Improving Basic Research, Clinical Trial Infrastructure, and Community Engagement to Support Drug Development for ALS

Day 1 – Wednesday, January 27th

Virtual Private Workshop — January 27 & January 28, 2021
Welcome & Introduction

Mark McClellan, MD, PhD
Director, Duke-Margolis Center for Health Policy
Remote Participation Instructions

• **Mute & Slides**
  • You have been placed on mute; speakers can mute/unmute throughout
  • We will advance the slide deck, please prompt us to advance

• **Meeting Information**
  • Meeting materials will be distributed after the meeting & are available on the calendar invite

• **Questions & Comments**
  • Please go on video and use the “raise hand” Zoom option if you’d like to speak, we’ll pass the microphone and you can unmute
  • Please feel free to type your question into the Zoom group chat or use the raise hand function

• **Zoom Issues?** Please Zoom message Sarah Sheehan or email sarah.sheehan@duke.edu
Meeting Agenda | Day 1

Fireside Chat: Perspectives from FDA Leadership

• Discuss challenges impeding therapeutic advancement and key lessons learned from clinical development and review
• Discuss ongoing efforts to support ALS research and therapeutic development
• Discuss approaches to addressing key challenges and strengthening the ALS drug development pipeline

Where Are We Now with Drug Development in ALS?

• Highlight the state of the science including basic research, innovative trial design and approaches to data collection

Session 1: Importance and Limitations of Basic and Preclinical Research

• Discuss efforts to address gaps and challenges in disease characterization
• Discuss efforts to increase collaboration and introduce efficiencies in basic and preclinical research
• Discuss efforts to enable the efficient movement of candidate therapies towards clinical trials

Session 2: Considerations for Innovative Trial Designs

• Discuss the potential of innovative trial designs to support more efficient evidence generation
• Discuss scientific and practical considerations for the conduct of trials with innovative designs
Meeting Agenda | Day 2

Session 3: Research Infrastructure and Data Sharing for ALS

• Discuss how the enhancement of a shared data infrastructure can support disease characterization, biomarker development, and the capture, efficient use and reuse of clinical data
• Discuss approaches for improving the utility and interoperability of shared data resources

Session 4: Understanding What is Meaningful for Patients - Recruitment, Patient Experience Data, and Expanded Access

• Discuss how to meaningfully incorporate patients’ experiences, perspectives and priorities into clinical trials
• Discuss approaches for increasing access to clinical trials and decreasing participant attrition

Session 5: Coordination, Collaboration, and Shared Strategy

• Discuss next steps and stakeholder roles to support ALS research and therapeutic development
• Discuss feasible approaches to improving the quality and availability of tools to support disease characterization
• Discuss next steps for maximizing the utility of innovative approaches to trial design
Fireside Chat: Perspectives from FDA Leadership
12:05pm – 12:30pm
Where are We Now with Drug Development in ALS?

Jinsy Andrews, MD, MSc, FAAN
Associate Professor of Neurology, Director of Neuromuscular Clinical Trials
Columbia University
WHERE ARE WE NOW WITH DRUG DEVELOPMENT IN ALS?

Jinsy Andrews, MD, MSc, FAAN
Director of Neuromuscular Clinical Trials, Investigator, Motor Neuron Center, Associate Professor of Neurology
Columbia University Irving Medical Center, NY, NY

Basic Research, Clinical Trial Infrastructure, and Community Engagement to Support Drug Development for ALS
Duke Margolis Center for Health Policy
January 27 & 28, 2021
Disclosures

- Served as on the DSMB for AL-S Pharma
- Serve as a consultant for Avexis, Biogen, Cytokinetics, Denali and Wave Therapeutics
- Receive research funding from Orion Pharma, Biogen, Novartis, Roche, Project ALS and the Healey Foundation
- Serve as NEALS Consortium Co-Chair, Board of Trustee Member for the National ALS Association, and serve on the Scientific Advisory Committee to the Healey Center at MGH
Objectives

• Discuss current ALS treatment landscape
• Review the clinical trial pipeline in the United States
• Highlight recent clinical trial results
• Innovations and collaborations in ALS clinical research
• Impact of increasing knowledge of genetics in ALS
Why are we here?
There has been exponential growth in scientific knowledge in ALS

CURRENT TREATMENT OPTIONS FOR ALS

Riluzole
Edaravone

https://www.medicalnewstoday.com/articles/321900
Current Treatment Landscape: Riluzole

- First of 2 trials was a randomized, double-blind, clinical study conducted in France/Belgium for 13 to 18 months
- 155 patients randomized to either 50 mg of riluzole twice daily v. placebo
- Statistically significant effect on the rate of survival (defined as time until tracheostomy or death)
- Benefit was on average 90 days longer in the riluzole-treated group than in the placebo-treated group

The survival advantage at the end of the placebo-controlled period:
- 37 % [29 of 78] placebo vs.
- 49 % [38 of 77] with riluzole
  \[(P = 0.046)\]
Current Treatment Landscape: Riluzole

**Oral tablet** was approved for the treatment of ALS in early 1995
- Showed modest benefit based on two controlled clinical trials
- Dosing: 50 mg twice daily

**Oral liquid** form of riluzole
- Thickened liquid formulation (5mg/ml = 50 mg) administered twice daily via oral syringe
- Received approval in September 2018

**Oral film** of riluzole
- Received approval November 2109
- Dosing 50 mg twice daily

Current Treatment Landscape: Edaravone

- Study conducted in Japan between 2011 to 2014
- 137 patients that completed the observation period were randomized: Edaravone (n= 69) Placebo (n=68)
- Primary outcome: **Change in ALSFRS-R**
- Edaravone: −5.01 (SE 0.64)
- Placebo: −7.50 (SE 0.66)
- LSM difference = **2.49** (SE 0.76, 95% CI 0.99–3.98; p=0.0013)

![Graph showing mean ALSFRS-R scores during treatment](image)

**Figure 2: Mean ALSFRS-R scores during treatment**

For patients with missing values at the end of cycle 6, data were imputed by the LOCF method, provided that they had completed at least cycle 3. ALS=amyotrophic lateral sclerosis. ALSFRS-R=Revised ALS Functional Rating Scale. LOCF=last observation carried forward. One patient’s evaluation at the end of cycle 2 was excluded from analysis as the clinician assessing ALSFRS-R score did not have adequate training.
Current Treatment Landscape: Edaravone

Edaravone was approved for ALS in 2017
Administered intravenously 60 mg over 60 min
- Once a day IV dosing
- One cycle of treatment for 28 days
  - 1\textsuperscript{st} cycle: 14 day administration & 14 days cessation
  - 2\textsuperscript{nd} cycle or after: 10 of 14 day administration & 14 days cessation
Targeting specific gene mutations in ALS

Inhibit specific mechanisms associated with motor neuron degeneration
  - e.g.: Glutamate excitotoxicity, Oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, complement inhibition, heat-shock protein inducing, kinase inhibition

Improving nerve and muscle communication

Improving the muscle response to diminished nerve input

Stem cells approaches
  - Regeneration/neuroprotection of nerve cells (direct injection)
  - Delivering protective factors to the motor neurons (MSC)
  - Improving the support cells surrounding the motor neurons (glial cells)
Evolving theory of how ALS happens

- **The six steps theory**
  Using a mathematical model, previously used by cancer researchers, Al-Chalabi and colleagues (2014) suggested that it takes six steps to trigger ALS. The number of steps might be different (and likely reduced) in ALS caused by specific genes. Each step represents a separate event that could be a genetic, environmental or lifestyle factor with the last one

CURRENT ALS CLINICAL TRIAL LANDSCAPE
Active clinical trials in the United States
### ALS Clinical Trial Pipeline (United States)

#### Phase 1
- **GDC 0134+**
- **AT 1501 (anti-CD40L)**
- Darunavir, ritonavir, dolutegravir, TAF (HERV-K suppression)*
- **Perampanel***
- **BIIB100***
- **BLZ945***

#### Phase 2
- **ANX005**
- **ALZT-OP1a***
- **AT-1501**
- Clenbuterol+
- Cipro/Celecoxib+
- Fingolimod
- **Inosine+**
- **L-serine***
- **Memantine***
- Pegacetacoplan*
- **Ranolazine***
- Retigabine
- **RNS60+**
- **Tocilizumab**
- **Theracurmin***
- **L-serine***

#### Phase 3
- **Arimoclomol+**
- **Edaravone (oral)***
- **Ravulizumab***
- **Ibudilast ***
- **Masitinib***
- **Reldesemtiv**

#### Approved Therapies
- **Riluzole**
- **Edaravone**
- **Nuedexta (PBA)**

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* = recruiting; + = active/JAN 2021

[www.neals.org; www.clinicaltrials.gov](http://www.neals.org; www.clinicaltrials.gov)
### ALS Clinical Trial Pipeline
(United States)

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<th><strong>Cell Therapies</strong></th>
<th><strong>Gene Directed</strong></th>
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<td><strong>T regs</strong> and IL2* <em>(Lymphocytes)</em>+</td>
<td>SOD1 – Tofersen+</td>
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<td>NurOwn™ <em>(Modified MSC)</em>+</td>
<td>C9orf72 – BIIB078+</td>
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<td>Q cell <em>(human glial progenitor)</em></td>
<td>C9orf72 – metformin*</td>
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<td>CNS10-NPC-GDNF</td>
<td>Ataxin 2 – BIIB105*</td>
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<tr>
<td>Adipose derived MSC *</td>
<td>FUS - Jacifusen</td>
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* = recruiting; + = active/JAN 2021

[www.neals.org; www.clinicaltrials.gov](http://www.neals.org; www.clinicaltrials.gov)
RECENT CLINICAL TRIAL PUBLICATIONS IN ALS

AMX0035 (NEJM 2020, Muscle & Nerve 2020)
Tofersen (NEJM 2020)
AMX0035 (Sodium Phenylbutyrate/Taurursodiol)

Trial of Sodium Phenylbutyrate–Taurursodiol for Amyotrophic Lateral Sclerosis

Sabrina Paganoni, M.D., Ph.D., Eric A. Macklin, Ph.D., Suzanne Hendrix, Ph.D., James D. Berry, M.D., Michael A. Elliott, M.D., Samuel Maiser, M.D., Chafic Karam, M.D., James B. Caress, M.D., Margaret A. Owegi, D.O., Adam Quick, M.D., James Wymer, M.D., Ph.D., Stephen A. Goutman, M.D., et al.
Trial of Sodium Phenylbutyrate and Tauroursodiol (AMX0035) for ALS

- 137 patients were randomized to AMX0035 v. placebo
- Mean rate of change in ALSFRS-R score was:
  - -1.24 in active
  - -1.66 in placebo
  - (difference 0.42 pts/month, 95% CI 0.03 to 0.81, p=0.03)
- AE mainly GI; fewer SAE in active arm

The clinical trial results for AMX0035 raises some questions for the ALS Community…

Considerations include:
• Rigor of statistical analysis
  - Pre-specified analyses
  - Several previous clinical trial failures in ALS related to carrying forward studies based on post hoc analyses
• Meaning of the endpoints
• Consistency of endpoints

Balance this with:
• Safety and tolerability
• Ease of administration (Frequency and route of administration)
• Potential costs for therapy
GENETICS IN ALS
Complexity of Genetics in ALS

- ALS can result from many possible underlying genetic variations (i.e. different genes can cause ALS)

- Many ALS-associated genes are also implicated in other conditions, including frontotemporal dementia and cerebellar disease

- The distinction between familial and sporadic ALS is not clear-cut, which greatly complicates genetic counselling in ALS
Tofersen (SOD1 Antisense Oligonucleotide)

Phase 1–2 Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS

Timothy Miller, M.D., Ph.D., Merit Cudkowicz, M.D., Pamela J. Shaw, M.D., M.B., B.S., Peter M. Andersen, M.D., Ph.D., Nazem Atassi, M.D., M.M.Sc., Robert C. Bucelli, M.D., Ph.D., Angela Genge, M.D., Jonathan Glass, M.D., Shafeeq Ladha, M.D., Albert L. Ludolph, M.D., Nicholas J. Maragakis, M.D., Christopher J. McDermott, M.D., Ph.D., et al.
Phase 1-2 Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS

- Phase 1-2 ascending dose trial
- Randomized 3:1
- Primary outcome safety and PK
- Dose dependent decrease of CSF protein

Neurofilament light as a potential biomarker of pre-symptomatic SOD1 ALS and phenoconversion

- The study population: 34 controls, 84 at risk individuals, 10 converters and 17 ALS patients (11 of which had no gene mutation)
- Of the converters all were SOD, except 1 FUS
- Among converters, serum NFL was higher than controls about 12 months prior to any symptoms or signs of disease

Benatar, et al. *Annal of Neurol* 2018; 84: 130-139
Morphology of SOD1 aggregates in human autopsies:

*wt/wt SOD1:*
fine granular aggregates morphologically very similar to the stable D90A SOD1 (6 autopsies)

*Unstable SOD1 mutants:*
larger more distinct aggregates

Pictures courtesy of Dr. Thomas Brännström and Dr. Karin Forsberg
Umeå University, Sweden

Forsberg, et al. *J Neurol Neurosurg Psychiatry* 2019
Rapid increase in genetic understanding in ALS and availability of technology to target gene mutations has an impact.

- Trial design needs to be carefully considered when developing investigational drug targeting specific gene
- Need to understand genotype/phenotype correlation in subpopulations/natural history
- Drug development pipeline may also enable targeting pre-symptomatic carriers or other subpopulations
- Clinical practice implications
  - Reducing time to diagnosis
  - Genetic testing
  - Genetic counseling
  - Observational studies to study symptomatic and pre-symptomatic cohort
EVOLVING DRUG DEVELOPMENT LANDSCAPE

Amyotrophic Lateral Sclerosis
Evolving Drug Development Landscape

A consensus committee comprising 140 key members of the international ALS community (ALS researchers, clinicians, patient representatives, research funding representatives, industry, and regulatory agencies)

- Preclinical Studies
- Biological/phenotypic heterogeneity
- Outcome measures
- Symptomatic/disease modifying tx
- recruitment/retention
- Statistical considerations
- Beyond clinical trials
- Clinical trial phases
- Biomarkers

Clinical Trial Guidelines for ALS
Evolving Drug Development Landscape

- 112 guidelines and their associated backgrounds and rationales were published

- The group prioritized 15 guidelines with the greatest potential to improve ALS clinical research

- The revised Airlie House ALS Clinical Trials Consensus Guidelines serve to help improve clinical trial design and accelerate the development of effective treatments for patients with ALS

Evolving Drug Development Landscape

Revised Airlie House consensus guidelines for design and implementation of ALS clinical trials

Leonard H. van den Berg, MD, PhD, Eric Sorenson, MD, Gary Gronseth, MD, Eric A. Macklin, PhD, Jinsky Andrews, MD, Robert H. Baloh, MD, PhD, Michael Benatar, MD, PhD, James D. Berry, MD, Adriano Chio, MD, Philippe Corcia, MD, PhD, Angela Genge, MD, Amelie K. Cubitz, PhD, Catherine Lomen-Hoerth, MD, PhD, Christopher J. McDermott, MD, Erik P. Pion, MD, PhD, Jeffrey Rosenfeld, MD, PhD, Vincenzo Silani, MD, Martin R. Turner, MBBS, PhD, Markus Weber, MD, Benjamin Rix Brooks, MD, Robert G. Miller, MD, Hiroshi Mitsumoto, MD, DSc, and for the Airlie House ALS Clinical Trials Guidelines Group

Evolving Drug Development Landscape

- From 2015 to 2018, there was a multi-stakeholder effort to develop a **Community Guidance** for drug development in ALS.

- The Food and Drug Administration (FDA) issued a **FINAL Drug Development Guidance** in 2019 to assist sponsors in the clinical development of drugs for the treatment of ALS.

- Specifically, this guidance addresses the FDA’s current thinking regarding the clinical development program and clinical trial designs for drugs to support an indication for the treatment of ALS.

Risk/Benefit Considerations:
“When making regulatory decisions about drugs to treat ALS, FDA will consider patient tolerance for risk, and the serious and life-threatening nature of the condition.”
INNOVATION AND COLLABORATIONS IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)
Moving Drug Development Forward for ALS
**GTAC**

**Genomic Translation for ALS Care**

- PI: Matthew Harms, MD matthew.harms@columbia.edu
- 13 sites in the United States and Scotland
- 1028 subjects enrolled (~1.5 new patients daily)
  - Longitudinal outcomes and phenotyping
  - Whole genomes + transcriptomes
  - pBMCs banked for iPSC work
- >900 new genomes analyzed and results returned
- Columbia IGM/GTAC: 6k ALS cases and 60k controls

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**GTAC Participating Sites**

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**ANSWER ALS**

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**CReATe Consortium**

- 20+ institutional members
- 15 clinical sites
- 4 PAG (patient advocacy group) partners
- 6 other strategic partners
Pooled Resource Open-Access ALS Clinical Trials Database

- Over 10,700 fully de-identified clinical patient records
- Placebo and treatment-arm data from 23 Phase II/III clinical trials
- Demographic, lab, medical and family history, and other data elements
- More than 10 million longitudinally collected data points

https://nctu.partners.org/ProACT/Home/Index
MASTER PROTOCOL
“N of 1” / Individualized Therapies

Milasen for Batten’s disease

- Feb 2019 - Clinical Diagnosis (FUS P525 was identified prior)
- March 2019 - Initiated discussion with collaborators to identify ASO, initiate testing, toxicology and manufacturing
- April 2019 - Initiated regulatory interactions
- May 2019 - Received permission to proceed
- June 2019 - First dose received
Lingering Questions with Individualized Therapies

- In these situations, What type of evidence is needed before exposing a human to a new drug? Even in rapidly progressing, fatal illnesses?
- What is the minimum assurance of safety that is needed?
- How persuasive should the mechanistic or functional data be?
- How should the dose and regimen be selected?
- How much characterization of the product should be undertaken?
- How should the urgency of the patient’s situation or the number of people who could ultimately be treated affect the decision-making process?
ALS Clinical Trials In The COVID Era

Primary Goal: to protect participants’ safety and to assess the effect of a study drug on ALS progression

Enabled learning how to adjust clinical trial protocols

• Virtual visits when in person is not possible
• Local/home collection of safety assessments (vitals, labs, EKG)
• Maintain study drug supply
• Remote collection of outcome measures (dynamometers, accelerometers, actigraphs and home spirometry)
• Telephone or telemedicine Visits

Andr

Open-label Study of Theracurmin: Piloting a Remote Clinical Trial in ALS

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Courtesy of PI: Dr. Richard Bedlack, Duke University

![Curcumin powder](image)
Concepts for Consideration in Drug Development for ALS

- For life threatening and serious diseases, the concepts that drive drug development
  - Speed
  - Innovation
  - Access

- Other important issues in drug development:
  - Patient voice
  - Data quality
  - Evidence generation

- Are there opportunities for efficiency in drug development?:
  - Expedited pathways with post-approval data
  - Innovative trial design including adaptive pathways and endpoint modification driven by patient focused drug development
  - Use of real-world evidence
Thoughts On Improving Clinical Trial Outcomes for ALS

- Need to focus on understanding the biological processes that trigger the disease and promote disease progression
- Facilitate the translation of genetic and cellular therapies into the clinic
- Develop effective high-throughput screening
- Refinement of clinical biomarkers and integration of biomarker discovery and validation in all trials
- Develop platforms for initial testing in small patient cohorts to identify a biological signal using biomarkers
- Develop patient stratification pathways that better reflect clinical populations
- Increase the use of self-reported patient outcomes
- Widen the use of multi-arm, multi-stage platform trials

Thank You!

**Eleanor and Lou Gehrig ALS Center**

Neil Shneider, MD, PhD  
Hiroshi Mitsumoto, MD  
Jinsy Andrews, MD, MSc  
Matthew Harms, MD  
Ikjae Lee, MD  
Elizabeth Harrington, MS, GC  
Julia Yasek, DNP  
Tara Charlton, LMSW  
Estephany Cabrera

**ALS Clinical Research Team**

Jessica Singleton, Research Mgr  
Sonya Aziz-Zaman, Asst Res Mgr  
Bri Dedi  
Meenakshi Rozenstrauch, MS  
Marie-France Likanje, MA  
Madison Gilmore  
Ben Hoover  
Sunil Jose, MBBS  
Simone Norris, MS

**ROAR Lab Collaborators**

Sunil Agrawal, PhD  
Hoahan Zhang, PhD

**ALS MDC Team**

Jessica Bottone, SLP  
Shayne Robinson, Dietitian  
Fondre Goulbourne, PT  
Matthew Ganulin, OT  
David Lasko, RT  
Madeline Ogust, RT

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**Project A.L.S.**

Finding & Funding a Cure for ALS

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Columbia University  
Irving Medical Center

MDA®

ALS Association  
Helping Cure Lou Gehrig's Disease
Session 1: Importance and Limitations of Basic and Preclinical Research

12:45pm – 1:40pm
Amelie Gubitz

Program Director, Division of Neuroscience
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Erin Fleming
Director of Research Operations
Project ALS
Michael Benatar
Professor of Neurology
Walter Bradley Chair in ALS Research
University of Miami
What are the challenges associated with validating biomarkers, and what approaches may support efficient biomarker validation?
What are the challenges associated with validating biomarkers, and what approaches may support efficient biomarker validation?
Discovery
• Establish proof of concept
• Clinical samples of convenience
• Begin defining context of use

Analytic Validation
• Pre-analytic considerations
• Assay performance characteristics
• Evaluate impact of potential confounding factors
• Refine context of use

Clinical Utility

Qualification

Assay Performance Characteristics
- Matrix effects
- Assay platform
- Analytic sensitivity
- Dynamic range
- Normal range
- Assay reliability
- Other: RT stability, freeze-thaw effects, diurnal fluctuation, etc.

Biomarker Development
Validation

Benatar, 2021

* Surrogate marker
Biomarker Development

Validation

Discovery
- Establish proof of concept
- Clinical samples of convenience
- Begin defining context of use

Analytic Validation
- Pre-analytic considerations
- Assay performance characteristics
- Evaluate impact of potential confounding factors
- Refine context of use

Clinical Utility
- Large, carefully-defined clinical cohort
- Well-defined SOPs
- Establish intended clinical use

Qualification
- Demonstrated clinical utility
- Written context of use
- FDA review for qualification

* Surrogate marker

Benatar, 2021
Context of Use

Diagnostic

Prognostic

Pharmacodynamic

Benatar, 2021
Approaches

• More nuanced understanding of biomarkers
  • Context-of-use
  • Surrogacy
• Close collaboration between discovery scientists and clinician investigators
• Resources: infrastructure, cohorts, funding
• Urgent unmet need: biomarkers of underlying biology
Lois Freed
Division Director
Division of Pharmacology/Toxicology, Office of Neuroscience
U.S. Food and Drug Administration
Session 1 | Discussion Questions

1. What innovative approaches are being taken to accelerate drug discovery in ALS (e.g., novel ways to identify potential druggable targets) and how can the research community benefit from continued investment in this work?

2. How can the predictive validity of disease models be improved to better support the conduct of clinical trials?

3. What are the challenges associated with validating biomarkers, and what approaches may support efficient biomarker validation?

4. What is the role of pre-competitive collaboration in helping to streamline and accelerate basic and preclinical ALS research?
Session 2: Considerations for Innovative Trial Designs

1:50pm – 2:55pm
Sabrina Paganoni
Co-Director
MGH Neurological Clinical Research Institute
HEALEY ALS Platform Trial

Sabrina Paganoni, MD, PhD

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

Sponsor Logos:
- Harvard Medical School
- Massachusetts General Hospital
- NEALS
- Barrow Neurological Institute
- UCB Pharma
- Biohaven Pharmaceuticals
- Clene Nanomedicine
- Prilenia
- SEELOS Therapeutics
- Berry Consultants
- MDA
- ALS Association
- The Arthur M. Blank Family Foundation
“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
Accelerating innovation for a cure

Merit Cudkowicz, MD, MSc
Sean M. Healey

Traditional Clinical Trial
vs.

HEALEY ALS Platform Trial

- Cuts time in 1/2
- Cuts costs by 1/3
- Reduces placebo by 1/3
Working with the entire ALS Community to launch the trial rapidly and efficiently

ALS Platform Trial
Industry Workshop

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

INDUSTRY
PATIENTS
SITES/INVESTIGATORS
FOUNDATIONS

FDA

54 TRIAL-READY SITES
1 Central IRB

NEALS Northwest Amyotrophic Lateral Sclerosis Consortium
CLINICAL OPERATIONS TEAM & KEY VENDORS

Marianne Chase  
MGH - Project Management

Alex Sherman  
MGH - Clinical Trial Systems

Hong Yu  
MGH - Data Management

Stacey Grabert  
MGH - Quality Assurance

Annette DeMattos  
MGH - Grants & Contracts

Megan Hall, Rebecca Randall & Gale Kittle  
BNI - Monitoring & Outcomes Training

Andrew McGarry, MD & Margherita Torti, MD  
Clintrx – Safety Monitoring

Patrick Bolger & Ahmed Fetouh  
CMSU – Central Pharmacy
Shared Infrastructure and Master Protocol Allow for Operational and Scientific Efficiencies

**Participant Flow**

- Enroll in HEALEY ALS Platform Trial
- Randomization

Shared infrastructure and Master Protocol, allowing sharing of placebo data

- Cuts time in 1/2
- Cuts costs by 1/3
- Reduces placebo

Regimen A
- Active
- Placebo

Regimen B
- Active
- Placebo

Regimen C
- Active
- Placebo
- Shared Placebo

Enroll in HEALEY ALS Platform Trial

Shared infrastructure and Master Protocol, allowing sharing of placebo data
The Platform Trial is Governed by a Master Protocol, a Common Protocol for Multiple Regimens

Key Master Protocol Elements:

- Target Population
- Endpoints
- Sample Size
- Treatment Duration
- Randomization Ratio
- Placebo Sharing
- Adaptive Features
- Perpetual Trial
Master Protocol – Schema for Each Regimen

<table>
<thead>
<tr>
<th>Screening Period</th>
<th>Treatment Period = 6 Months*</th>
</tr>
</thead>
<tbody>
<tr>
<td>~160 Randomized 3:1</td>
<td>~120 Participants on Active</td>
</tr>
<tr>
<td></td>
<td>~40 Participants on Placebo</td>
</tr>
</tbody>
</table>

* Double Blind Period followed by Open Label Extension
Master Protocol – Target Population

Key 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

* Selected based on extensive statistical modeling
Master Protocol – Endpoints

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

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

Safety Endpoints

Exploratory Endpoints
Exploratory Endpoints

Endpoint Development Engine

- DNA
- Neurofilaments
- Biomarkers (Blood, Urine, CSF)
- Speech Analysis
- Home Spirometry
Each Regimen is Described in a Regimen Specific Appendix, an Addendum to the Master Protocol

Regimen Specific Appendix Elements:

- Investigational Product Characteristics
- Dosage
- Route of Administration
- Safety Profile
- Additional Assessments, if any
- Additional Inclusion/Exclusion Criteria, if needed for safety
The HEALEY ALS Platform Trial is a Perpetual Adaptive Trial

Regimen A
- Screening
- 3:1 Randomization within each Regimen
- (n=160 for each regimen)
- 24 weeks on study drug (active:placebo = 3:1)

Regimen B
- 3:1 Randomization within each Regimen
- (n=120 for active drug; n=40 for placebo)

Regimen C
- 3:1 Randomization within each Regimen

Regimen D
- 3:1 Randomization within each Regimen

Zilucoplan
- Placebo

Verdiperstat
- Placebo

CNM-Au8
- Placebo

Pridopidine
- Placebo

Shared Placebo

Open Label Extension

Screening
Platform Trials Change the Pace of Drug Development

The HEALEY ALS Platform Trial:
- The first platform trial for ALS in the world opened in 2020
- Results for the first 4 investigational products are expected about one year after initial launch
- We expect to launch 2-3 new regimens each year

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

E-mail:
spaganoni@mgh.harvard.edu
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Melanie Quintana
Director and Senior Statistical Scientist
Berry Consultants
Efficiencies in Adaptive/Platform Trials

Melanie Quintana, PhD
Director & Senior Statistical Scientist
Berry Consultants
ALS Example: When will we find first effective therapy?

**Traditional Drug Development**
- Sequence of fixed 1:1 trials
- Each N=240 (120 vs. 120)
- Lag of 3 months between trials

**Adaptive Platform Trial**
- Perpetually enrolling max. of 3 regimens
- Max N=160 (120 vs. 40)
- Shared controls across regimens

*Assumes 10% of therapies tested are effective with a 30% slowing in rate of progression*
Adaptive/Platform Statistical Efficiencies

• **Shared controls** allow higher power with fewer participants on control

• **Adaptive features** allow us to screen more agents faster and quickly reject ineffective therapies
  - Shorter trial durations & fewer patients enrolled

• Careful considerations
  - Shared controls require *similar patient populations* & *robust analysis methods* that can adjust for potential differences across shared control
  - Pre-specification of adaptive rules with good operating characteristics -- *Simulate, simulate, simulate!*
Clinical Trial Simulation

- Understand operating characteristics of proposed design
- Optimize design under key trial parameters
- Quantify efficiencies
Jeremy Shefner
Kemper and Ethel Marley Professor, Chair of Neurology
Senior Vice President
Barrow Neurological Institute
Richard Bedlack
Director, Duke ALS Clinic
Professor of Neurology
Duke University
Virtual ALS Trials: 10 Lessons Learned and a Path Forward

Richard Bedlack MD PhD
Duke University
Outline

• Definition & examples

• 10 lessons I have learned so far about virtual ALS trials

• Where these can take us in the future
Definition

A virtual trial is one that evaluates the effects of a drug or device with few or no required in-person visits.

There are several recent examples in ALS:

- PLM Lithium Trial *(Nature Biotechnology 2011;29:411-414)*
- NIH HERV-K Suppression Trial *(NCT02437110)*
- R.O.A.R-Theracurmin trial *(NCT04499963)*
Lesson 1: There is a need for virtual trials (now more than ever!)

- Travel burdens for PALS can be enormous
  - *Amyotrophic Lateral Scler Frontotemp Degen* 2018;19:126-133
  - *Amyotroph Lateral Scler* 2010;11:502-507

- Travel burdens are one of the main reasons that patients decline to enroll in or drop out of trials
  - *Amyotroph Lateral Scler* 2010;11:502-507

- During a pandemic, in person visits can become unsafe or even impossible
  - Many traditional trials halted
Lesson 2: They can have better enrollment & retention rates than more traditional trials

<table>
<thead>
<tr>
<th>Trial Type</th>
<th>Enrollment Rate (patients/site/month)</th>
<th>Retention Rate (% of surviving patients who complete all visits)</th>
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Lesson 3: They can start and be completed faster and with less expense than more traditional trials

- PLM virtual trial of lithium started within 3 months of PNAS article, was completed 9 months later (NINDS lithium trial took more than a year to start, another year to get results)
- Lunasin trial (50 patients, 1-year f/u, clinical and biomarker outcomes) cost $250K (comparable traditional trials would cost 5-10x this much)
  - *Amyotroph Lateral Scler Frontotemporal Degener* 2019;20:285-293
Lesson 4: They can enroll a more “real world” population

• Traditional trials tend to enroll younger, healthier, faster progressing patients
  • Not representative of patients in ALS clinics *Neurology 2011;77:1432–7*

• Virtual trials can have wider range of ages, disease severity, progression *Amyotroph Lateral Scler Frontotemporal Degener 2019;20:285-293*
  • Ex. Lunasin trial had some patients with disease duration >10 years, several with NIV, trach, PEG
  • More similar to patients in clinics
  • Results more likely to generalize
Lesson 5: There are good existing options for efficacy measures

- **Patient "Perceived Effectiveness"**
  - Part of PLM (used in Lunasin and Theracurmin trials)

- **ALSFRS-R**
  - Primary in all 4 virtual trials
  - With training, can be accurately measured and recorded by patients
    (Amyotroph Lateral Scler Frontotemporal Degener 2019;20:285-293)
  - More frequent measurements can reduce noise, improve sensitivity
    (Ann Clin Transl Neurol. 2020 Jul; 7(7): 1148–1157)
Lesson 6: There are exciting emerging options for efficacy measures

- PLM “Thrive” questionnaire
  - Used in Theracurmin trial

- Home VC, home hand grip dynamometry, remote EIM, wearables, remote speech analytics
  - As with ALSFRS-R, more frequent measurements result in less noise, improved sensitivity (*Ann Clin Transl Neurol*. 2020 Jul; 7(7): 1148–1157)
Lesson 7: There are existing options for safety measures

• Patient “Perceived Side Effects”
  • Part of PLM, used in Lunasin and Theracurmin trials

• Coordinator telephone screening for adverse events
  • Used in Lunasin and Theracurmin trials

• Home blood draws
  • Used in HERV-K Suppression Trial

• But: I still feel more confident in safety monitoring when I can see and examine patients

Distribution of treatment overall side effects

Amyotroph Lateral Scler Frontotemporal Degener 2019;20:285-293
Lesson 8: There are good options for controls

• Historical (ex. PLM method)
  • For each treated patient, 3 controls matched according to pre-treatment ALSFRS-R progression (*Nature Biotechnology* 2011;29:411-414)
  • Used in PLM Lithium trial, Lunasin and Theracurmin trials


• Concomitant (used in part of Duke Theracurmin trial)
Lesson 9: PLM can be very helpful

- Existing infrastructure allows patients to enter ALFRS-R, perceived effectiveness, perceived side effects, perceived burdens, perceived adherence

- With more than 12,000 registered PALS contributing longitudinal data, great ability to generate matched historical controls

- Data publicly available throughout a trial

- Motivated and reliable partner in my Lunasin, Theracurmin trials
Lesson 10: Clinician oversight still needed

- Informed consent
- Diagnosis confirmation
- Outcome training
- Adverse event screening, classification, reporting
- Adherence/compliance monitoring, prompting

Figure 7. Adherence in participants versus those “playing along at home”. This figure shows that participant adherence (% completing at least 2 out of 3 PLM outcome measures) was high for the first 6 months of the study, then dropped off after that (solid line). On the other hand, a “play along at home” cohort (54 PLM users who started self-experimentation with Lunasin during our trial enrollment period) had much lower adherence (dashed line).
Future Directions

• Virtual trials cannot yet completely replace more traditional ones
  • Safety monitoring not as thorough

• Stand alone virtual trials best for studying GRAS products (ex. supplements)

• Virtual adjuncts to more traditional trials
  • Phase 4 trials
  • Expanded access programs of safe products
Philip Green
ALS Research Ambassador
Lei Xu
Chief of General Medicine Branch 2
Division of Clinical Evaluation and Pharmacology/Toxicology
U.S. Food and Drug Administration
Teresa Buracchio
Deputy Director
Division of Neurology 1
U.S. Food and Drug Administration
Session 2 | Discussion Questions

1. What steps can be taken to make therapeutic development for ALS more efficient while ensuring the collection of robust clinical data to support regulatory and clinical decision making?

2. What benefits can remote monitoring and decentralized trials bring to researchers and patients? What are the barriers to increasing the use of remote monitoring and decentralized trials?

3. What steps can be taken to increase patient enrollment in innovative clinical trials? What are successful examples of this? What are the barriers?

4. How can trials be designed to best support patient access and subgroup analysis?
Day 1 Adjournment & Day 2 Instructions

Mark McClellan, MD, PhD
Director, Duke-Margolis Center for Health Policy
Improving Basic Research, Clinical Trial Infrastructure, and Community Engagement to Support Drug Development for ALS

Day 2 – Thursday, January 28th

Virtual Private Workshop — January 27 & January 28, 2021
Welcome & Overview of Day 2

Mark McClellan, MD, PhD
Director, Duke-Margolis Center for Health Policy
Session 3: Research Infrastructure and Data Sharing for ALS

12:05pm – 1:05pm
Alexander Sherman
Director
Center for Innovation and Bioinformatics
MGH Neurological Clinical Research Institute
Research Infrastructure and Data Sharing in ALS

Center for Innovation and Bioinformatics
Neurological Clinical Research Institute
avsherman@mgh.harvard.edu
www.data4cures.org
January 28, 2021
Research Infrastructure for Big Data

Big Data Inventory
International inventory of Big Data resources in ALS https://www.data4cures.org/resources

Work Groups/Committees
Big Data Committees (Sustainability, Genomics, Biobanking, Imaging, and Data Access)

Collaborations in Patient Identification for Future Information Exchange
Utilizations of Unique Identifiers in basic research, clinical studies and trials

NeuroBANK® ALS Ecosystem
6051 pALS from 23 clinical studies, 80+ clinical sites, 14 countries, 108K+ vials of biofluids, 3.4K DNA samples

ALS/MND Natural History Consortium
Enrollment from 9 member-sites 1541 people with ALS/MND

ALS/MND Patient Portals (Patient-Reported Outcome Measures)
ALS Focus
Everything ALS

PRO-ACT/PRO-ACE
Pooled Resource Open-Access Clinical Trials/clinical rEsearch databases
The **BIG Data in ALS/MND** committee’s interests comprise broad spectrum of projects in supporting international patient-centric approaches in clinical research, from developing recommendations and specifications for existing and new regulatory-compliant platforms, to unique research participants’ identification, to identifying new sources of clinical and research data, to data capture, analyses, visualization, and distribution, to sharing best practices, research protocols, and research agreements.

Big Data Committees with national and international representation, focus on identifying global ALS resources, creating and promoting common practices and regulatory-compliant language, creating internationally-applicable SOPs for collection and sharing of information, and a single set of policies for data sharing addressing regulatory, IP, dissemination, and publication concerns:

- Sustainability
- Genomics
- Biobanking
- Imaging
- Data Access
## Big Data Inventory

https://www.data4cures.org/resources

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# Big Data Sustainability Committee

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<td>The ALS Association</td>
<td>Neil Thakur</td>
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<td>David Taylor</td>
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# Genomics Committee

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<td>Dr. Mathew Harms</td>
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<td>University of Massachusetts</td>
<td>Dr. John Landers</td>
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<td>Kings College</td>
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![Genomics Committee Members](image-url)
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NEALS ALS Consortium BioRepository

https://www.neals.org/for-als-researchers/neals-sample-repository/

Bob Bowser James Berry

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<td>Plasma</td>
<td>1706</td>
<td>63707</td>
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<tr>
<td>Serum</td>
<td>1735</td>
<td>19636</td>
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<tr>
<td>PBMC (iPSC)</td>
<td>2346</td>
<td>7203</td>
</tr>
</tbody>
</table>

Subjects Characteristics
- Subject Types:
  - Non-Neurologic Controls
  - Neurologic Controls (Non-ALS)
  - Asymptomatic ALS Genes Carrier
  - ALS
  - Sporadic ALS
  - Site of Symptom Onset:
    - Bulbar
    - Extremities
    - Both
    - Upper
    - Lower
  - Age at Symptom Onset (years):
    - From
    - To

Known Genetic Mutations:
- SOD1
- C9ORF72
- TDP43
- FUS
- Other

Subject's Sex:
- Male
- Female

Click here for Search User Manual

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Target ALS Human Postmortem Tissue Core

<table>
<thead>
<tr>
<th>Biospecimen</th>
<th># Participants</th>
<th># Samples</th>
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<tbody>
<tr>
<td>Post-mortem tissues</td>
<td>253 cases</td>
<td>~18K tissues</td>
</tr>
</tbody>
</table>

http://www.targetals.org/inventory_search.html

Lyle Ostrow  Manish Raisinghani
Collaborations in Patient Identification for Information Exchange

http://www.NeuroGUID.org

Neurological Global Unique Identifier

GUIDE your Neuro research with NeuroGUID™!

• The Center for Disease Control’s National ALS Registry generated 5K+ NeuroGUIDs /NeuroSTAmPs from pALS population with 10%+ having data in NeuroBANK-based studies

• Clinical Trials (Platform Trial, CENTAUR, VITALITY) utilize NeuroGUIDs/NeuroSTAmPs

• ALS Focus and EverythingALS patient platforms utilize NeuroSTAmPs for pALS, caregivers, and controls

• New York Genome Center and Institute of Genetic Medicine use NeuroGUIDs/ NeuroSTAmPs for DNA files identification

• NeuroGUID Platform was a 2020 Bio-IT World Innovative Practices Awards Winner as “outstanding example of how technology innovations and strategic initiatives can be powerful forces for change in the life sciences, from basic biomedical research to drug development and beyond”
NeuroBANK® ALS Ecosystem

Patients == Research Participant

Tools/Platforms

- NeuroGUID™: Neurological Global Unique Patient ID
- NeuroBANK®: Accelerated Research Environment
- NeuroBIO™: Distributed BioRepository
- NeuroPRO™: Patient-Reported Outcomes (Portal)
- NeuroCHARTS™: Analytical Tools

- EHR
- Observational Studies
- Bio Banks
- Image Banks
- PRO
- Genetics
- Omics
- Cell Lines
- Mobile Apps

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## NeuroBANK® ALS Ecosystem

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<th>#</th>
<th>Projects</th>
<th>CLN</th>
<th>CGN</th>
<th>NTR</th>
<th>BFL</th>
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<td>18</td>
<td>C9orf72 Genomic Assessment Protocol (C9GAP)</td>
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| TOTAL STUDIES | 22 | 7 | 2 | 15 | 2 | 3 | 11 | 8 | 5 | 2 | 4 | 3 |

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<th>Clinical and phenotypical data</th>
<th>CGN</th>
<th>Cognitive assessment</th>
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<th>Post-mortem tissues</th>
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<th>Imaging</th>
<th>DNA</th>
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<th>RNA</th>
<th>RNA</th>
<th>iPSC</th>
<th>Cell lines</th>
<th>EHR</th>
<th>EHR Integration</th>
<th>PRO</th>
<th>Patient-reported outcomes (PRO)</th>
<th>MOB</th>
<th>Integration with mobile apps</th>
</tr>
</thead>
</table>

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NeuroBANK® ALS Ecosystem

- **23** ALS-related research projects
- **83** participating sites from **14** countries with **436** NeuroBANK-trained personnel
- **6051** people with ALS and controls
- **493 (8.1%)** volunteers participate in more than one study
- **15** volunteers participate in **4+ (!), 6 in 5+ (!!), and 1 in 6(!!) research projects**
- **3392** DNAs samples collected for WGS
- **2346** PBMC samples collected for cell lines generation
- **253** cases of postmortem tissue collection (18K tissue samples)
- **108K+** vials of biofluids are in NeuroBIO™ virtual biobank

<table>
<thead>
<tr>
<th>Biofluid</th>
<th># Participants</th>
<th># Vials</th>
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<tbody>
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<td>10800</td>
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<td>CSF</td>
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<td>Plasma</td>
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<td>PBMC (iPSC)</td>
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<td>7203</td>
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<tr>
<td>Post-mortem tissues</td>
<td>253 cases</td>
<td>~18K tissues</td>
</tr>
</tbody>
</table>
REAL WORLD DATA

Patients == Research Participant

Tools/Platforms

- NeuroGUID™
  - Neurological Global Unique Patient ID
- NeuroBANK™
  - Accelerated Research Environment
- NeuroBIO™
  - Distributed BioRepository
- NeuroPRO™
  - Patient-Reported Outcomes (Portal)
- NeuroCHARTS™
  - Analytical Tools

EHR

Observational Studies

Bio Banks

Image Banks

PRO

Genetics

Oomics

Cell Lines

Mobile Apps
Welcome! Sign in or create your account

Your registered e-mail:

Password:

New User? Sign up new account

What is ALS Focus?
The ALS Association website
ALS Focus surveys to date

- **1500 Members** (pALS and Caregivers)
- **Survey on Insurance Needs and Financial Burdens**
  - N=419 people with ALS and caregivers
- ‘About Me’ **Demographics/Dx History** Survey
  - Ongoing
  - N≈1,000 people with ALS and caregivers
- **Survey on What Matters Most**
  - Based on ALS Health Index developed by Chad Heatwole at the University of Rochester
  - N≈685 people with ALS and caregivers
- **Health Status Survey**
  - Ongoing
  - N≈257 people with ALS
Sign in

Your registered e-mail:

Password:

Forgot Password?

New User? Sign up new account

EverythingALS is a patient-focused non-profit, part of Peter Cohen Foundation (PCF) 501(3)c organization.
Big Data and Machine Learning in ALS

- Negotiating with Data Donors
- El Escorial Criteria added
- Incorporated Neuraltus NP-001 Phase II trial’s dataset
- PRO-ACT 3-year grant funded by ALS Association

BRING YOUR TRIALS’ DATA TO PRO-ACT!!!

Impacts of PRO-ACT on ALS R&D

Scientific Benefits:
- Understanding of natural history and disease heterogeneity
- Novel biomarkers and pathways of disease
- 50+ papers and 100+ symposia abstracts

Clinical Development Benefits
- Simulations
- Test stratification theories
- Reduce costs of future ALS clinical trials
- Explore link between disease progression and medication use

Other Benefits
- Grow quantitative workforce with interest in/exposure to ALS data
Big Data and Machine Learning in ALS

PRO-ACE: Bring Your Own Data (BYOD)

4K+ patient-records from observational studies and clinical visits
Enrollment from 9 member-sites reached 1561 pALS/MND
Expanded Access Program in ALS

NeuroREACH™ EAP Platform

ALSFRS-R per patient

ALSFRS-R per question R3

ALSFRS-R per patient questions R1-R3 total

ALSFRS-R data table

SVC data table

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Jane Larkindale

Executive Director

Duchenne Regulatory Sciences Consortium; Rare Disease Cures Accelerator-Data and Analytics Platform

Critical Path Institute
The Rare Disease Cures Accelerator- Data and Analytics Platform (RDCA-DAP) is a neutral, independent data collaboration and analytics hub to promote the sharing of critically important data across rare diseases in order to accelerate the understanding of disease natural history and optimize clinical trial design.
Paul Mehta
Principal Investigator
National ALS Registry
Centers for Disease Control and Prevention
National ALS Registry Overview

Data for Advancing ALS Research
Neil Thakur  
Chief Mission Officer  
The ALS Association
Carolina Mendoza-Puccini
Program Officer, Division of Clinical Research
National Institute of Neurological Disorders and Stroke
National Institutes of Health
NINDS CDE Project

- A repository of validated instruments
- Readily available Case Report Forms (CRFs) for documentation
- Readily available data dictionaries to be uploaded into electronic data capture systems
- Open-Access for the scientific community (NIH and non-NIH funded)

Use of CDEs at NINDS
For NINDS grants:
- Phase 2-3 Trials, Epi studies
- Built into NoA milestones

Funding Opportunities
NIH
NLM
ODSS

ALS Data
- CReATe
- dbGaP
- NINDS Archived Clinical Research Datasets

NIH Data Sharing Policy (2003)
- Final research data
- $500,000 or more in DC in any year of the proposed project period
- Funding Institute additional requirements

New DS Policy (eff. Jan 2023)
- Data management and sharing plan
- NIH IC additional requirements

www.commondataelements.ninds.nih.gov
Session 3 | Discussion Questions

1. What are the barriers to data sharing in clinical research for ALS and how can research consortiums and funders facilitate open data exchange?

2. How can researchers and trialists maximize the interoperability of data collected as part of preclinical studies and clinical trials for ALS?

3. How can data sharing policies for federally funded research maximize the scientific value of clinical data collected as part of ALS trials?

4. What other mechanisms are needed to increase effective collaboration and minimize competition in ALS research?
Session 4: Understanding What is Meaningful for Patients - Recruitment, Patient Experience Data, and Expanded Access

1:05pm – 2:05pm
Fernando Vieira
Chief Scientific Officer
ALS Therapy Development Institute
Understanding What is Meaningful to pALS
Understanding What is Meaningful to pALS

Our personal background surveys explore four broad domains:

- Lifestyle
- Medical History
- Occupation
- Participants’ experiences with ALS
Understanding What is Meaningful to pALS

Key learnings regarding what is meaningful for patients:

- Cast a wide net to collect information.
- Participants appreciate participating from home.
- Participants appreciate access to their data.
- Participants are motivated by interaction with people who interface with their data.
Sandy Morris
ALS Patient Advocate
I AM ALS
Developing the PaCTD Rating System

- I AM ALS Clinical Trials Team created the Patient-Centric Trial Design (PaCTD) Rating System.

- Overarching Goal:
  - Partnership between patient and sponsor to create humane & efficient trials that will increase ROI. Key elements include:
    - Patient-centricity in design
    - Align with the FDA’s 2019 *Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry.*
The PaCTD Criteria

1. Optimizes access to investigational therapies (60%). This category addresses whether a trial includes:
   ○ Open-Label Extension
   ○ Minimal placebo usage
   ○ An Expanded Access Program

2. Advances scientific progress (30%). This category addresses whether a trial includes the following elements:
   ○ Consideration of disease heterogeneity
   ○ Use of scientifically-justified eligibility criteria
   ○ Investigation of one or multiple biomarkers
   ○ Independent unblinded review panel

3. Is patient friendly (10%). This category addresses whether a trial includes the following elements:
   ○ Use of run-in observation period
   ○ Reduces travel burden by use of novel methods
Weighting of the Nine Trial Elements

- Prioritization matrix
  - Twelve members participated in the exercise to determine priority of the nine criteria using the prioritization matrix.

- Method
  - Criteria #1 was compared to Criteria #2, asking the question, "Is Criteria #1 of more, equal, or lesser value than Criteria #2?"
  - A score of “10” was given if the evaluator thought that Criteria #1 was "much more value" than #2.
  - A score of “5” was given for "more value" and a score of “1” for "equal value."
  - If the criteria was deemed "less value" a score "0.2" was given and for "much less value" a score “0.1” was given.
  - This process continued by comparing Criteria #1 to each subsequent criteria items 2-9 on the clinical trial ratings priority list.
  - This process was replicated for each subsequent criteria element down the list.
  - The results from all twelve participants were aggregated into the final priority list based on score. And informed how much weight should be allocated to each criteria.
The PaCTD Ratings

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<tr>
<th>PaCTD Rating*</th>
<th>Drug/Treatment</th>
<th>Sponsor</th>
<th>Country</th>
<th>Recruitment Status</th>
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<td>MGH</td>
<td>USA</td>
<td>Recruiting</td>
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<td>NurOwn</td>
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<td>USA</td>
<td>Not Recruiting</td>
</tr>
</tbody>
</table>
Paul Melmeyer
Director of Regulatory Affairs
Muscular Dystrophy Association
Kristina Bowyer
Vice President
Patient Centric Drug Development
Ionis
A commitment to science, to medicine and to patients

January 28, 2021
Kristina Bowyer,
VP Patient Centric Drug Development
Clinical trials have greater chance of success through:

- Understand Patient Needs
- Interconnect Science and the Need
- Improved Study Design
- Meaningful Clinical Endpoints
- Important Patient Benefits
- Patient Wellness & Quality of Life
thank you

love

hope
Julia Tierney
Chief of Staff
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
Session 4 | Discussion Questions

1. How can researchers better engage patients in the design of clinical trials?

2. How do researchers balance the needs of a trial while minimizing the burden on patients?

3. What are the barriers to the development and validation of novel endpoints that correlate to clinically meaningful benefits for ALS patients?

4. How can qualitative research contribute to improved patient-informed endpoint development?

5. What role can digital tools play in complimenting data collected thought traditional clinical outcome assessments, including patient-reported outcomes (PROs)? How can patients and their caregivers play a role in collecting patient experience data that can inform ALS drug development?

6. What are the key considerations for the development and implementation of expanded access programs that allow access to therapeutics outside of traditional clinical trials?
Session 5: Coordination, Collaboration, and Shared Strategy

2:15pm – 3:25pm
Merit Cudkowicz
Chief of the Neurology Service
Director, Sean M. Healey & AMG Center for ALS
Massachusetts General Hospital
Toby Ferguson
Head of the Neuromuscular Development Unit
Biogen
Bryan Traynor

Neurologist & Senior Investigator
National Institute on Aging
National Institutes of Health
Richard White
Policy Analyst
National Organization for Rare Diseases
Wilson Bryan

Director
Office of Cellular, Tissue, and Gene Therapies
U.S. Food and Drug Administration
Eric Bastings
Deputy Director, Office of Neuroscience
Acting Director, Division of Neurology 1, Office of Neuroscience
U.S. Food and Drug Administration
Session 5 | Discussion Questions

1. What are the next steps to accelerate ALS drug development? How do you envision the role of patient, industry, research, and regulatory stakeholder groups in advancing drug development?

2. To what extent is ALS research siloed and/or unnecessarily duplicative? If this is a problem, how can it be addressed?
Closing Remarks & Meeting Adjournment

Mark McClellan, MD, PhD
Director, Duke-Margolis Center for Health Policy
Thank You!

Contact Us

healthpolicy.duke.edu

Subscribe to our monthly newsletter at dukemargolis@duke.edu

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Washington, DC 20004

DC office: 202-621-2800
Durham office: 919-419-2504

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