CLINICAL TRIALS TRANSFORMATION INITIATIVE

Advancing Real-Time Adaptive Platform Trials

CTTI Convening
December 10th, 2025

Clinical Trials Transformation Initiative (CTTI) Introduction & Welcoming Remarks

Morgan Hanger, Executive Director

Clinical Trials Transformation Initiative (CTTI)

The Clinical Trials Transformation Initiative (CTTI)

MISSION

To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials.

VISION

A high-quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based therapeutic prevention and treatment options.

PUBLIC-PRIVATE PARTNERSHIP

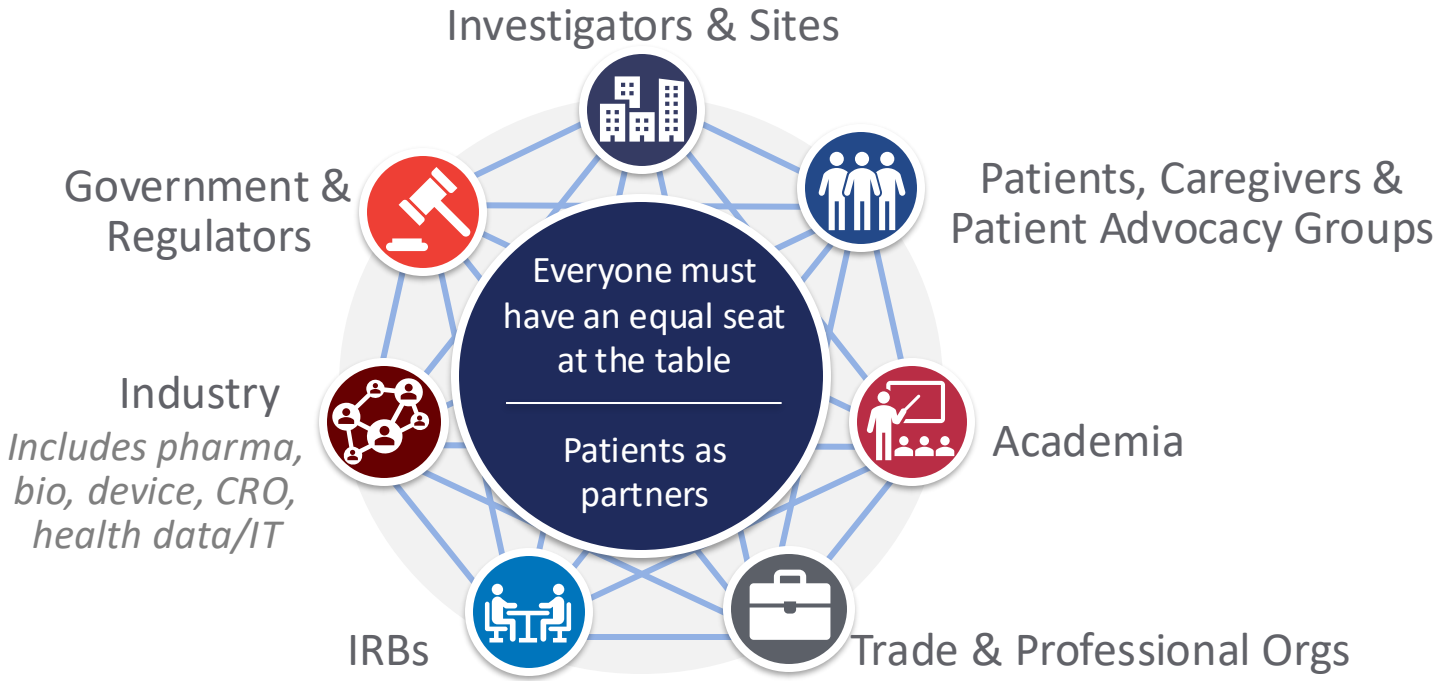
- Co-founded in 2007 by FDA and Duke University
- Active collaboration with +500 individuals and groups
- All materials are freely available

SCOPE

Focus on clinical trials of FDA-regulated medical products, recognizing that clinical trials are international and acting as a collaborative global citizen.

CTTI

Who We Are


Investigators & Sites
Government & Regulators
Patients, Caregivers & Patient Advocacy Groups
Everyone must have an equal seat at the table
Patients as partners
Industry
Includes pharma, bio, device, CRO, health data/IT
Academia
IRBs
Trade & Professional Orgs

Who We Are: CTTI's Cross-Sector Membership

Version: September 16, 2025

CTTI

What We Do

- Provide **leadership** across the Clinical Trials Enterprise through vision-setting, collaborating, convening, measurement

- Produce evidence-supported, consensus **recommendations and tools** to improve quality and efficiency of clinical trials

- Drive innovation through **strategic communication and engagement** efforts that support organizational and overall system transformation

Topic-focused convenings
FDA public meetings
State of Clinical Trials

30+ Recommendations
80+ Implementation Tools
50+ Case Studies

30,000+ downloads / year
40,000+ media impressions / year
550+ presentations & workshops
130+ articles & publications

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Engagement Principles

CTTI fosters a forum for collaborative, multi-sector dialogue – a safe space to discuss issues, exchange ideas, and come to consensus on solutions

Discussion Norms

- Open discussion is fostered by respect and collaboration
- All ideas are welcome: to maximize the benefit of collaborating, you often need to diverge before you converge
- Those with minority perspectives are encouraged to speak up and help prevent the group's thinking from becoming lopsided

Ground Rules

- Insights are shared widely; individual comments are private
- Be transparent about conflicts of interest
- Absolutely no promotional or business development activities

*Please see CTTI's conflict of interest policy:
https://ctti-clinicaltrials.org/wp-content/uploads/2023/05/CTTI-Conflict-of-Interest-Policy-26Apr2023.pdf

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Current Environment in the US

- Accelerations in federal activities to achieve valuable clinical interventions: pricing and affordability, direct consumer access, collaborations across FDA and CMS
- Deceleration of federal investment in scientific and clinical research, economic headwinds, and the offshoring of research investments
- Regulatory focus on transparency, faster development and review, and common-sense flexibility around evidence of safety and efficacy
- Policies and activities intended to incentivize efficiency in clinical development

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Real-Time Adaptive Platform Trials Meeting Overview

Sara Bristol Calvert, Director of Projects

Clinical Trials Transformation Initiative (CTTI)

Definitions

- **Real-time:** continuous or near-instantaneous collection, transmission, and analysis of trial data as it is generated
- **Adaptive design:** clinical trial design that allows for prospectively planned modifications to one or more aspects of the trial based on interim analysis of accumulating data from participants in the trial
- **Master protocol:** a protocol designed with multiple substudies, which may have different objectives and involve coordinated efforts to evaluate one or more medical products in one or more diseases or conditions within the overall study structure
- **Platform trial:** a trial designed to evaluate multiple medical products for a disease or condition in an ongoing manner, with medical products entering or leaving the platform

Source: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E20 & FDA Master Protocols Draft Guidance

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Background: CTTI Master Protocols Resources

Study Stage	Tools
Pre-Planning	• **High-Level Roadmap**: Describes key deliverables and problem-solving approaches critical to different stages • **Value Proposition Guide:** Outlines design & operational considerations to demonstrate the value of adopting a master protocol approach • **FDA Engagement Tool:** Describes formal mechanisms to facilitate early engagement with FDA • **Master Protocol Reference & Resources:** Summary of key references
Planning	• **Master Protocol Content Development Guide:** Describes key clinical trial partners and consensus-building deliverables required to build the content of master protocol studies • **Operational Partner Assessment Tool:** Summarizes factors that should be used to assess operational partners that may be useful to operationalize a master protocol design • **Statistical Simulation Tool**: Lists core simulation modules and tips for how to best communicate findings of simulations

Study Execution	• **Study Execution Case Studies**
	  • ALCHEMIST – Central Labs in Master Protocol Trials
	  • STAMPEDE – Master Protocol Approach to Improve Outcomes in Prostate Cancer

Hosted *Using Master Protocols Public Summit* advocating for broader implementation of master protocol studies

https://ctti-clinicaltrials.org/about/ctti-projects/master-protocol-studies/

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Meeting Objectives

- Discuss opportunities for improved technology infrastructure, as well as advanced analytics and simulation tools, to make adaptive trials more attractive

- Examine operational processes and design for real-time adaptations

- Review oversight considerations in adaptive platform designs and conduct, including regulatory, safety, and ethics

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Related Guidance Documents

https://www.fda.gov/media/188961/download
https://www.fda.gov/media/120721/download
https://www.fda.gov/media/176107/download

ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

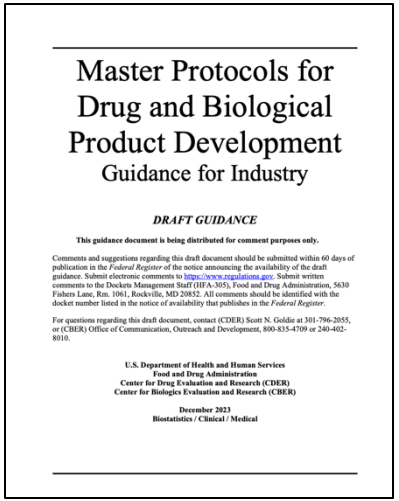
ICH HARMONISED GUIDELINE

ADAPTIVE DESIGNS FOR CLINICAL TRIALS
E20

Draft version

Endorsed on 25 June 2025

Currently under public consultation



Master Protocols for Drug and Biological Product Development
Guidance for Industry

DRAFT GUIDANCE

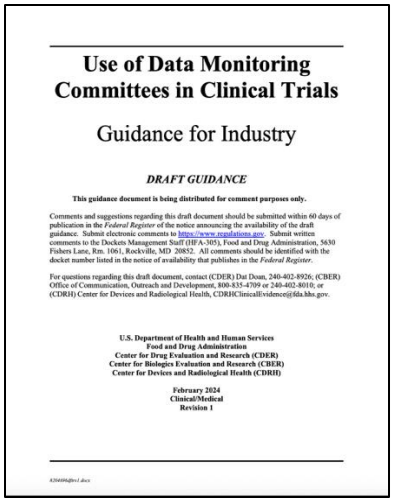
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Scott N. Goldie at 301-796-2055, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2023
Biostatistics / Clinical / Medical



Use of Data Monitoring Committees in Clinical Trials

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Dat Doan, 240-402-8926; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CDRH) Center for Devices and Radiological Health, CDRHClinicalEvidence@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

February 2024
Clinical/Medical
Revision 1

CTTI

Example Content – Draft Guidance Documents

ICH E20

- Advantages & Challenges of Adaptive Design
- Types of Adaptations
- Planning and Pre-specification
- Statistical Considerations
- Trial Conduct and Integrity
- Documentation and Reporting

FDA Master Protocols

- Definitions and Opportunities/Challenges
- Types of Master Protocol Studies (e.g., Platform, Umbrella, Basket)
- Considerations for Trial Design, Biomarker Development, Statistics, and Safety
- Regulatory Submission & Documentation

FDA Use of DMCs

- General Guidance, 2024 update includes information on role of DMCs in adaptive design trials
- Specialized Expertise
- Adaptation Committees

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Agenda	
9:30 a.m.	CTTI Introduction, Welcoming Remarks, and Meeting Overview
9:40 a.m.	Adaptive Platform Trials Meeting Overview
10:00 a.m.	Session I: Innovations in Technology and Infrastructure
10:40 a.m.	Group Discussion: Session I
11:10 p.m.	**Break**
11:20 p.m.	Session II: Operationalizing Real-Time Adaptations
11:50 p.m.	Group Discussion: Session II
12:20 p.m.	**Break**
12:30 p.m.	Session III: Oversight for Adaptive Designs - Regulatory, Safety, and Ethical Considerations
1:00 p.m.	Group Discussion: Session III
1:30 p.m.	Session IV: Open Discussion/Wrap Up
1:55 p.m.	Closing Remarks
2:00 p.m.	**Adjourn**

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Session I: Innovations in Technology and Infrastructure

Melanie Quintana (Berry Consultants)

Nijat Hasanli (Lindus Health)

Jen Dumbleton (Protas)

Sara Bristol Calvert (CTTI)

Adaptive Platform Trials: Efficiencies, Benefits, and Practical Solutions to Real-Time Challenges

CTTI Real Time Adaptive Platform Trials
Session 1: Innovations in Technology and Infrastructure

Melanie Quintana, PhD
Director & Senior Statistical Scientist
Berry Consultants

BERRY

Adaptive Platform Trial Innovations

Goal: Shorter, more powerful clinical trials that treat participants better along the way

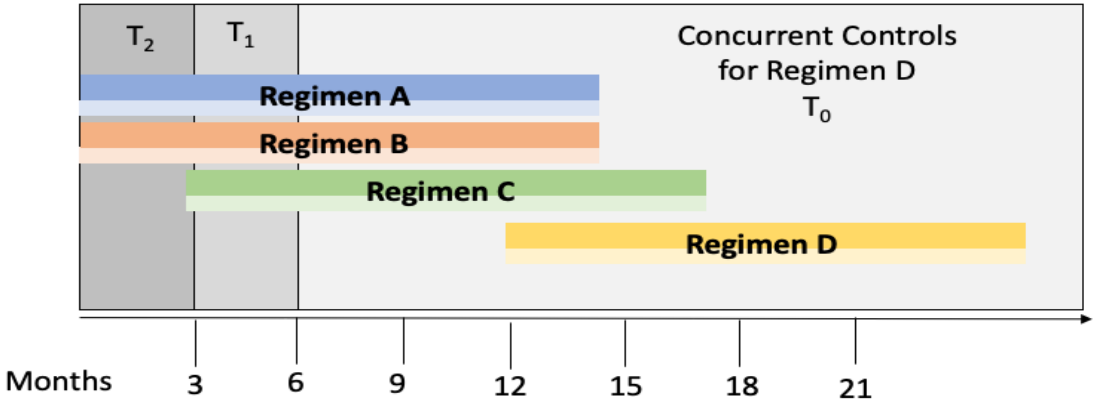
Incorporate All Information: Master protocols

- Sharing resources/information within the trial!

- **Master Protocol:**
  - Single perpetual free-standing arena – agree to a set of common rules
  - Multiple treatments in single disease OR single treatment in multiple diseases OR BOTH
  - Don’t tear the arena down each time we want to test a new hypothesis
  - Information is shared across hypotheses that are being tested
  - Shared infrastructure & resources = very efficient!
- ***Benefit: Sharing information results in higher power and less patients***

Example: HEALEY ALS Platform Trial

- Platform trial in ALS
- Regimen = Active treatment vs. matched control
- Randomize: 1) to an available regimen and 2) 3:1 active vs. control within the regimen



Primary Analysis
Regimen D

R_D Treated

Vs.

Shared Control

Potential Differences in Shared Control from R_D Control

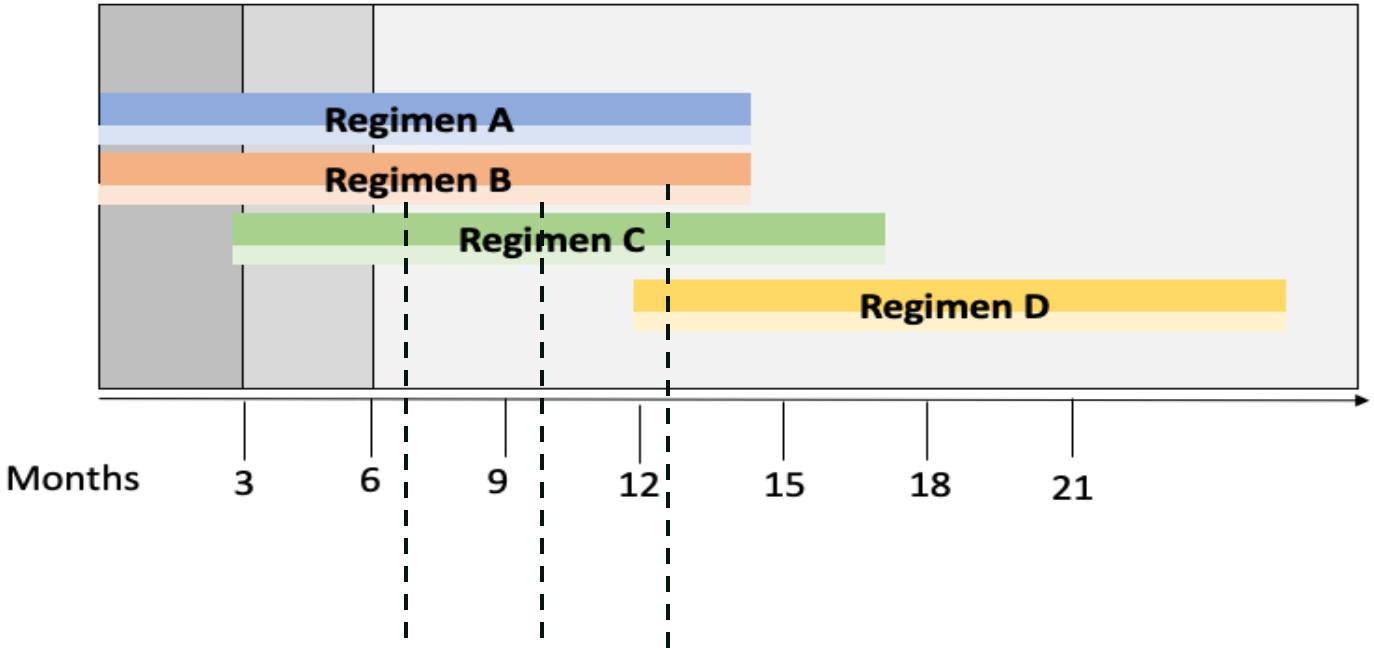
- Enrollment time
- Mode of administration
- Minor Inclusion / Exclusion

Adapt to Accruing Evidence
Adaptive designs

- Key design parameters change during trial execution based upon pre-defined rules and accumulating data from the trial
  - ***Planned:*** All possible adaptations defined *before the trial starts*
  - ***Well-defined:*** Criteria for adapting clearly explained
  - ***Key trial parameters***: Sample sizes, doses, allocation rules, timing of analyses, transitions to next phases. *Not* minor inclusion or exclusion criteria, routine amendments, etc.
- Example Adaptations:
  - Early stopping for overwhelming efficacy or lack thereof
  - Seamlessly transition from early drug development to confirmatory phase
  - Adaptively allocate more patients to better performing interventions

Example: HEALEY ALS Platform Trial

- Frequent platform-wide interim analyses to determine if a regimen should be stopped for futility



Powerful analysis methods:

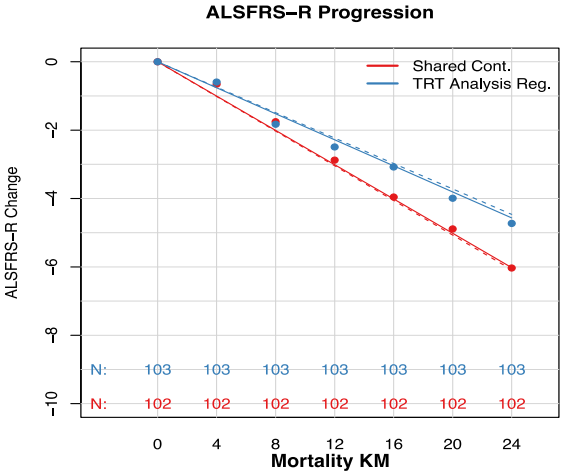
- Efficient use of all available data to evaluate if a treatment is effective
- Don’t throw data away just because it may be “different” – we can account for these differences and still allow the data to inform our inference
- Examples: multiple timepoints, multiple endpoints and multiple sources of information
- Benefit: **Higher power & provides a synthesis of all available information**

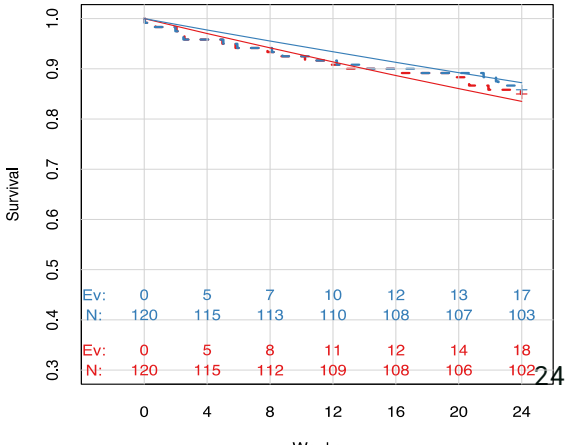
Example: HEALEY ALS Platform Trial

Primary endpoint: change in disease severity through 36 weeks as measured by ALSFRS-R and mortality

Primary analysis: Bayesian shared parameter analysis of ALSFRS-R and mortality

- ALSFRS-R: Repeated measures model with linear rate of progression
- Mortality: Exponential time to event
- **Treatment Effect:**
  - *Common slowing in disease*
  - Disease rate ratio (DRR): 1-% slowing in the rate of progression of disease for treatment relative to control between ALSFRS-R and Mortality
  - Weight each component contributes to treatment effect depends on mortality rates
- Adjust for differences in shared controls across regimens





HEALEY ALS Platform Trial: Benefits of Innovation

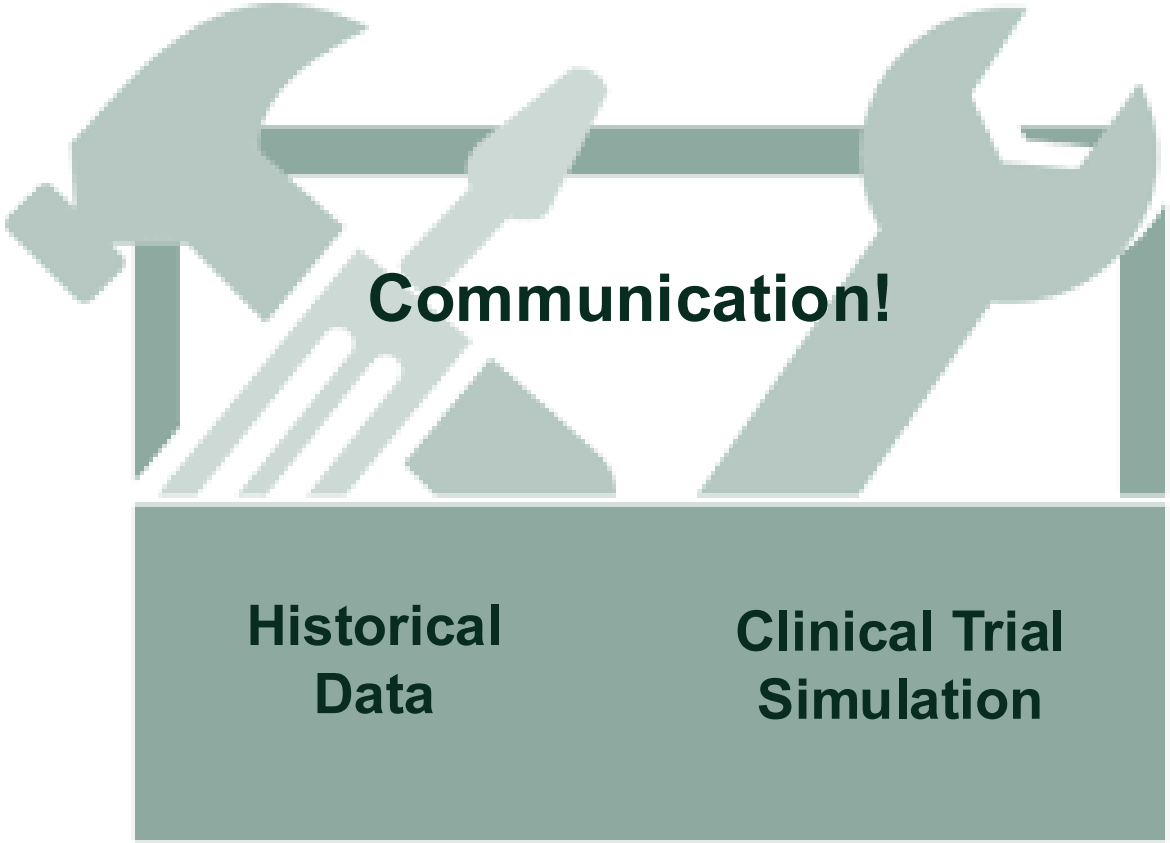
> *This groundbreaking approach cuts the time to find an effective treatment in half, decreases costs by a third or more, and is supported by our patients, the FDA, ALS clinicians and scientists and our pharma colleagues.*

Merit Cudkowicz, MD, MSc
Director, Sean M. Healey & AMG Center for ALS

Challenges in Designing Adaptive Platform Trials

- Takes a lot of (team) work upfront!
- Hard to find the right balance between synergy and flexibility within a platform trial
- Innovation is unfamiliar and may be harder to get buy in from a diverse set of stakeholders
- Traditional approaches to understand power/type I error of a trial do not apply

Toolkit for Designing Adaptive Platform Trials



Example Challenge Adaptive Platform Trials: Balancing Synergy & Flexibility

Need to find a balance between the global rules (what goes in the Master Protocol) and the local rules (what goes in the regimen-specific appendices).

The more we agree to common set of rules = better efficiency! However, need to balance that with flexibility to accomplish the goals of a diverse set of partners.

Example sticking point: Each regimen having their own inclusion/exclusion
Concern: This could lead to major differences in the populations

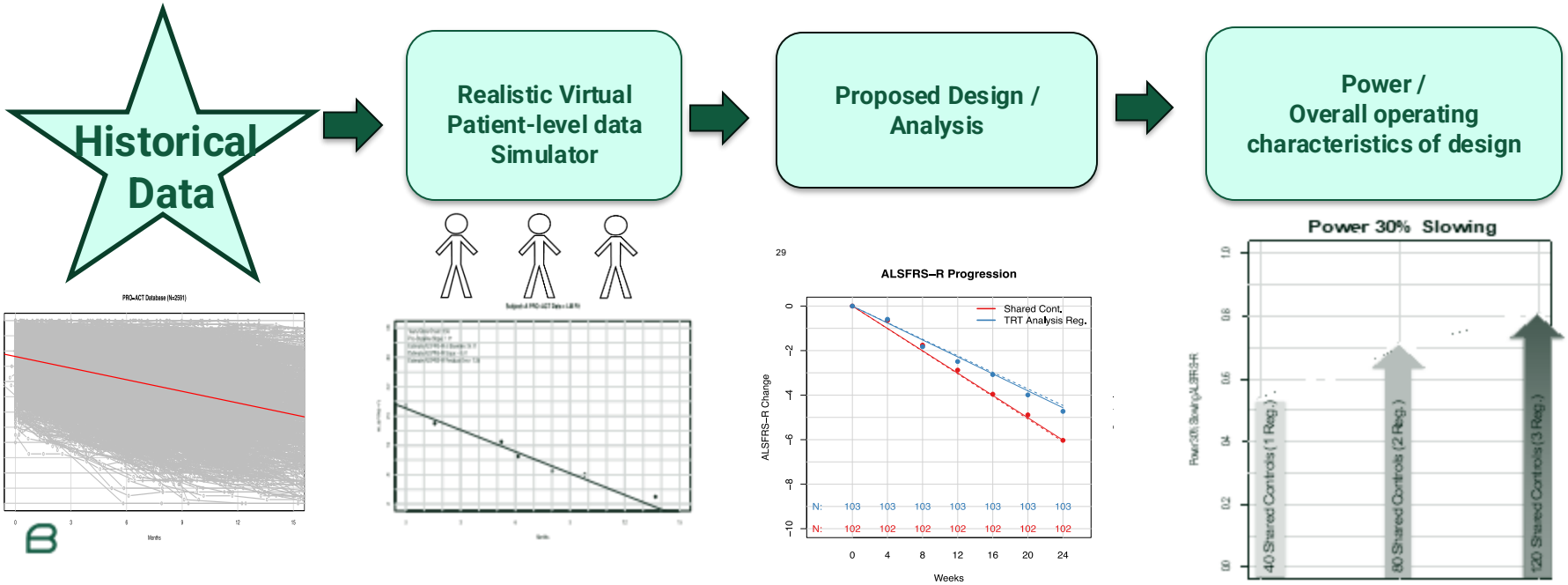
Solution: Back up decisions / discussions with data!

- Can we quantify the likelihood that differences in inclusion/exclusion would lead to meaningful differences in shared controls?

Historical Data + Clinical Trial Simulation

Evidence based decisions making! Quantify the benefit and risk of making a different design decision.

- Understand operating characteristics /implications of proposed design decisions
- Optimize design/analysis under key trial parameters
- Understand robustness of results to different assumptions



General Advice

- Speak with partners early and often – important that all parties are comfortable with the novel approach
- Natural history / Historical patient-level databases + Clinical trial simulation is the key to understanding + getting approval of novel / complex approaches
- Invest in innovation – it may take more time / resource upfront but will lead to a more efficient and powerful clinical trial

References

Platform trials

- Woodcock J, LaVange LM. **Master protocols to study multiple therapies, multiple diseases, or both**. N Engl J Med 2017;377:62-70.
- Bateman RJ, Benzinger TL, Berry S, et al. **The DIAN-TU next generation Alzheimer's prevention trial: adaptive design and disease progression model.** Alzheimers Dement 2017;13:8–19.
- 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. doi: 10.1002/ana.26285. Epub 2022 Jan 10. PMID: 34935174.
- Quintana M, et al. **Design and Statistical Innovations in a Platform Trial for Amyotrophic Lateral Sclerosis**. Ann Neurol. 2023 Sept.; 94 (3): 547-560

FDA Guidance

- Food and Drug Administration Center for Drug Evaluation and Research. Center for Biologics Evaluation and Research. Research Oncology Center of Excellence. Master Protocols: Efficient Clinical Trial Design Strategies To Expedite Development of Oncology Drugs and Biologics**.** 2018. FDA-2018-D-3292.
- Food and Drug Administration Center for Devices and Radiological Health. Center for Biologics Evaluation and Research**. Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials.** February 2010.
- Food and Drug Administration Center for Drug Evaluation and Research. Center for Biologics Evaluation and Research. **Adaptive Designs for Clinical Trials of Drugs and Biologics**. November 2019
- Food and Drug Administration Center for Drug Evaluation and Research. Center for Biologics Evaluation and Research. **Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products**. December 2020.

Innovative analyses in Progressive disease

- Wang G, Berry S, Xiong C, et al. **A novel cognitive disease progression model for clinical trials in autosomal-dominant Alzheimer's disease**. *Stat Med*. 2018;37(21):3047-3055.
- Lake SL, Quintana MA, Broglio K, et al. **Bayesian adaptive design for clinical trials in Duchenne muscular dystrophy.** Stat Med 2021;40: 4167–4184.
- Quintana M, Shrader J, Slota C, et al. **Bayesian model of disease progression in GNE myopathy**. *Stat Med*. 2019;38(8):1459-1474.

Innovations in Technology and Infrastructure

Nijat Hasanli, Head of Product

Lindus Health

Where Real-Time Breaks Down Today

- Most trials today: fragmented systems, manual handoffs, data reconciliation
- Statisticians see real data late, in unfamiliar structures
- For adaptive trials, this is fatal—adaptations require timely, structured interim data
- The unlock: **front-load validation through simulation**
  - Integrated data architecture
  - Synthetic data generation before enrollment
  - Field-level data quality flags
- What's still hard: external data sources, cross-platform interoperability

The Coordination Gap

- Technology largely exists—the barrier is coordination
- Two questions collide and create paralysis:
  - "Should we run an adaptive design?" (statistical question)
  - "Can we execute this?" (technical question)
- These get asked separately, by different people → spiral of meetings and uncertainty

The unlock: "Middle-Out" collaboration.

- Bring together: Biostatistician + Solution Architect
  - Benefit 1: Technology expands what's possible ("We *can* do that")
  - Benefit 2: Design becomes tech-aware without compromising integrity
- What would accelerate adoption
  - Regulatory clarity and encouragement
  - Published case studies on operational execution—not just statistical methodology
  - Guidance on how technology and AI can be used

From Exception to Norm — The Next Five Years

- The vision: Adaptive, agile trial design becomes the *default*
- The question shifts from:
  - "Which of my 10 candidates do I take a risk on?”
  - "How many candidates can I test at once?"
- Result: faster treatments to market, higher rigor, science advances

- What gets us there:
  - Normalize experimentation—create permission to try, learn, iterate
  - Regulatory green light + honest guidance on pitfalls

The AI opportunity

- AI is commoditizing. Access ≠ Advantage
  - Real advantage: giving AI the right **context**
  - Blocker: fragmented data, undocumented workflows, scattered protocols
  - AI assists, it does not decide
- **AI use cases for adaptive trials**
  - Generate synthetic data
  - Flag data quality issues
  - Translate between statistician and solution architect
  - Automate validation of trial builds

Closing Thoughts

Call to action

- **Experiment.** Find the cheapest way to run a real experiment.
- Design a simple adaptive schedule. See if your technology supports it.
- Use middle-out collaboration to spread awareness.

Caution:

- Cross-org collaboration is harder—explore partnerships
- Human remains accountable; AI assists

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Nijat Hasanli, Head of Product

Lindus Health

THANK YOU

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protas and Cantata

Jen Dumbleton

Head of Trial Management and Product Owner

Drug discovery is accelerating yet clinical trials remain broken

- Nearly 100-fold increase in clinical trial cost (adjusted for inflation) over the last 40 years with no improvement in quality, speed, patient experience or predictability
- $2.4 billion average cost of clinical trials to bring a new drug to market in 2024
- 86% of clinical trials delayed or behind schedule
- 95% of trials during COVID never achieved a meaningful result
- 30% of patients drop out during a trial and overwhelmingly patient experience is poor

Enabling clinical trials to succeed

Not-for-profit set up to revolutionise how large clinical trials are designed and delivered for common diseases

Founded by Prof Sir Martin Landray, Professor of Medicine & Epidemiology at Oxford and co-lead of the RECOVERY trial during COVID-19, which is estimated to have saved 1 million lives

Based on decades of experience developed at Oxford University's Clinical Trials Service Unit

Working with Protas:

- Reduce cost and improve results with smarter clinical trials
- Better quality and security with seamless trial management technology
- Deliver change together across the global trial ecosystem

"We must urgently reduce barriers to the development of better treatments for common diseases. At Protas, we do just that."

Our Solution

We have re-thought eClinical end-to-end based on decades of experience enabling streamlined, truly technology enabled, data driven & AI enhanced clinical trials

protas

Practice defining **Study Strategy, Design and Planning Consulting Services** provided by globally recognised trial experts

Cantata

Revolutionary **eClinical platform** designed by leading trialists, moving from technology-enabled data capture to high fidelity trial protocol adherence & conduct

protas

25%
Reduction in site costs

75%
Reduction in monitoring costs

10x
Reduction in data management cost

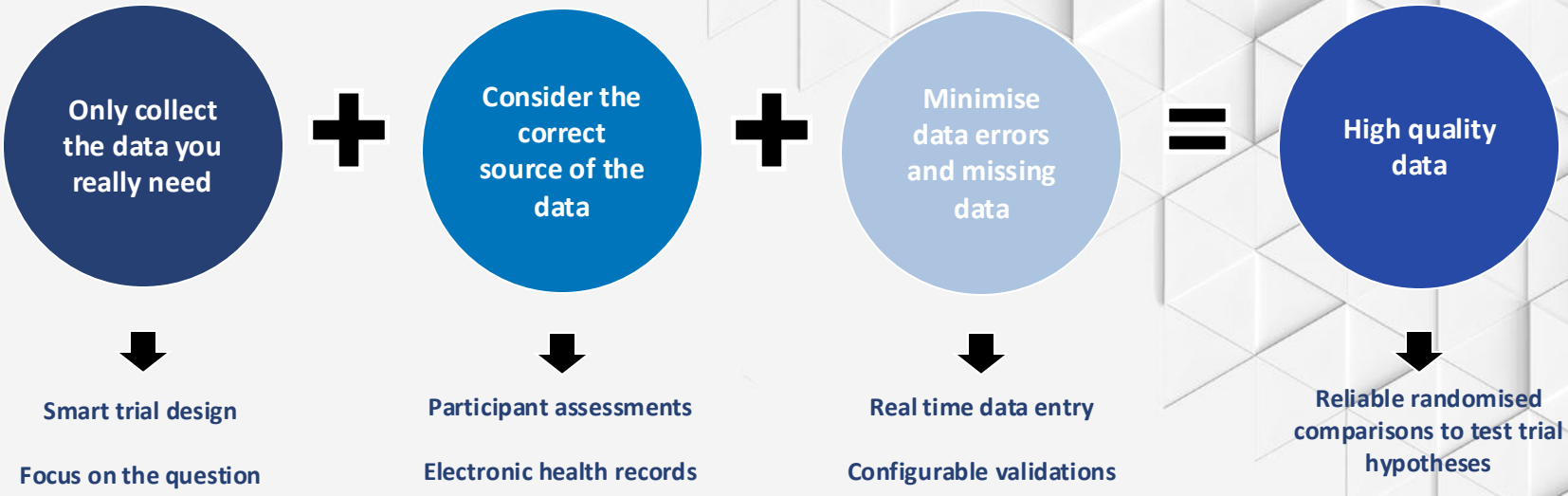
10x
Improvement in patient retention

40%
Faster study Startup

CTTI


Integrated Logistics Management
Workforce Management
Integrated Quality Management
Candidate and Participant Management
Cantata
Unified Clinical Trials Management Platform
Outcome and Adverse Event Management
Trial Administration
Trial Data Analysis
General Cross Platform Capabilities

Approach to Data



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Highly-configurable, streamlined, integrated processes on a unified data model

Protocol as Code
Data entry forms, processes and rules tailored to the trial, guide site staff, improve data quality, reduce protocol deviations, reduce data management and remove the need for costly front-line staff.

Smart eSource / Capture Once
Smart approach to eSource allows data to be captured once removing the need for transcription, significantly reducing the need source data verification, data management and monitoring.

Study as data in real-time
Having the full study represented as data in real-time enables global trial oversight using small central teams, improves safety and enables real-time remote and central statistical monitoring.

Smart use of health data
Smart trial design combined with smart use of health data accelerates enrolment and reduces the need for patient visits and significantly increases the number of patients that stay on the trial.

Liked by clinicians & site staff

93.75%
Users agree Cantata is **easy to use** and makes it **easy to conduct visits**

Deployed globally in 15 countries

Data partners with access to 60m patient records

Optum
NHS

Deployed in high-throughput clinics & traditional settings

EDC | eSource | eConsent | ePRO | eCOA | eCRF | CTMS | IRT | RTMS | Safety

Traditional fragmented eClinical landscape re-imagined into a single end-to-end solution

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Use of AI

- POC for user manual / protocol questions
- POC for querying the data in Cantata (e.g. which site has the most protocol deviations)
- Next steps: AI for faster configuration, Ingestion of Lab Results, Monitoring, Undertaking actions (e.g. participant notes, raise tasks, …)
- Technology not to replace front-line staff, but to give them more time to do what humans do best

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Jen Dumbleton

Head of Trial Management and Product Owner

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THANK YOU

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Group Discussion: Session I

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Break

Reconvene at 11:20 AM

Session II: Operationalizing Real-Time Adaptations

Maria Pitsiouni (Quantum Leap Healthcare)

Lindsay Heyd (Mass General Hospital)

Diane Heditsian (deClarity)

Morgan Hanger (CTTI)

CTTI Advancing Real-Time Adaptive Platform Trials

December 10th, 2025

I-SPY 2 TRIAL

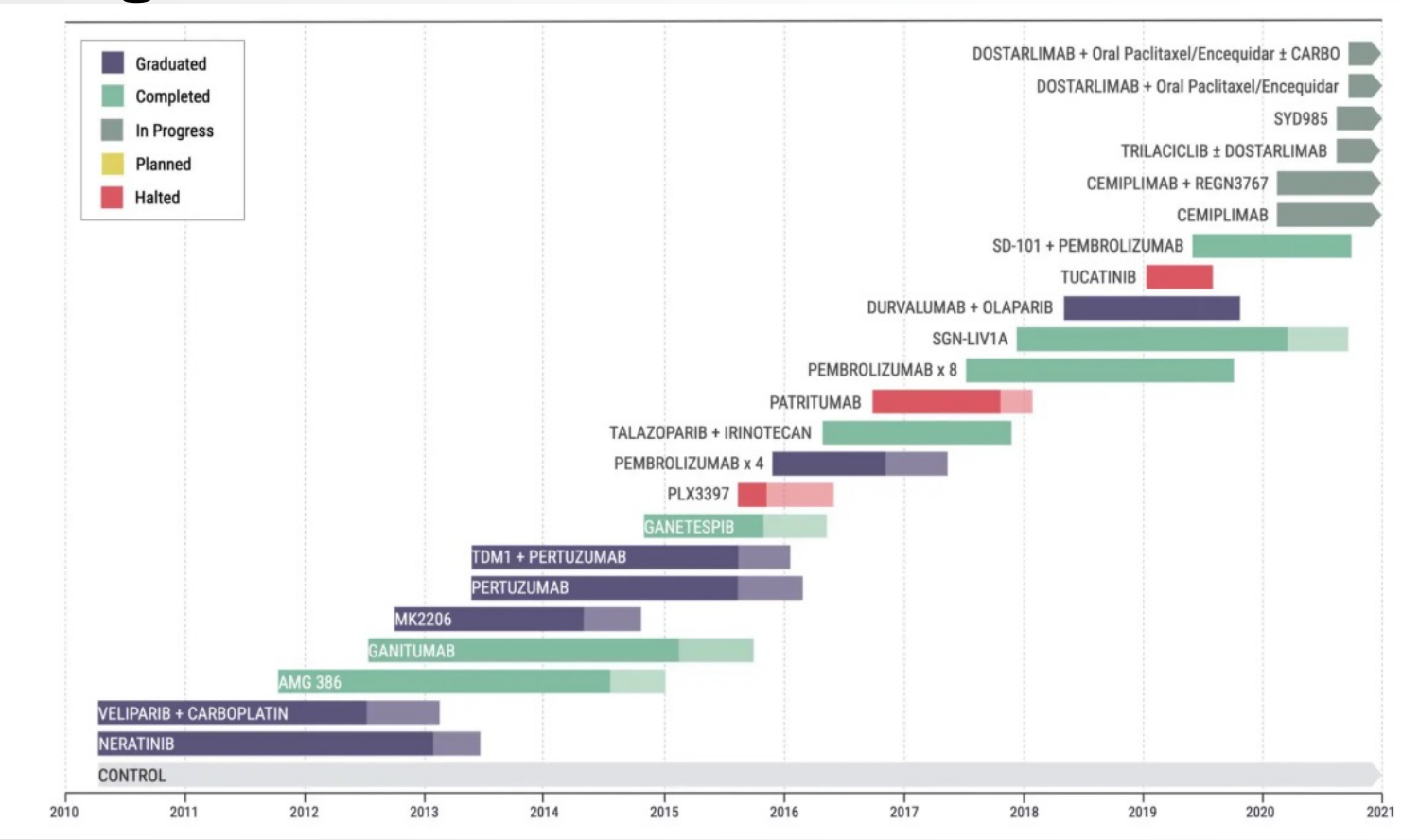
Investigation of Serial studies to Predict Your Therapeutic Response with Imaging And moLecular analysis 2

Maria Pitsiouni

Quantum Leap Healthcare Collaborative

Non-Profit Organization & Study Sponsor

25 + Agents Since 2010

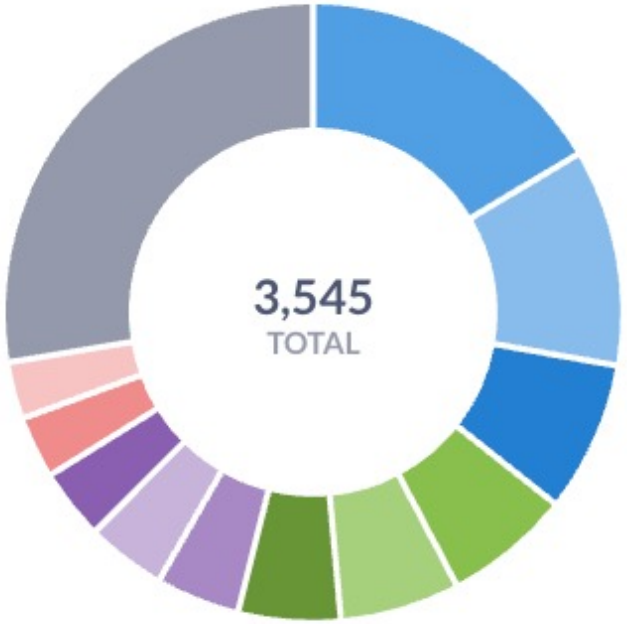


45 Active Sites: 27 Main + 18 Satellite

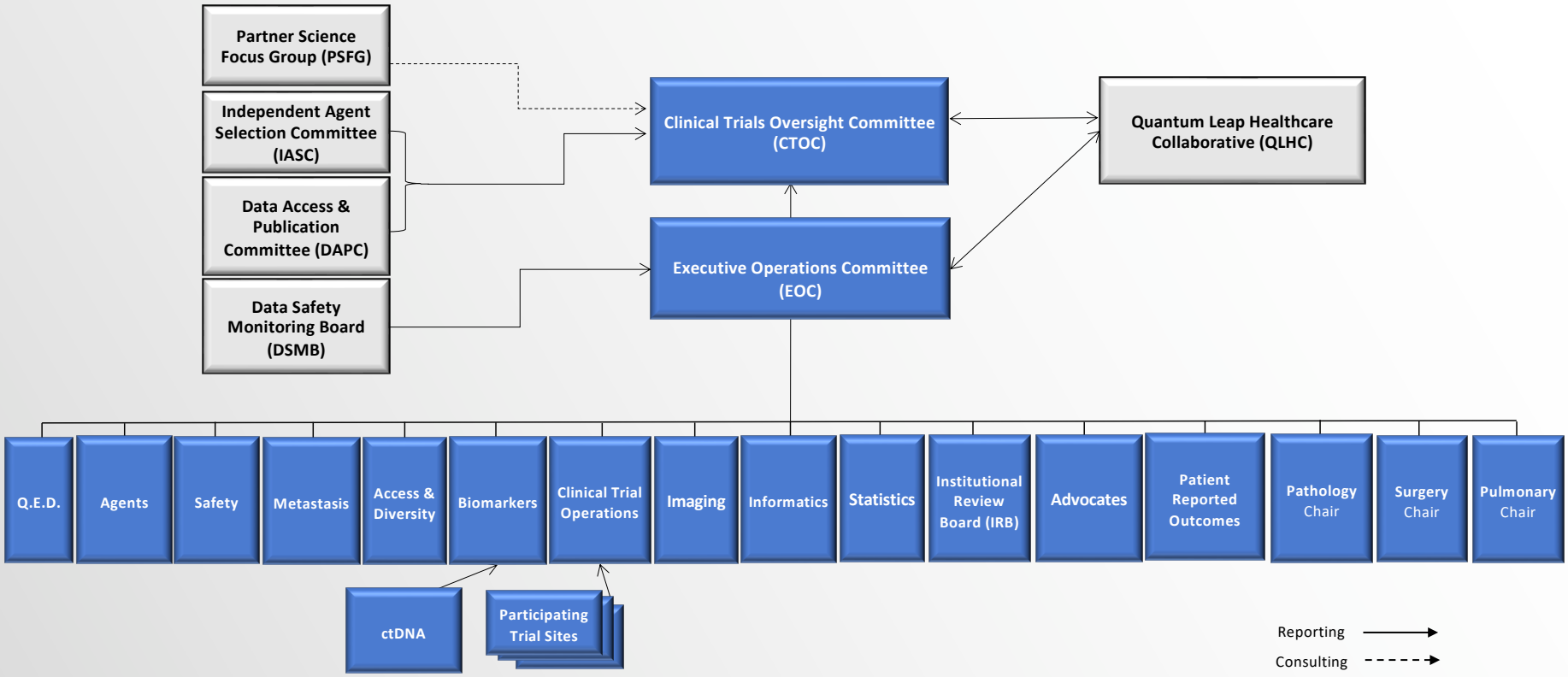
3,545 Patients Enrolled to Date

Enrollment by Site (include all data in OC, completed CRFs only)

University of California San Francisco	16.73%
University of California San Diego	11.42%
University of Alabama Birmingham	7.87%
Mayo Clinic, Rochester - MN	6.57%
University of Minnesota	6.21%
University of Colorado - Main	5.25%
University of Chicago - Main	4.26%
Loyola University Medical Center	4.01%
University of Pennsylvania	3.55%
Georgetown University	3.07%
Moffitt Cancer Center	2.79%
Other	28.27%



Governance: 16+ Investigator Working Groups



QLHC In-House Operations Teams = Communication + Efficiency

- Program Management
- Site Regulatory
- Clinical Monitoring
  - Risk Based Monitoring
- Safety
- Drug Management
- Quality

Centralized Processes = High Quality + Efficiency

- Central Wake Forest IRB
  - One set of ICFs + Minimal Site specific ICFs (as needed)
  - Patient Facing Document Translations
  - One IRB submission and one IRB Approval
- Central Protocol Review Committee (PRC)
- Chemotherapy Treatment order templates

Advantages

- 3 weeks from IRB/PRC/FDA protocol amendment submission to site activation
- Activate most sites on new protocol amendments on the same day
  - Increases efficiency for the all teams, Ops, EDC & Stats
  - Activate up to 5 protocol amendments in a year to introduce brand new arms

Ideal Operational Model?

- Investigator Working Groups

  → Investigator Buy In → Increased Study Participant Accrual

- In-House Operations

  → Cost Effectiveness + Enhanced Communication for Sponsor

- Centralized Processes

  → Cost Effectiveness + Increased Operational Efficiency for Sponsor + Sites

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Advocate Involvement in the I-SPY Trial

Lessons from a Patient-Centric Breast Cancer Trial

Diane Heditsian, Research, Patient, Policy Advocate,
University of California, San Francisco

Traditional Trials

Historically, trial design focused primarily on answering scientific hypotheses. This often led to limited consideration for patient needs, resulting in slow enrollment, high dropout rates, and limited generalizability.

Patient Centric Trials

Patient-centricity incorporates the patient's perspective at every level—from design to data interpretation. The goal is to maximize benefits and minimize burdens, making participation feasible for diverse populations.

Advocate Involvement in I-SPY 2 Trial: Lessons from a Patient Centric Breast Cancer Trial

How Advocates Shape Patient-Centric Design

- **Neoadjuvant Therapy:** One of the first trials to treat before surgery which provides immediate feedback on effectiveness, informing future care decisions.
- **pCR Endpoint:** Using Pathological Complete Response as an endpoint allows faster FDA approval, getting effective drugs to the patient years sooner.
- **Early Switching:** If MRI shows no response after 6 weeks, switch therapy to avoid toxicity.
  Early Surgery: If pCR is predicted early, skip remaining chemo to minimize side effects.
- **Minimizes Control Arms:** Adaptive randomization means fewer patients are assigned to the standard control arm as the trial learns what works best.
- **Efficacy & Safety:** Prioritizes candidates that are both more effective *and* have less side effects
- **Return of Patient Test Results:** Enables shared decision making

I-SPY Advocate Philosophy

Involvement Early and Often

- Planning
- Ongoing engagement
- Review
- Dissemination

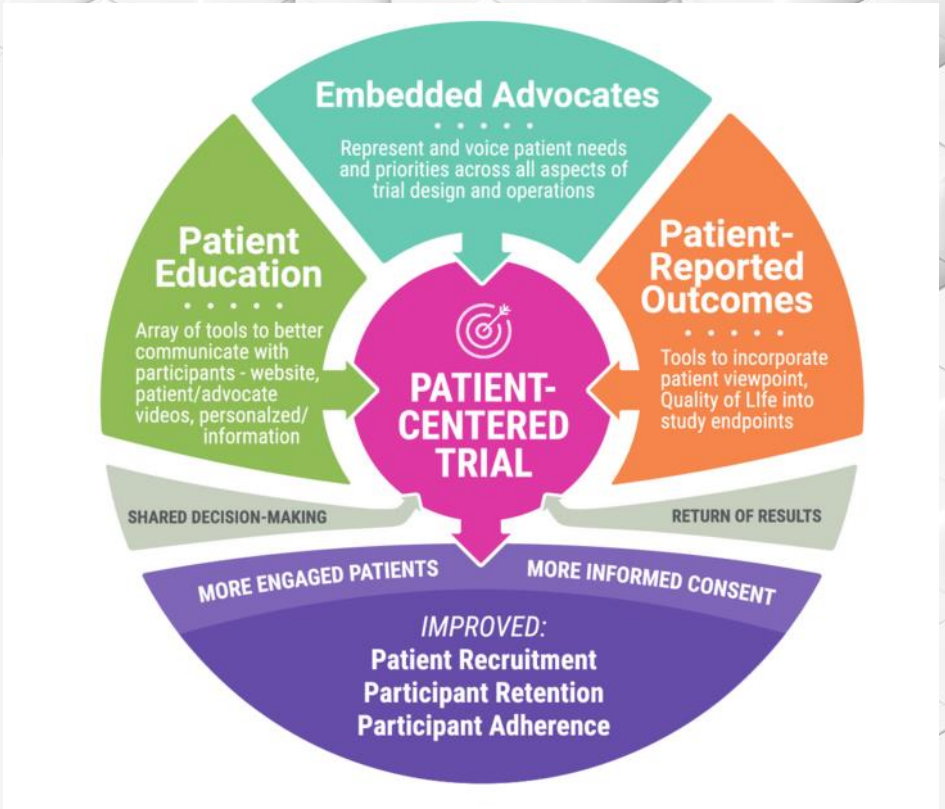
Diversity of Advocates

- Advocates are diverse
  - Breast Cancer experience
  - Professional experience
  - Cultural background
- Advocate time commitments vary

Continuous Learning

- Participating in I-SPY activities
- Take advantage of other cancer advocacy opportunities

Embedded advocates are a key element to creating patient-centered trials



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I-SPY ADVOCATE ACTIVITIES

>Advocate Webinars (monthly)

>Investigator Calls (monthly)

>Working Group Participation

>Informed Consent Form (ICF) Review

>Patient Website and Educational

>Material Review

>Abstract and Manuscript Involvement and Review

>Peer Support Counseling Program

>Plain Language Summary Development

>Advocate Journal Club

Advocate Working Group Participation

- Access and Diversity
- Agents
- Biomarkers
- Imaging
- IRB
- Investigator
- Locoregional
- Metastatic
- Microbiome
- Pathology
- Patient Advocates
- QoL/PROs
- Safety
- Statistical Core

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I-SPY Patient Website

The I-SPY Patient Website provides comprehensive information about the I-SPY clinical trials, including the history, purpose, and key features of the adaptive platform trial design. It serves as a valuable resource for patients interested in learning more about the innovative approach to clinical research.

FOR MORE IN-DEPTH LEARNINGS: GOOGLE ISPY ESMED

https://esmed.org/MRA/mra/article/view/4085/99193547164

Medical Research Archives

ESMED
European Society of Medicine

RESEARCH ARTICLE

Advocate involvement in Clinical Trials: Lessons from the Patient-centric I-SPY2 Breast Cancer Trial

Jane Perlmutter*[1], Susie Brain[1], Thelma Brown[1], Deborah Collyar[1], Amy Delson[1], Diane Heditsian[1], Barbara LeStage[1], Bev Parker[1], Susan Samson[1], Joan Venticinque[1], Jeff Matthews[2]

[1] I-SPY Patient Advocate
[2] Quantum Leap Heathcare Collaborative

***Corresponding author:** janep@gemini-grp.com

#Side Note

ABSTRACT

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CLINICAL TRIALS TRANSFORMATION INITIATIVE

Session II: Operationalizing Real-Time Adaptations

Lindsay Heyd, Clinical Trial Project Director

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

HEALEY ALS Platform Trial

Launched in 2020 (perpetual and simultaneous)

Completed testing of 7 investigational treatments

Cost effective, faster trial time, accelerated development

Published 9 primary manuscripts and widely presented

Broadly sharing data and biosamples

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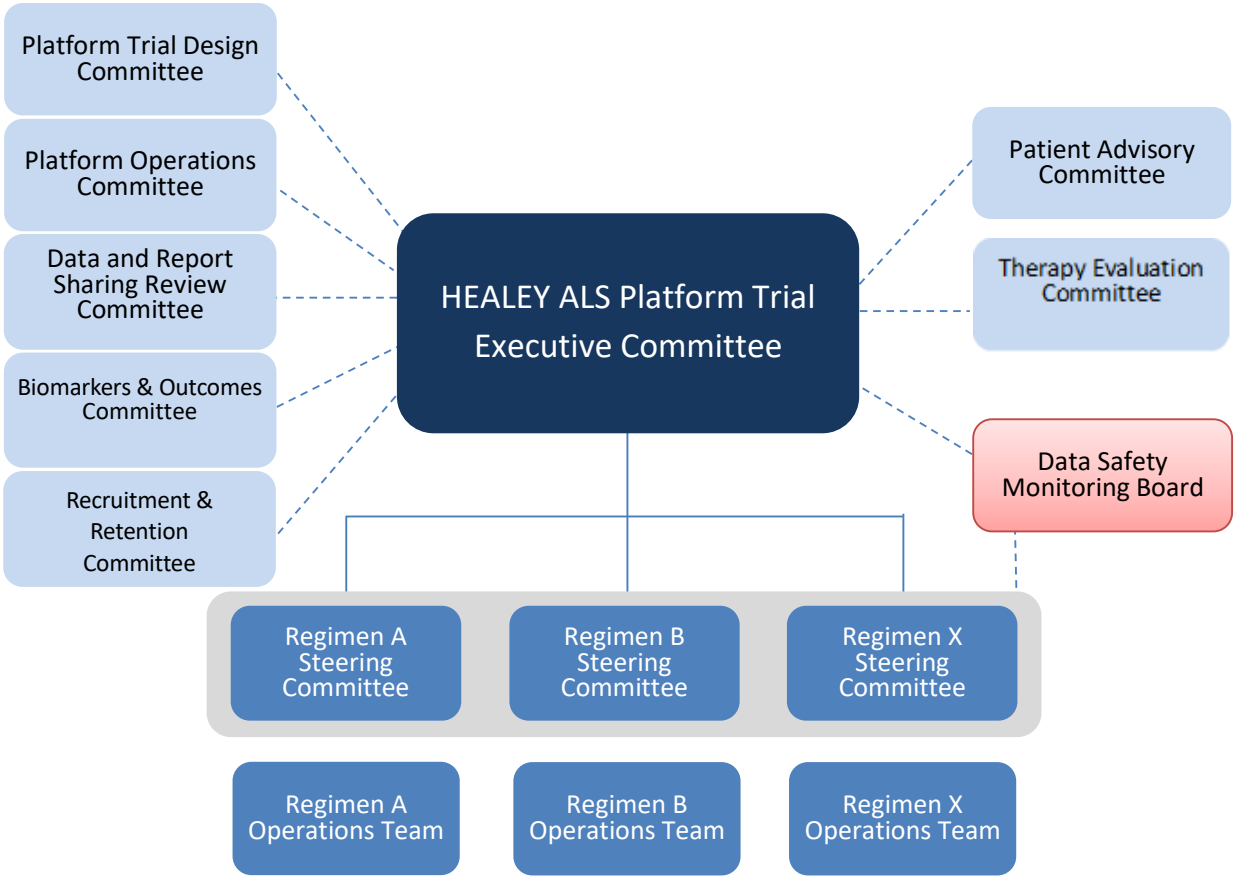
Multi-center, double blind, placebo-controlled, simultaneous, perpetual, adaptive, multi-regimen study

Consortium and Industry Collaboration

Governance and Committees

Coordination Centers


Platform Trial Design Committee
Platform Operations Committee
Data and Report Sharing Review Committee
Biomarkers & Outcomes Committee
Recruitment & Retention Committee
HEALEY ALS Platform Trial Executive Committee
Patient Advisory Committee
Therapy Evaluation Committee
Data Safety Monitoring Board
Regimen A Steering Committee
Regimen B Steering Committee
Regimen X Steering Committee
Regimen A Operations Team
Regimen B Operations Team
Regimen X Operations Team

Bayesian shared parameter analysis of function and survival

Master Protocol

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

Regimen Specific Appendix

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

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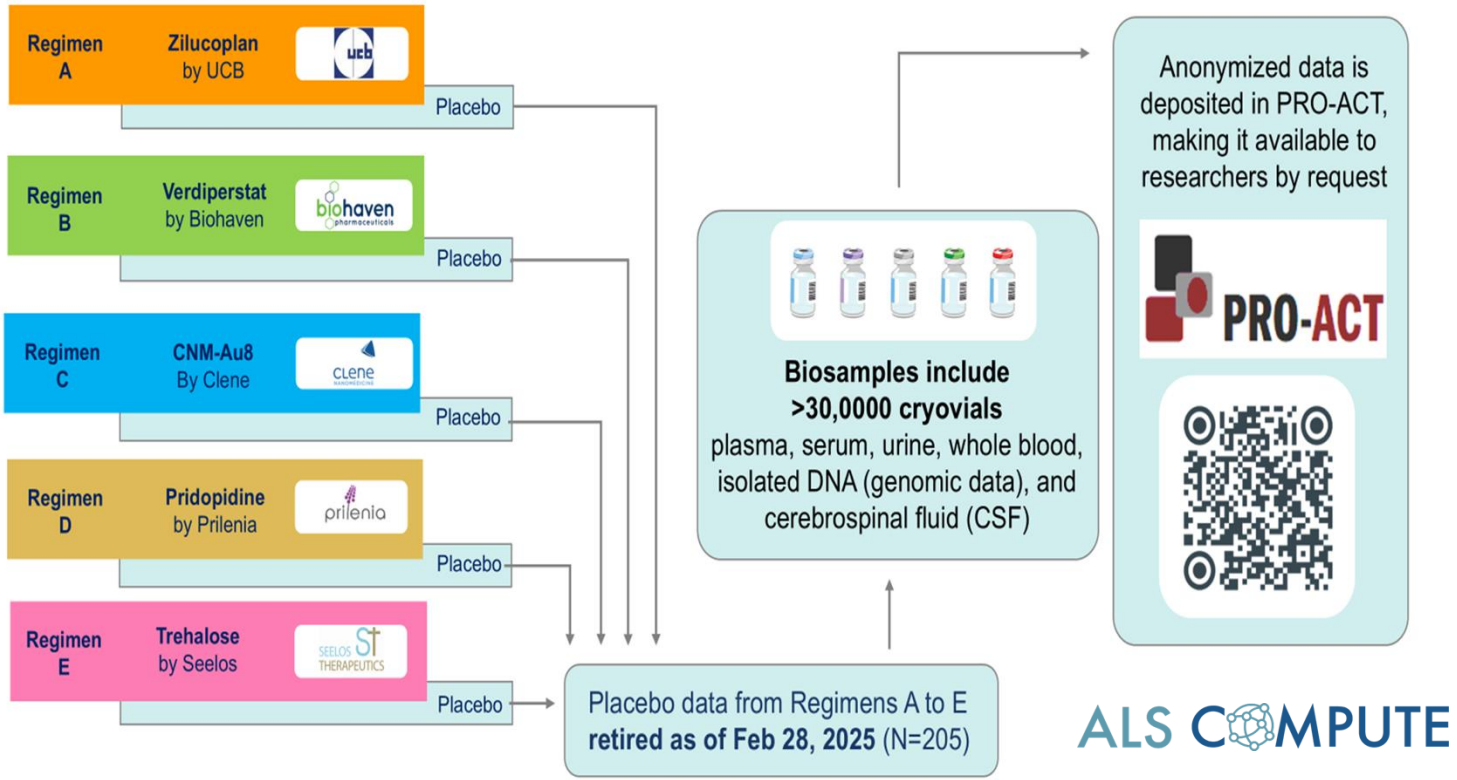
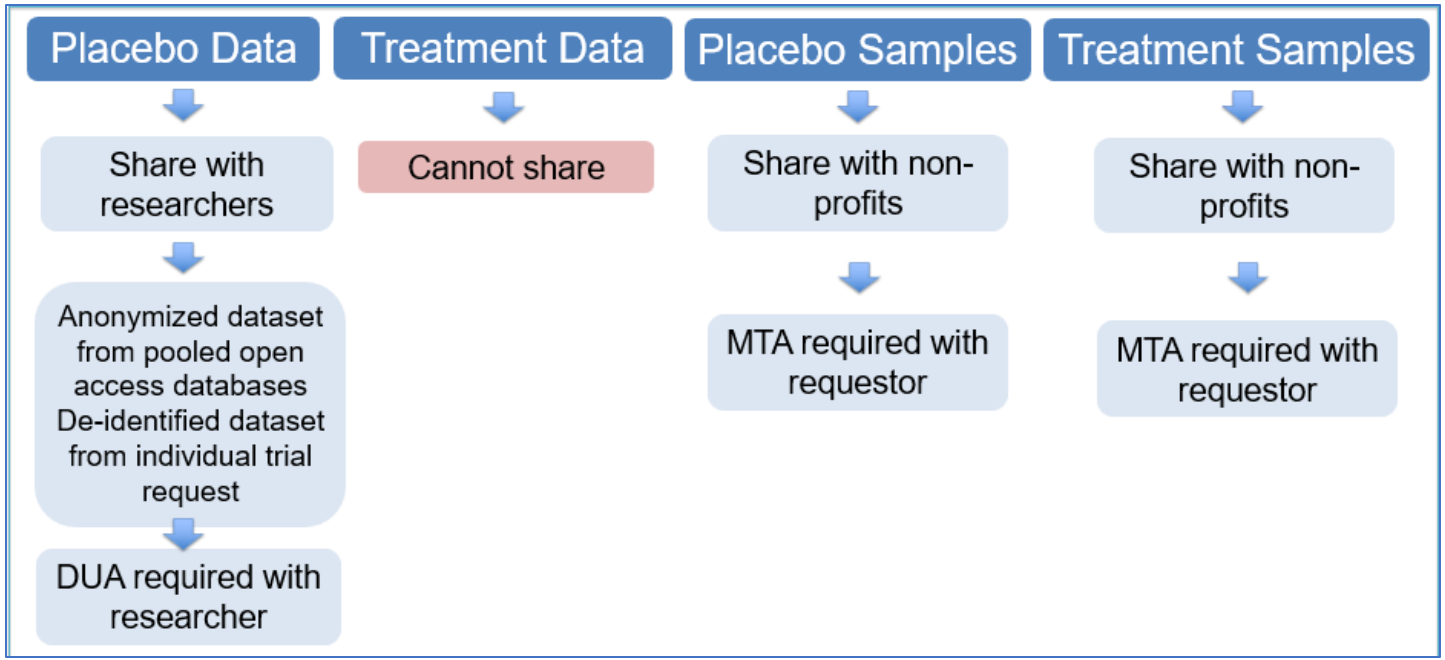

Regimen A
Zilucoplan by UCB
Placebo
Regimen B
Verdiperstat by Biohaven
Placebo
Regimen C
CNM-Au8 By Clene
Placebo
Regimen D
Pridopidine by Prilenia
Placebo
Regimen E
Trehalose by Seelos
Placebo
Placebo data from Regimens A to E retired as of Feb 28, 2025 (N=205)
Biosamples include >30,0000 cryovials
plasma, serum, urine, whole blood, isolated DNA (genomic data), and cerebrospinal fluid (CSF)
Anonymized data is deposited in PRO-ACT, making it available to researchers by request
PRO-ACT
ALS COMPUTE

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



Group Discussion: Session II

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Break

Reconvene at 12:30 PM

Session III:
Oversight for Adaptive Designs -
Regulatory, Safety, and Ethical Considerations

Luke Gelinas (Advarra)

Victoria Manax (DSMB Chair, REMAP)

Sara Bristol Calvert (CTTI)

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Adaptive Platform Trials and the IRB

Luke Gelinas, PhD

Sr. Chair Director, Advarra IRB

luke.gelinas@advarra.com

Adaptive trials and the IRB

- For adaptive studies with built-in flexibility, what must the IRB know? When should they know it?

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Adaptive trials and the IRB

- For adaptive studies with built-in flexibility, what must the IRB know? When should they know it?
  - Prospectively approving *particulars* (e.g., actual dosage) versus *decision-rules* (e.g., how actual dosages will be determined)

Adaptive trials and the IRB

- For adaptive studies with built-in flexibility, what must the IRB know? When should they know it?
  - Prospectively approving *particulars* (e.g., actual dosage) versus *decision-rules* (e.g., how actual dosages will be determined)
  - Decision rules = specify how decisions will be made and general parameters of choice without pre-specifying actual result.

Adaptive trials and the IRB

- For adaptive studies with built-in flexibility, what must the IRB know? When should they know it?
  - Prospectively approving *particulars* (e.g., actual dosage) versus *decision-rules* (e.g., how actual dosages will be determined)
  - Decision rules = specify how decisions will be made and general parameters of choice without pre-specifying actual result.
  - For the IRB, ensuring clear and reasonable decision-rules may in many cases be sufficient.

Adaptive trials and the IRB

- For adaptive studies with built-in flexibility, what must the IRB know? When should they know it?

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Adaptive trials and the IRB

- For adaptive studies with built-in flexibility, what must the IRB know? When should they know it?
  - Role of independent DSMBs and internal safety monitoring boards

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Adaptive trials and the IRB

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  - Role of independent DSMBs and internal safety monitoring boards
    - Often adaptive protocols will make implementation of planned changes depend on review/approval by a monitoring committee.

Adaptive trials and the IRB

- For adaptive studies with built-in flexibility, what must the IRB know? When should they know it?
  - Role of independent DSMBs and internal safety monitoring boards
    - Often adaptive protocols will make implementation of planned changes depend on review/approval by a monitoring committee.
    - IRBs should review acceptability of the proposed review process, monitoring panel, and timepoints for evaluation

Adaptive trials and the IRB

- For adaptive studies with built-in flexibility, what must the IRB know? When should they know it?
  - Role of independent DSMBs and internal safety monitoring boards
    - Often adaptive protocols will make implementation of planned changes depend on review/approval by a monitoring committee.
    - IRBs should review acceptability of the proposed review process, monitoring panel, and timepoints for evaluation
    - May remove need for IRB to approve specific changes mid-study, as long as consistent with protocol

Adaptive trials and the IRB

- Informed consent…

Adaptive trials and the IRB

- Informed consent
  - What must be disclosed? How should it be disclosed?

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Adaptive trials and the IRB

- Informed consent
  - What must be disclosed? How should it be disclosed?
  - At least three options:
    1. Disclose general information/plan regarding adaptive features
    2. Disclose actual, specific changes in detail
    3. Do not disclose at all

Adaptive trials and the IRB

- Informed consent
  - What must be disclosed? How should it be disclosed?
  - For example … **Adjusting dosage mid-study**

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Adaptive trials and the IRB

- Informed consent
  - What must be disclosed? How should it be disclosed?
  - For example … **Adjusting dosage mid-study**
    1. *General*: 'Throughout this study, the dosage of study drug may be changed for different groups based on incoming data.'
    2. *Specific changes:* 'The dose you will receive, 50mg, is 20mg higher than the earlier dosage used in this study, and has been changed based on incoming data'
    3. *Neither:* Disclose neither plan for dosage change nor actual dosage/change.

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Adaptive trials and the IRB

- Informed consent
  - What must be disclosed? How should it be disclosed?
  - For example… **Adaptive randomization**

Adaptive trials and the IRB

- Informed consent
  - What must be disclosed? How should it be disclosed?
  - For example… **Adaptive randomization**

1. *General:* ‘‘You currently have a set chance of being assigned to Arm A or Arm B, but the odds may change as the study progresses, to favor the arm that evidence suggests is doing better.’
2. *Specific changes:* ‘You currently have a 66% chance of being assigned to Arm A, but earlier cohorts *had* a 50% chance. The odds of being assigned to Arm A have increased as evidence suggests it’s currently doing better than Arm B’
3. *Neither:* Disclose neither general plan for changing randomization odds nor that odds have changed.

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Adaptive trials and the IRB

- Informed consent

Adaptive trials and the IRB

- Informed consent
  - When deciding what should be disclosed…

Adaptive trials and the IRB

- Informed consent
  - Beware fostering misconceptions.

Adaptive trials and the IRB

- Informed consent
  - Beware fostering misconceptions…
    - For dosing changes: Do not want to suggest that there is certainty over whether dose is safe/unsafe or effective/ineffective
      - ‘They must know this dose is safe, else they would not have raised it from the previous dose.’ Or: ‘They had to lower the dose, so this drug must not be very safe.’

Adaptive trials and the IRB

- Informed consent
  - Beware fostering misconceptions…
    - For dosing changes: Do not want to suggest that there is certainty over whether dose is safe/unsafe or effective/ineffective
      - ‘They must know this dose is safe, else they would not have raised it from the previous dose.’ Or: ‘They had to lower the dose, so this drug must not be very safe.’
    - For adaptive randomization: Do not want to foster therapeutic misconception
      - ‘They know x works, else they would not change the odds to favor getting it!’

Adaptive trials and the IRB

- Informed consent
  - Beware fostering misconceptions…
  - The more specific about changes, the more effort may be needed to mitigate misconceptions

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Adaptive Platform Trials and the DSMB

Victoria Manax, MD

DSMB Chair, REMAP

DSMB Oversight in Adaptive Clinical Trials

- For adaptive studies with built-in flexibility, the 3 main focuses of the DSMB

  - Safeguarding patient safety
  - Guiding strategic adaptations
  - Ensuring regulatory integrity

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Adaptive DSMBs: Core Responsibilities

Independent safety monitoring

Review of interim efficacy data

Authority to recommend trial continuation, modification, or termination (dependent upon charter)

Oversight of adaptation decisions in real time

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DSMB Charter: Governance Backbone

Defines Scope & Authority	Clarifies DSMB mandate, responsibilities Decision-making power in adaptive designs
Establishes Communication Pathways	Specifies who is informed, when, and how Ensuring transparency without breaking blinding
Protects Trial Integrity	Enforces confidentiality rules and session structures to prevent bias or data leaks
Pre-Defines Decision Rules	Documents stopping boundaries, adaptation triggers, and safety thresholds for consistency
Aligns Stakeholders	Reassures sponsors and regulators that adaptations are objective and ethical
Supports Regulatory Compliance	Demonstrates robust governance and oversight to satisfy regulatory expectations

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Adaptive DSMBs: Must Knows

- Pre Specified Adaptive design rules (e.g., arm dropping, dose escalation)
- Interim Data Access
- Statistical frameworks (Bayesian, alpha-spending)
- Safety signals across all arms
- Regulatory Boundaries

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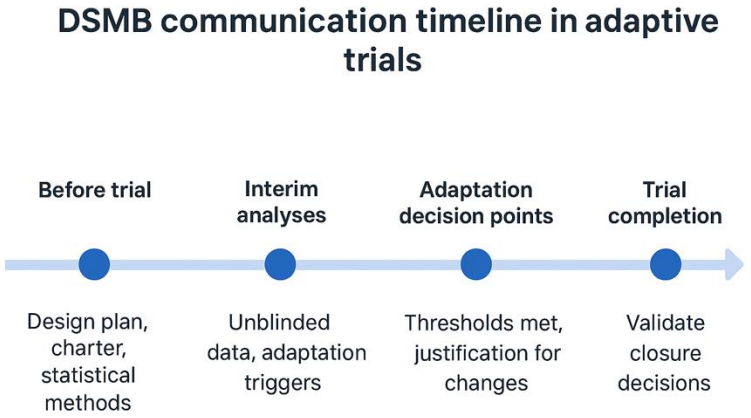
Adaptive DSMBs : When You Must Know It

Timing of Information Flow is Critical

- Before trial initiation: design plan, charter, statistical methods
- Interim analyses: unblinded data, adaptation triggers
- Safety alerts: immediate notification of adverse events
- Adaptation decisions: thresholds met, justification for changes
- Trial completion: validate closure decisions



DSMB: Traditional vs Adaptive

Aspect/Challenge Area	Traditional Trial DSMB	Adaptive Trial DSMB
Frequency of Review	Periodic (few interim locks)	More frequent, tied to adaptation points
Focus	Safety monitoring, efficacy only at endpoints	Safety + efficacy + adaptation triggers
Statistical Complexity	Conventional methods	Advanced adaptive designs, error control
Decision Authority	Stop/continue trial	Stop/continue + approve/guide adaptations
Confidentiality Needs	Standard	Heightened, to prevent bias in adaptive changes
Bias Risk	Moderate	High, due to adaptation impact
Regulatory Documentation	Standard reports	Detailed adaptation rationale
Expertise Needed	Clinicians + Statisticians	Expanded team w/ adaptive specialists

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Adaptive DSMBs: Strategic Takeaways

- DSMBs in adaptive trials are safety guardians + strategic stewards of trial integrity
- Expanded expertise and closer regulator collaboration are essential
- Know more (design rules, statistical models, adaptation triggers)
- Know earlier (before initiation, at interim checkpoints)
- Act faster (respond to safety signals and adaptation decisions in real time)

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Group Discussion: Session III

Session IV:
Open Discussion/Wrap Up

Closing Remarks

Morgan Hanger, Executive Director

Clinical Trials Transformation Initiative (CTTI)

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