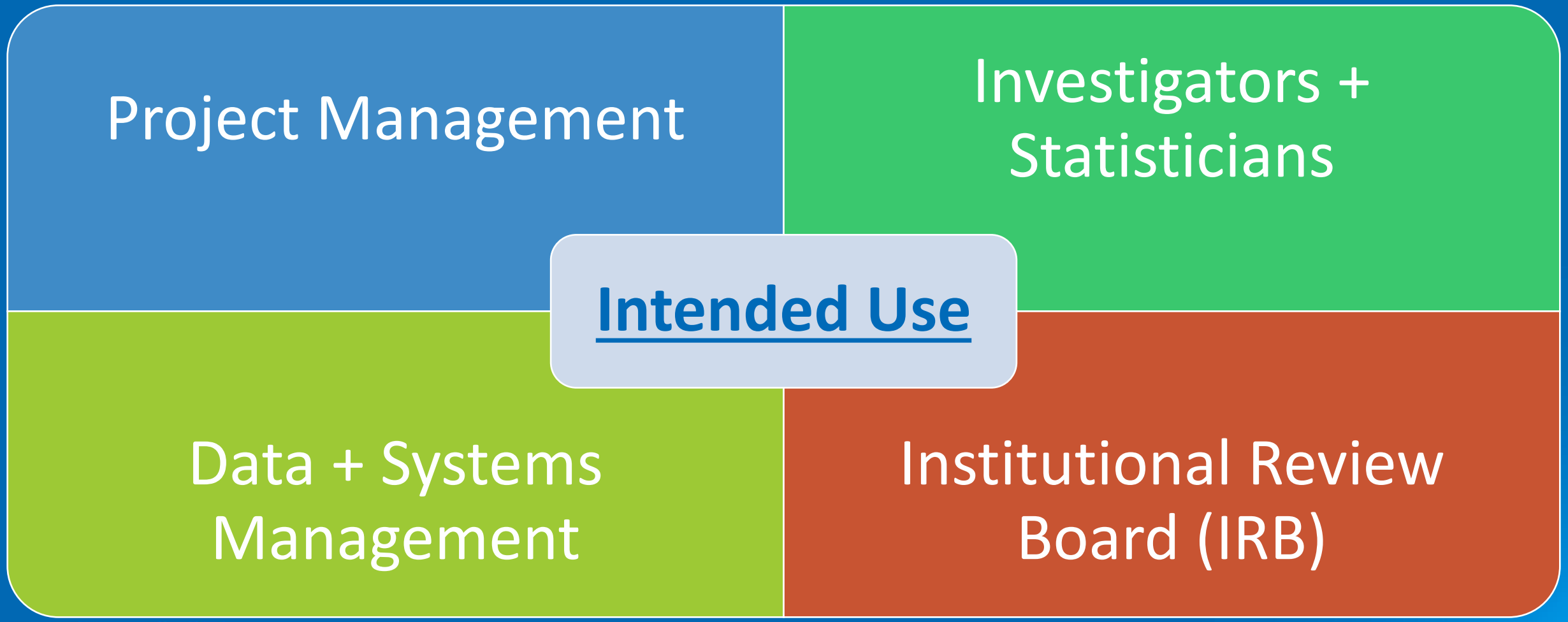
- **Considerations:** contractual due diligence, perpetual scalability

DUA and MTA -secondary analysis

Data use and material transfer agreement sharing and license for use

- Data Set(s) are provided “as is”
- Use Term = 5 years
- New Intellectual Property owned by Requestor
- Expected that results derived from analysis/analyses thereof will become available to the research community (publish or disseminate discoveries)
- Requestor to follow applicable laws and Trial policies
- No cost but Requester must cover the cost of material shipping

Cross functional expertise



Tools and Committees

HEALEY ALS Platform Trial Biomarker and Outcome Measures Committee

HEALEY ALS Platform Trial Data and Report Sharing Review Committee

Impact

- **Enabling reuse of clinical trial data**: data and biosample sharing holds promise to inform clinical trial design and support other data reuse practices
- **Informing future trial design**: upholding the Trial's equally important mission of advancing ALS science through transparent and structured access to clinical trial resources

- **Building a culture of responsible sharing**: emphasizes accessibility, ethical and contractual due diligence, and data/sample governance
- **Collaborating**: supports innovation, collaboration, and access to provide opportunities beyond a single study

Acknowledgements

- We acknowledge the altruism of the participants and the contributions of the participating sites of the NEALS Consortium.

It Takes a Village!

NEALS

Arthur M. Blank Family Foundation

ALS ONE

MDA Muscular Dystrophy Association

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

I AM ALS

BARROW Neurological Institute

Berry Consultants Statistical Innovation

AMG The AMG Foundation

SALSA For a Cure

RUN2REVIVE MIND · BODY · POTENTIAL

TAMBOURINE

1850 MELIORA

LES TURNER ALS FOUNDATION

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