HEALEY ALS Platform Trial

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Healey Center
Sean M. Healey & AMG Center
for ALS at Mass General
1. **Why Now?**

2. **Why Platform?**
   Scientific and Statistical Advantages

3. **HEALEY ALS Platform Trial**
ALS is the neuromuscular disease with the largest drug pipeline

- Over 130 companies in ALS space
- Thousands of investigators worldwide - many targets

“I lost the privilege of working on the human time clock on January 6, 2018 – the ALS clock is a lot faster”
Sandy – Person with ALS

- Platform approach decreases time to finding effective therapies
When will we find first effective therapy?

10 Therapies Tested

2400 Participants
1200 Placebo

1600 Participants
400 Placebo

12 Years

4 Years

Traditional Platform

*Assumes 10% of therapies tested are effective with a 30% slowing in rate of progression
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Disease</th>
<th>Therapy A</th>
<th>Therapy B</th>
<th>Therapy C</th>
</tr>
</thead>
</table>

**Traditional**
Less placebo, more access, more options

Enroll in Platform Trial

Consent Randomization

Placebo-Controlled 24 WEEKS

Therapy A

Therapy B

Therapy C

Active

Placebo

Active

Placebo

Active

Placebo

Shared Placebo

Open Label Extension
ENDPOINTS

Primary Endpoint
Change in disease severity - **ALS Functional Rating Scale-Revised (ALSFRS-R)**

Secondary Endpoints
1. Change in respiratory function - slow vital capacity (SVC)
2. Change in muscle strength - hand held dynamometry (HHD)
3. Survival
4. Treatment-specific biomarkers as applicable

Exploratory Endpoints

Safety Endpoints
Exploratory Endpoints

- DNA
- Neurofilaments
- PBMCs > Stem Cells
- Biomarkers (Blood, Urine, CSF)
- Speech / Digital

Endpoint Development Engine
Bringing together a community to launch the first platform trial for ALS very fast

Concept to Launch
1 Year

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General
Experienced Clinical Operations Team

Marianne Chase
NCRI Project Management

Annette DeMattos
NCRI Grants & Contracts

Megan Hall
BNI Monitoring & Outcomes training

Alex Sherman
NCRI Clinical Trial Systems

Hong Yu
NCRI Data Management

Eric Macklin
MGH Biostatistics

- Raji Bhat
- James Chan
- Derek D’Agostino
- Catherine Gladden
- Brittney Harkey
- Katie Jentoft
- Lindsay Pothier
- Rebecca Randall
- Melissa Ricker
- Aileen Shaughnessy
- Lisa Spagnuolo
- Eric Tustison
- Jason Walker
20+ years experience; 57 ALS studies with >20K participants already completed including 21 industry-sponsored trials
Patient Engagement

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

“Thank you for ensuring that patient voices are involved in every facet of this effort”
Therapy Selection: Selection Committee
From Healey and NEALS Science Advisory Committees

Request for Proposals (RFP)

- Almost 30 applications from 10 countries
  - industry and academic
- Five were selected to enter the platform now

How to Participate:

https://www.massgeneral.org/neurology/als/research/platform-trial
Zilucoplan – complement C5 inhibitor

Verdiperstat – myeloperoxidase inhibitor

CNM-Au8 – gold nanocrystals

Pridopidine – Sigma 1 Receptor agonist

IC14 – immunotherapy targeting CD14
Partnership with the FDA: very positive meetings
IND submission 12/2019

- **July 9, 2019** – FDA Type C Meeting in Washington DC
- **November 5, 2019** – Brought three companies together to meet with us and the FDA to finalize the HEALEY ALS Platform trial design.
Concept to Launch = 1 year

Protocol Design + Infrastructure Build

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for ALS at Mass General
ALS Platform Trial

The trial is governed by a Master Protocol – a common protocol for multiple therapies

- Defines global rules that govern the therapies being investigated and how participants flow through the trial

Appendix: The mechanism through which therapies are added to the platform and attached to the master protocol
THE CHANGING FACE OF CLINICAL TRIALS
Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D.,
and Janet Woodcock, M.D., Editors

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both
Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

HIGH-QUALITY EVIDENCE IS WHAT WE USE TO GUIDE MEDICAL PRACTICE. The standard approach to generating this evidence — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. As a result, important clinical questions go unanswered. The conduct of "precision medicine" trials to evaluate targeted therapies creates challenges in recruiting patients with rare genetic subtypes of a disease. There is also increasing interest in performing mechanism-based trials in which eligibility is based on criteria other than traditional disease definitions. The common denominator is a need to answer more questions more efficiently and in less time.

A methodologic innovation responsive to this need involves coordinated efforts
Master Protocol Overview

• **Primary Endpoint**
  • Change in disease severity through 6 months
  • ALS Functional Rating Scale-Revised (ALSFRS-R)

• **3:1 randomization** for each therapy, Active Treatment vs. Placebo
  • Regimen: A therapy being investigated; includes active and matched placebo
  • Shared placebo among all regimens
  • Uses concurrent and non-concurrent controls
  • Inclusion/Exclusion: Broad ALS patient population

• **Adaptive Trial**
Master Protocol Primary Analysis

Bayesian Repeated Measures of ALSFRS-R

• Model the linear rate of progression in ALSFRS-R for control participants

• Treatment Effect:
  \textit{Percent Slowing} in the rate of progression relative to control

• Increases power relative to simplified analyses

• Accommodates additional platform complexities
  • Regimen-level differences of control arm
  • Time-trend effects in rate of progression of control arm
  • Covariates: ALSFRS-R baseline value and pre-slope
  • Mortality: Exponential proportional hazards time to event with shared treatment effect
Shared Control Across Regimens

Share ALL controls across all regimens including:
- Different modes of administration
- Minor differences in inclusion/exclusion
- Concurrent and non-currently randomized

Analysis Model accounts for:
- Differences in controls over time in analysis (time-trend effect)
  - Concurrent vs. non-concurrently randomized controls
- Potential additional unexplained differences in controls across regimens (regimen-specific random effect)
  - Mode of administration
  - Different minor inclusion/exclusion

*N=160 per Regimen; 3:1 Rand.; Type I Error: 2.5%
Clinical Trial Simulation

• Understand operating characteristics of proposed design
• Optimize design under key trial parameters
• Quantify Efficiencies of Proposed Platform Trial over Traditional
When will we find the first effective treatment?

- **Traditional Drug Development**
  - Sequence of fixed 1:1 trials
  - Each N=240 with 120 treated and 120 placebo
  - Lag of 3 months between trials

  - **12 Years**
  - **2400 Participants**
    - **1200 on Placebo**
    - **10 Treatments Tested**

- **Adaptive Platform Trial**
  - Perpetually enrolling max. of 3 regimens
  - Max N=160 with 120 treated and 40 controls
  - Shared controls across regimens

  - **4 Years**
  - **1600 Participants**
    - **400 on Placebo**
    - **10 Treatments Tested**

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

Platform trials can greatly accelerate the path to effective treatments for ALS

There is strong support for the platform approach - regulators, industry, clinician scientists, and patients

This is a perpetual trial and will continue to test more interventions until cures are found for all people with ALS

To participate:
https://www.massgeneral.org/neurology/als/research/platform-trial
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