Thank you for joining the webinar!

We are admitting audience members from the waiting room.

**Please allow a few moments for the webinar to begin.**

# HEALEY ALS Platform Trial

## Community Q&A – February 27, 2025

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# Evaluating and Optimizing an ALS Platform Trial Design: Insights for Future Directions

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for the HEALEY ALS Platform Trial
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# HEALEY ALS Platform Trial (first 5 regimens)

- Target Population – Inclusion Criteria
  - Sporadic or familial ALS (possible, probable, lab-supported probable, or definite by revised EEC)
  - Time since onset of weakness due to ALS ≤ 3 years (36 months)
  - Slow vital capacity (SVC) ≥ 50% of predicted capacity for age, height, and sex
  - Able to swallow
  - Participants must either not take riluzole or be on a stable dose of riluzole for ≥ 30 days
  - Participants must either not take edaravone or have completed at least one cycle of edaravone
- Duration
  - 24 weeks – blinded, placebo controlled
  - Optional Open Label Extension (OLE) or Active Treatment Extension (ATE) 6-12 months

# HEALEY ALS Platform Trial (first 5 regimens)

- Randomization into Regimen
  - Stratified randomization based on baseline medication use
    - A/B/C/D/E: edaravone & riluzole (4 strata)
    - F/G edaravone, riluzole & Relyvrio (8 strata)
- Sample Size
  - 160 per regimen is per Master Protocol, but can regimens can modify
    - n = 160 in each A, B, C, D, E
    - n = 300 in F
    - n = 240 in G
  - 3:1 Active:Placebo stratified randomization within each regimen
    - 75% chance of assignment to active study drug, 25% chance of assignment to placebo

# Background

The Healey Platform trial is a *perpetual, adaptive* Phase 2 trial

Perpetual: allows us to learn from past regimens and use our own data to inform design of future regimens
Adaptive: allows us to modify the protocol with every new regimen

Today we will present what goes into making these decisions and what modifications are being made

# Adaptation for future regimens

Adaptive and Perpetual!

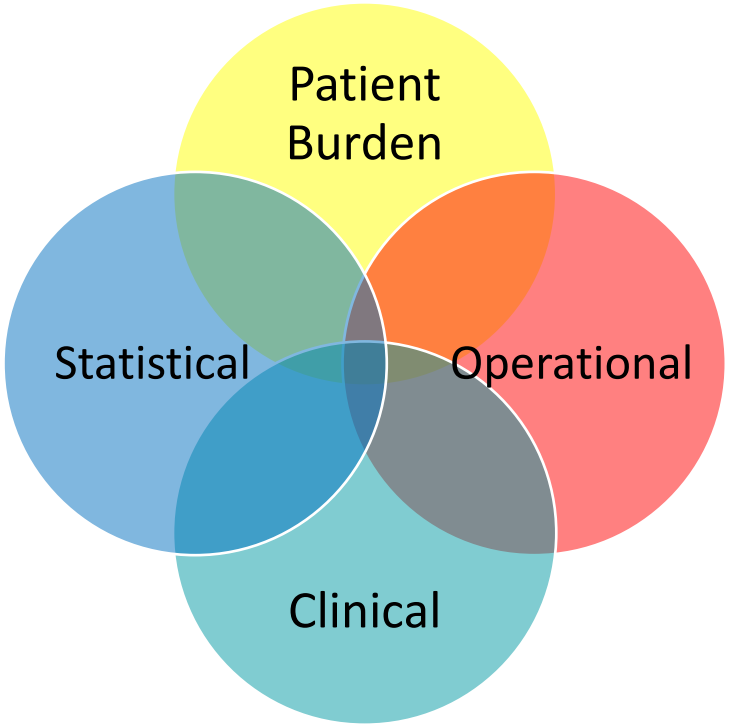
The goal is to enrich our participant population for people who are most likely to respond to treatment
We hypothesize this will be patients who are

- Faster progressors
- Earlier in disease

But first let's talk about how we think about this decision

# Considerations

- Every decision has pros and cons
- The goal is to find the best balance




3 Considerations

1. Statistical
   - Does it increase our chances of finding an effective treatment?
2. Operational
   - Is it doable in terms of materials, cost, accessibility?
3. Patient Burden
   - Does it put too much additional burden on the patients?
4. Clinical
   - What is a clinically meaningful response?

# Statistical Considerations

The goal is to enrich our participant population for people who are

- Most likely to respond to treatment
- Most likely to show the biggest response
- Be similar to others in the study (homogeneous)

In other words: We want to maximize signal and minimize noise

However, we should be cautious that we don’t also limit our generalizability

# Statistical Power


Power =

- probability of finding a significant effect **assuming that effect exists**
- probability of concluding drug is effective **when in fact it is effective**

What increases statistical power (simplified)

- Larger expected effect size (bigger difference between the drug and placebo)
- Lower variability in measures (more homogenous population)
- Increase number of participants (sample size)
- Type 1 error – probability of getting a false positive  (we don't mess with this)

- A study design that accounts for how we believe the drug works

We usually aim for 80-90% power

# Modifications we considered

Inclusion / Exclusion Criteria

- Helps find the most homogeneous group, most likely to have a larger response to treatment
- We considered
  - Time since symptom onset
  - Baseline NfL levels
  - Limit based on El Escorial Criteria
  - TRICALS score (an aggregate score composed of many baseline measures)

Length of double-blind period of study

- Randomized controlled portion of trial lasted 24 weeks for Regimens A-E
- Increasing length of study will allow time for a drug with a delayed response to be seen

Number of participants in each regimen

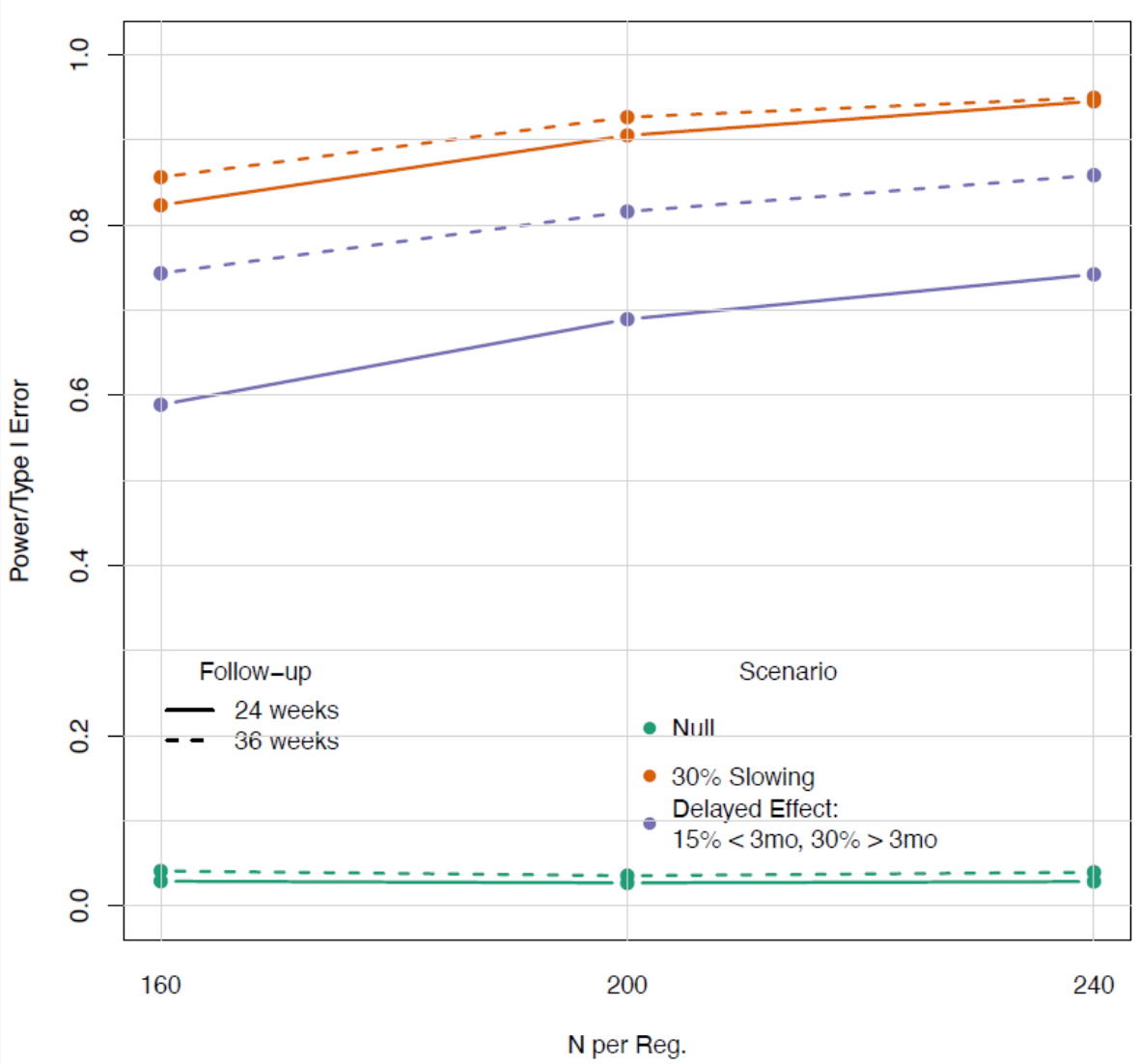
# Is there an optimal subset?

Need to balance increase in power with drop in potential participants
Limiting participation will also limit generalizability

| Criteria | Slope Mean/SD | Power* | % of current population | % with early disease** |
|---|---|---|---|---|
| Current Design | -1.28 | 82% | 100% | 40% |
| <2 yrs since sx onset | -1.34 | 87% | 73% | 64% |
| EEC definite only | -1.56 | 92% | 40% | 41% |
| EEC def/prob only | -1.32 | 86% | 72% | 39% |
| Baseline NfL >50 | -1.45 | 88% | 74% | 46% |

* Assuming 30% Slowing; n=160, 3 Regimens sharing placebos
** Early disease = <1.5 yrs since symptom onset

# Changes: Length of double-blind follow-up




Design for Regimens A-E assumes

- n=160
- 3 regimens sharing placebos
- 30% slowing

Red lines show A-E assumptions

- Modest increase in power with increase in length of trial (solid to dotted)

Purple lines show scenario with a delayed treatment effect

- 15% effect in <3months
- 30% effect in >3months
- Increase in power if we follow for longer time (solid to dotted)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# Modifications to be implemented in 2025

Inclusion / Exclusion Criteria

- Limit to those within 2 years of symptom onset (i.e. weakness symptoms began within last 24 months)
- More homogeneous and enriches for those most likely to show effect

Length of double-blind period of study

- Increase double-blind period to 36 weeks (little more than 8 months)
- More power to see drug with delayed effect

Number of participants in each regimen

- Suggested n=160, but regimens can increase based on scientific rationale

# The HEALEY ALS Platform Trial is a perpetual, adaptive trial

NEWS · 5 MINUTE READ · DEC | 12 | 2024

## Sean M. Healey & AMG Center Announces Updates to HEALEY ALS Platform Trial Master Protocol

View Press Release:

https://bit.ly/4iKxSNO

- The duration of the Randomized Controlled Trial (RCT) period is **extended from 24 to 36 weeks**
- The inclusion criteria were modified, with the **time since symptom onset now set at 24 months**
- The visit schedule has been made more streamlined and flexible, offering **increased opportunities for remote visits** in the Active Treatment Extension (ATE)
- Addition of **peripheral blood mononuclear cell (PBMC) collection**, which will be banked for future generation of induced pluripotent stem cells (iPSCs)
- **Thank you to our Patient Advisory Committee for invaluable feedback**