CHANGING LANDSCAPE OF THERAPEUTIC DEVELOPMENT FOR GENETIC ALS & ALL ALS

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Massachusetts General Hospital

Harvard Medical School, Boston, MA

2023 South Florida Neuroscience Symposium |Fort Lauderdale | June 10, 2023

AGENDA

1. Approval of the first gene targeted therapy for ALS
2. Current clinical trials for ALS
3. Healey ALS Platform Trial for all ALS
4. New era of Expanded Access Protocols (EAPs) in ALS

APPROVAL OF THE FIRST GENE TARGETED THERAPY FOR ALS

Tofersen for SOD1(+) ALS

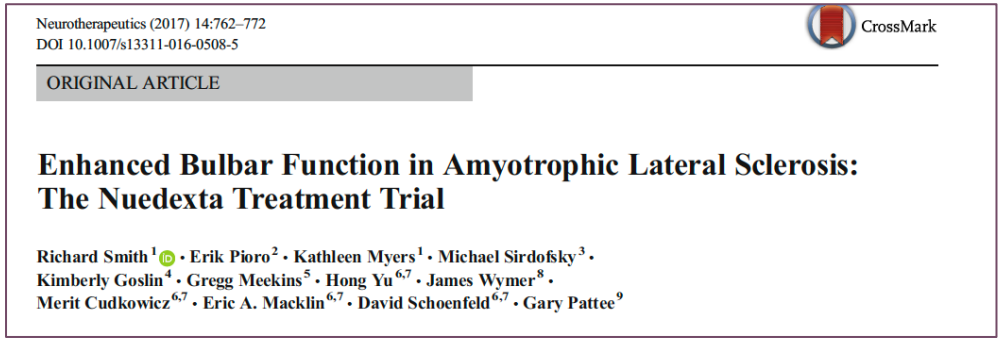
STANDARD OF CARE TREATMENTS FOR ALL ALS

- Riluzole 9% longer survival; Early initiation and long-term treatment offers greater benefit. [1995]
- Edaravone 33% slowing [2017 IV, 2022 Oral]
- Sodium PB/TURSO 25% slowing on top of riluzole and/or edaravone [2022]
- Dextromethorphan/Quinidine –symptomatic benefit for PBA symptoms. [2010]

Andrews JA 2020; Mandrioli 2018, Edaravone Writing Group May 2017, Paganoni 2020

STANDARD OF CARE TREATMENTS FOR ALL ALS

- Dextromethorphan/Quinidine capsules – Two recent trials show benefit for bulbar symptoms



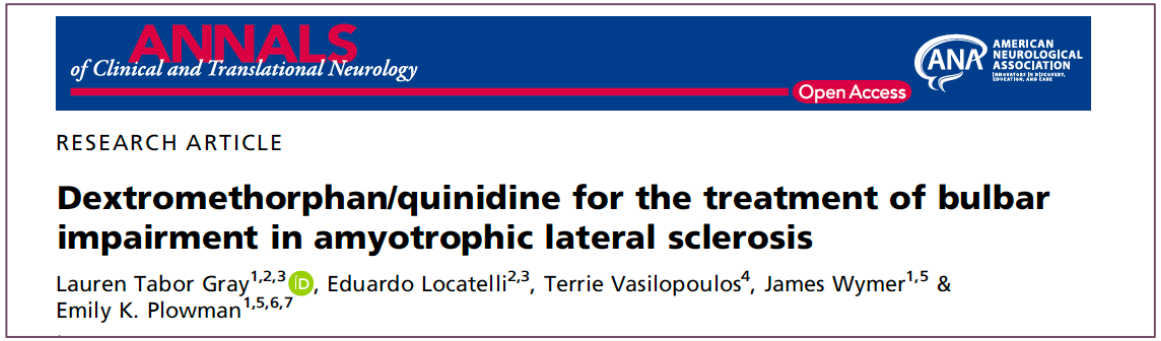
Neurotherapeutics (2017) 14:762–772
DOI 10.1007/s13311-016-0508-5

CrossMark

ORIGINAL ARTICLE

Enhanced Bulbar Function in Amyotrophic Lateral Sclerosis: The Nuedexta Treatment Trial

Richard Smith[1] · Erik Pioro[2] · Kathleen Myers[1] · Michael Sirdofsky[3] · Kimberly Goslin[4] · Gregg Meekins[5] · Hong Yu[6,7] · James Wymer[8] · Merit Cudkowicz[6,7] · Eric A. Macklin[6,7] · David Schoenfeld[6,7] · Gary Pattee[9]



ANNALS of Clinical and Translational Neurology

Open Access

ANA AMERICAN NEUROLOGICAL ASSOCIATION

RESEARCH ARTICLE

Dextromethorphan/quinidine for the treatment of bulbar impairment in amyotrophic lateral sclerosis

Lauren Tabor Gray[1,2,3], Eduardo Locatelli[2,3], Terrie Vasilopoulos[4], James Wymer[1,5] & Emily K. Plowman[1,5,6,7]

Andrews JA 2020; Mandrioli 2018, Edaravone Writing Group May 2017, Paganoni 2020

TOFERSEN FOR SOD1 POSITIVE ALS

ASO gene targeted therapy administered intrathecally (via spinal taps) and on a monthly basis, indefinitely

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

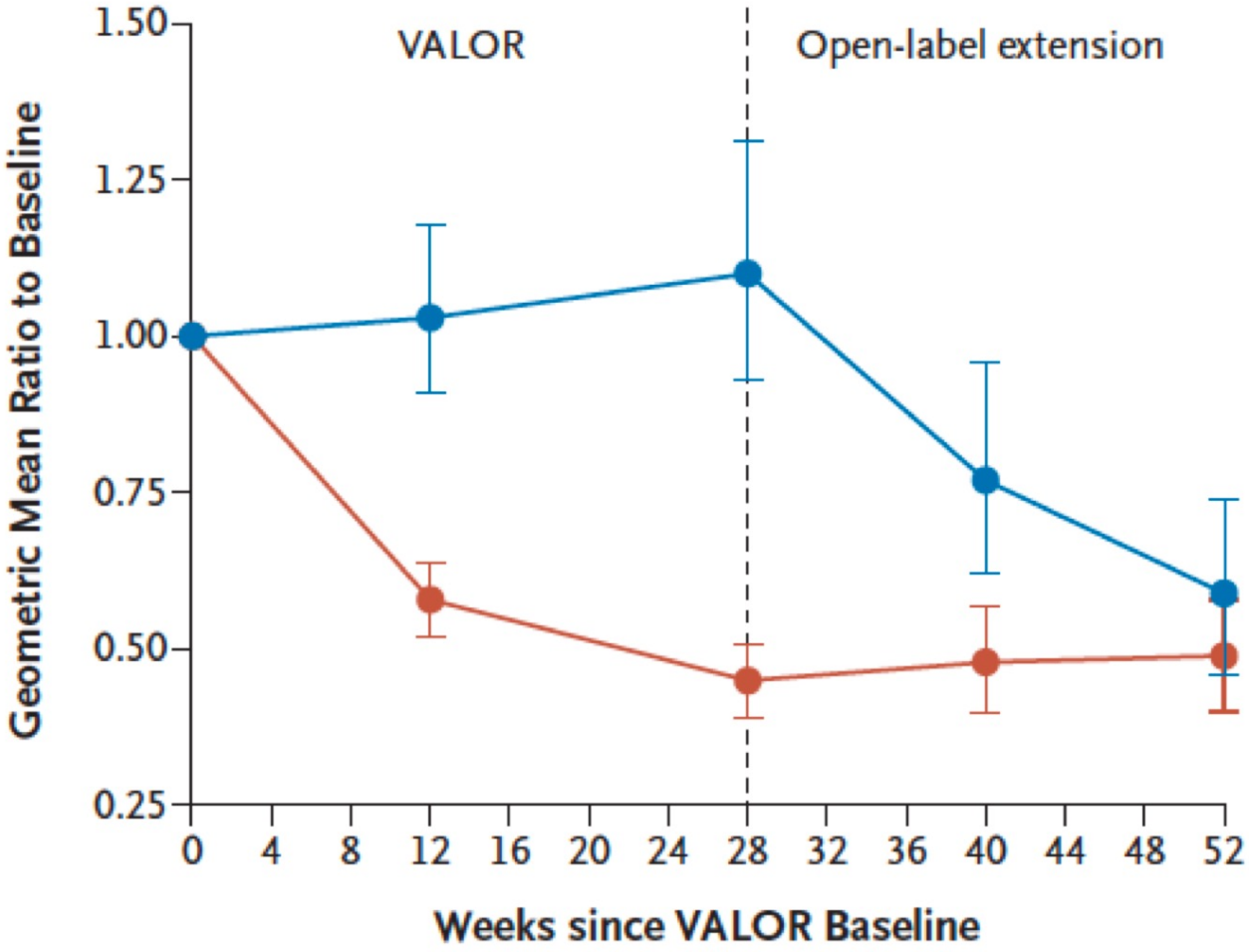
STANDARD OF CARE FOR SOD1(+) ALS (AS OF APRIL 25, 2023)

- Riluzole 9% longer survival; Early initiation and long-term treatment offers greater benefit.
- Edaravone 33% slowing
- Sodium PB/TURSO 25% slowing on top of riluzole and/or edaravone
- Dextromethorphan/quinidine – Symptomatic benefit for PBA. One trial shows benefit for bulbar symptoms.
- Tofersen is for SOD1 genetic form of ALS only!

Andrews JA 2020; Mandrioli 2018, Edaravone Writing Group May 2017, Paganoni 2020, Miller T et al, 2022

STUDY RESULTS LEADING TO ACCELERATED APPROVAL

B Concentration of NfL in Plasma



The NEW ENGLAND JOURNAL of MEDICINE

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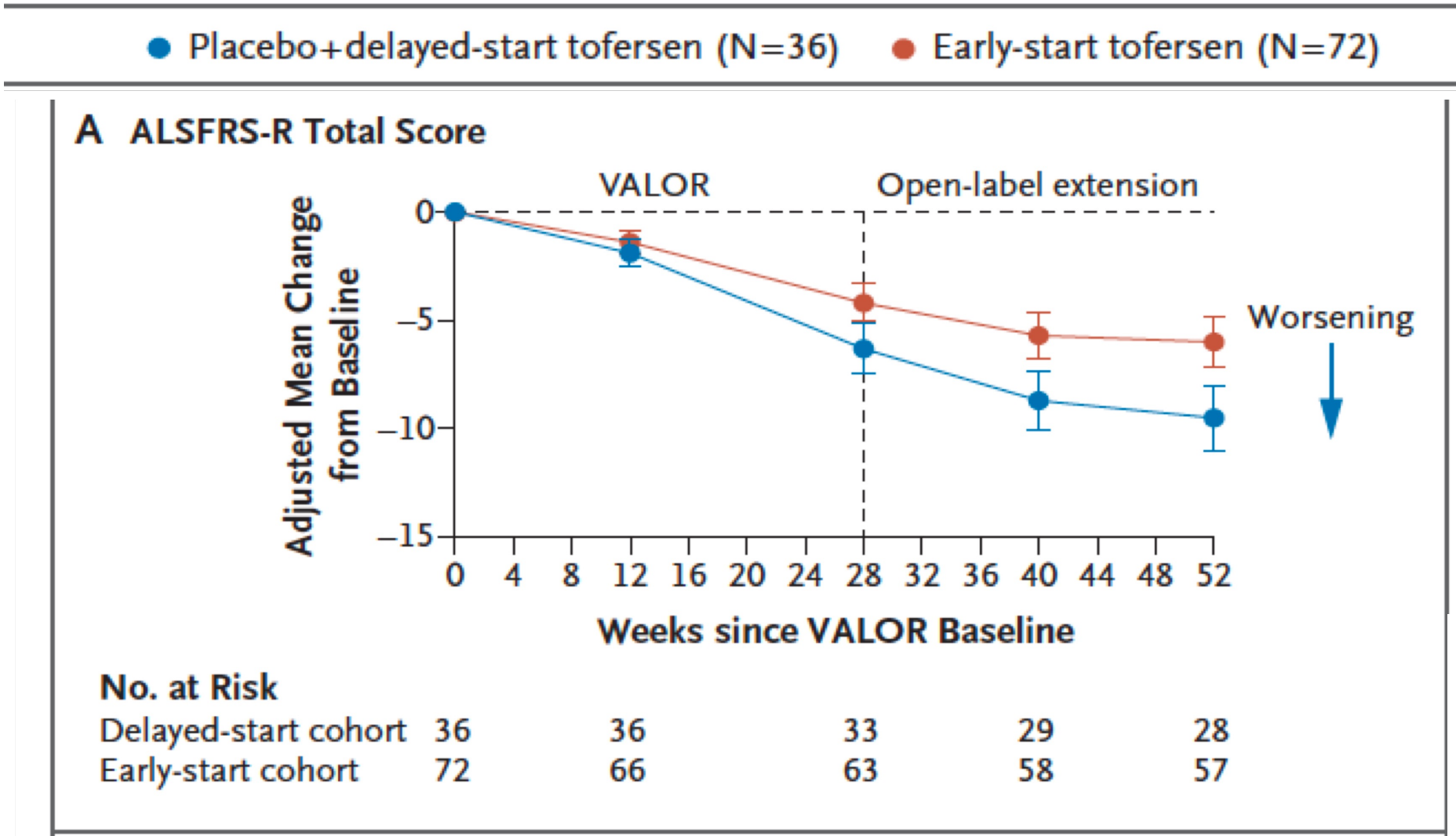
Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS

T.M. Miller, M.E. Cudkowicz, A. Genge, P.J. Shaw, G. Sobue, R.C. Bucelli, A. Chiò, P. Van Damme, A.C. Ludolph, J.D. Glass, J.A. Andrews, S. Babu, M. Benatar, C.J. McDermott, T. Cochrane, S. Chary, S. Chew, H. Zhu, F. Wu, I. Nestorov, D. Graham, P. Sun, M. McNeill, L. Fanning, T.A. Ferguson, and S. Fradette, for the VALOR and OLE Working Group*

STUDY RESULTS LEADING TO APPROVAL



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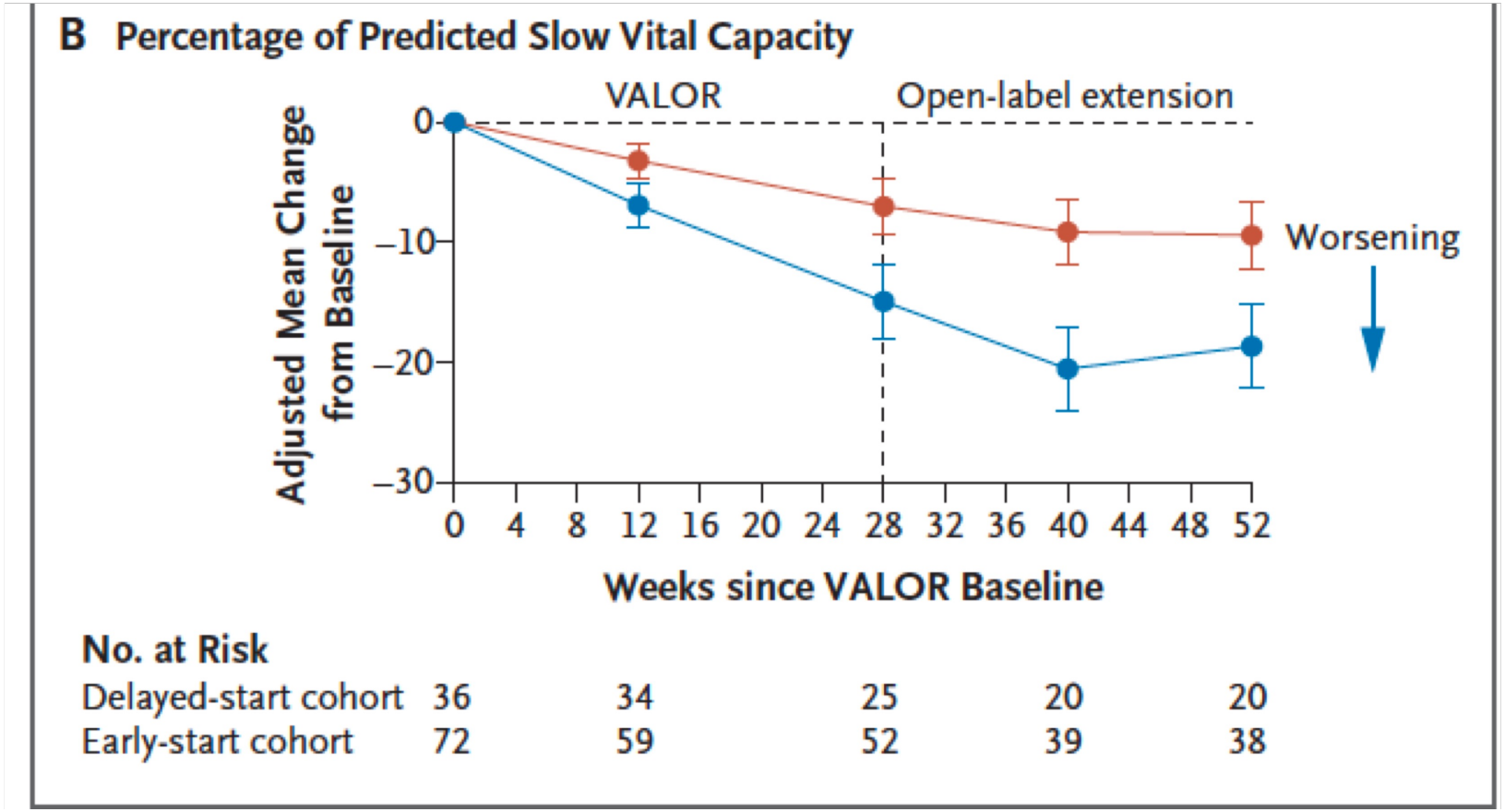
STUDY RESULTS LEADING TO APPROVAL

● Placebo+delayed-start tofersen (N=36) ● Early-start tofersen (N=72)



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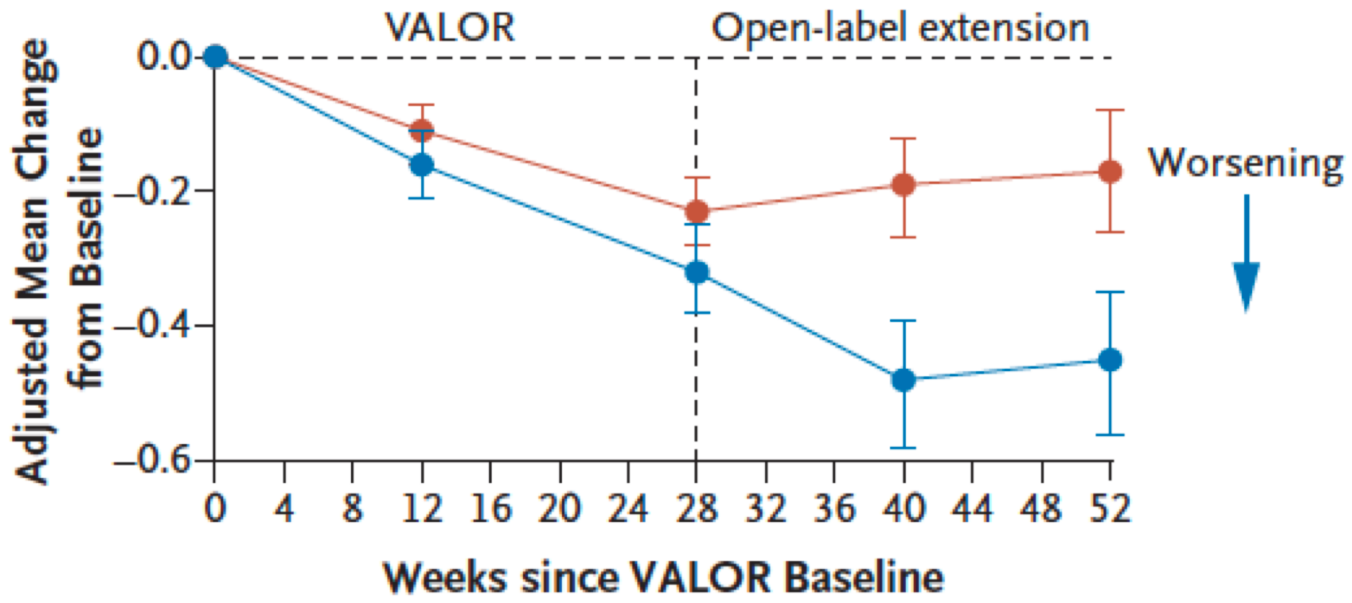
C Handheld Dynamometry Megascore



No. at Risk

Delayed-start cohort	36	35	27	24	25
Early-start cohort	72	64	58	47	42

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SAFETY PROFILE OF TOFERSEN

- Common side effects: Mild and related to LP/spinal tap (back soreness, headaches, muscle aches), CSF lab abnormalities, fatigue
- Rare (but serious) side effects: CNS inflammation (Chemical meningitis, transverse myelitis, radiculitis), intracranial hypertension (IIH) and papilledema (Swelling in the back of the eye, near the optic disc)

THINGS TO KNOW ABOUT QALSODY (TOFERSEN)

- “Accelerated approval” status based on reduction in plasma neurofilament light chain (NfL) with tofersen
- “Continued/Full approval” contingent upon verification of clinical benefit in confirmatory trial(s) [The ongoing ATLAS trial for asymptomatic gene carriers will serve as the confirmatory trial]

- LOADING PERIOD: BIWEEEKLY X3 | MAINTENANCE PERIOD: MONTHLY & INDEFINITELY

- ROUTINE SAFETY LABS & MONITORING FOR EVERY DOSING VISIT, AS PER YOUR CLINIC’S LP GUIDELINES

NEXT STEPS FOR CLINICAL ACCESS TO TOFERSEN

YOUR INVOLVEMENT:

Step 1 [PATIENT/ALS Neurologist]: Discuss whether patient qualifies for the medication (genetic testing must be positive for SOD1 and must have ALS)

Step 2a [PATIENT and ALS Neurologist]: Send a completed and signed START FORM & Insurance Card to Optum Frontier specialty pharmacy.

Step 2b [PATIENT and ALS Neurologist]: Clinic completes the Insurance PA. Send clinical progress notes, letter of medical necessity, genetic test results (and anything else insurance requires) to patient's insurance to initiate the Prior Authorization

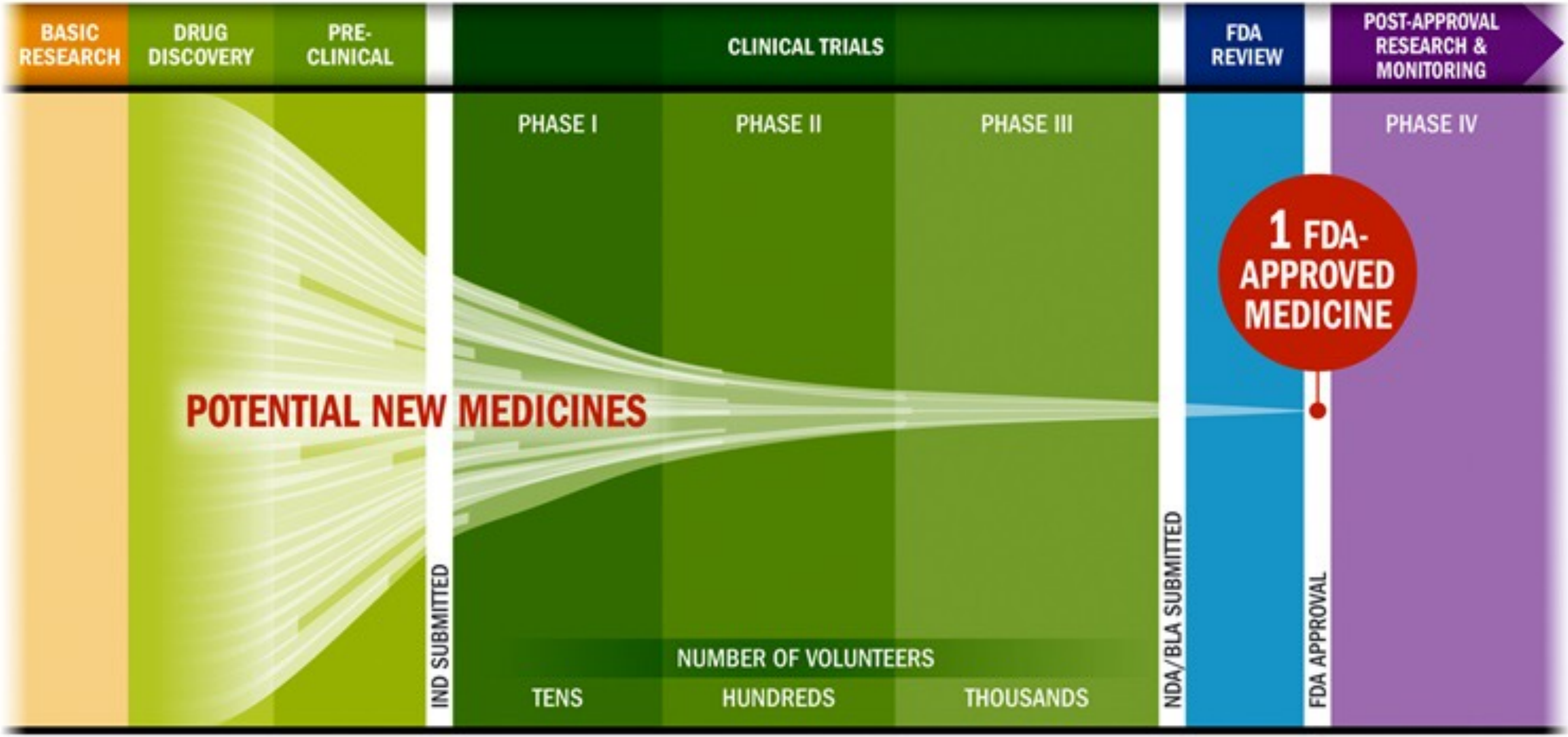
Step 3 [PATIENT and Biogen]: Once the START FORM has been received by company, patient will be contacted by a tofersen Lead Case Manager (LCM) to help navigate the process

Step 4 : Once the insurance PA approved, ALS clinic and patient will coordinate the dosing visit and complete any copays

PENDING STEPS FOR CLINICS AND INSURANCE

- Tofersen needs to be added to clinic formulary & contracts need to be completed with specialty pharmacy
- Establishing clinic, insurance and specialty pharmacy workflows

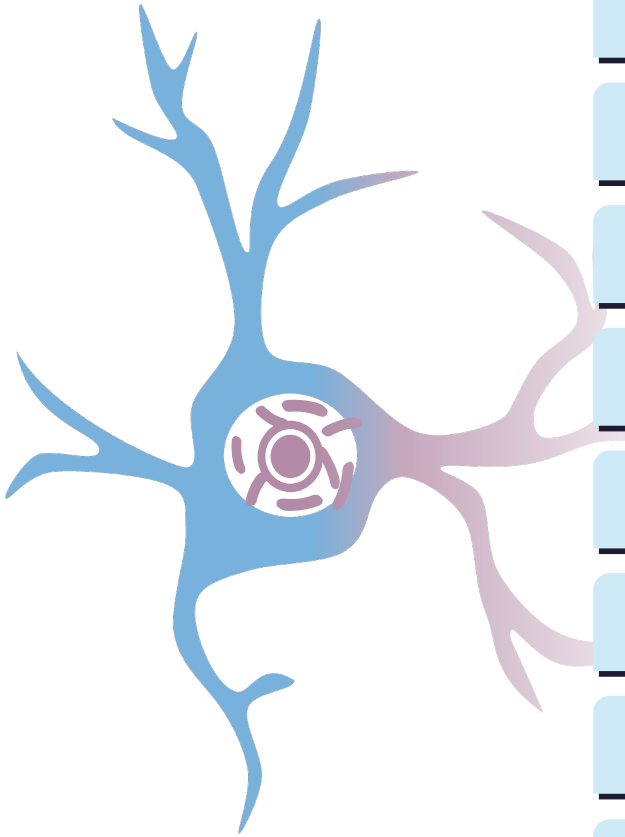
CURRENT CLINICAL TRIALS & EXPANDED ACCESS PROGRAMS FOR ALL ALS



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

Multiple cellular mechanisms identified for ALS and multiple druggable targets available for drug development



- Genetic abnormalities causing protein aggregates[1,2]
- Oxidative stress[3-5]
- Axonal degeneration[6,7]
- Aberrant mRNA processing & transport[8,9]
- Neuroinflammation[10,11]
- Synaptic dysfunction[12,13]
- ER stress[2,14]
- Mitochondrial dysfunction[15,16]

Motor Neuron damage in Brain and Spinal Cord

1. Chung, 2018; 2. Edenharter, 2018; 3. Chen, 2012; 4. Hardiman, 2017; 5. Cunha-Oliveria, 2020; 6. Fischer, 2007; 7. Brunden, 2017; 8. Liu, 2017; 9. La Rosa P, 2020; 10. Stephenson, 2018; 11. Liu, 2017; 12. Wishart, 2006; 13. Ling, 2020; 14. Lindholm, 2006; 15. Johri, 2012; 16. Manfredi, 2016.

CLINICAL TRIALS AT MGH: WITHOUT 36-MONTH DISEASE DURATION CRITERIA

All ALS

- ❑ BLZ945

(Phase 2, Enrolling)

- ❑ RAPA-501

(Phase 1, Enrolling)

- ❑ BIIB105

(Phase 1, Active, Cohort based enrollment for sporadic ALS)

Genetic ALS only

- ❑ BIIB105

(ATAXIN2 positive ALS- Phase 1, Active, Cohort based enrollment)

- ❑ ION-363

(FUS ALS–Phase 1-3, Cohort Based Enrollment)

- ❑ Tofersen ATLAS trial

(Phase 3 trial for Presymptomatic SOD1 gene carriers)

ALLOWS > 36-MONTH DISEASE DURATION

BLZ945

- Oral capsules, 800mg x 3 months, followed by 6 month OLE
- 3 PET scans or LPs to measure effect on reducing inflammation
- No placebo, Phase 2 trial
- Potent anti-inflammatory medication CSF-1R inhibitor
- US and European sites (Currently 6 sites, more sites are being added)
- SVC≥ 60%
- Disease duration <48 months
- Gtube/NIV/Trach allowed
- 3-month stable dose of riluzole, edaravone and PB/TURSO
- Antidepressants exclusionary due to DDI

RAPA-501

- IV infusion, Cell-based therapy
- Autologous Regulatory T cell infusion
- Apheresis procedure will be used to collect immune T cells, used to expand Reg T and helper T cell population and infused back
- Cohorts 1 &2: 4 infusions
- Cohort 3: 4 cycles x 6 infusions
- 2 sites- MGH & Hackensack University Medical Center
- SVC ≥50%
- No disease duration cutoff
- G-tube/NIV/Trach allowed
- 30-day stable dose of riluzole and/or edaravone

ASO/GENE THERAPY TRIALS

BIIB105 (Intrathecal)

- Parallel cohorts for ataxin2 als and sporadic ALS
- For SPORADIC ALS (2:1, SVC ≥60%) & for ATAXIN-2 ALS (3:1, SVC ≥50%)
- 7 month long RCT followed by OLE
- 13 sites
- No Ports/PICC lines allowed
- 60-day stable dose of edaravone, 30-day stable dose of riluzole |
- Sodium PB/TURSO NOT ALLOWED IN RCT, but can start in OLE
- Poorly controlled diabetes excluded

ION-363 (Intrathecal)

- Only for FUS+ ALS
- Randomization ratio 2:1 drug to placebo, SVC ≥ 50 %
- 7 intrathecal doses over 14 months, followed by OLE
- 14 sites, FRS slope for various age-based stratification cohorts
  - For cohort A, slope ≥ 0.4/month if 30-65. If < 30, no slope requirement
  - For cohort B, must be >30 years old and slope <0.4/month
- No ports/picc/ anticoagulants
- 28-day stable dose required (at screening) of edaravone, riluzole, Sodium PB/TURSO

PHOENIX, A GLOBAL PHASE 3 TRIAL OF AMX0035 IS NEARING COMPLETION IN EUROPE

PHOENIX

600 participants
48 weeks

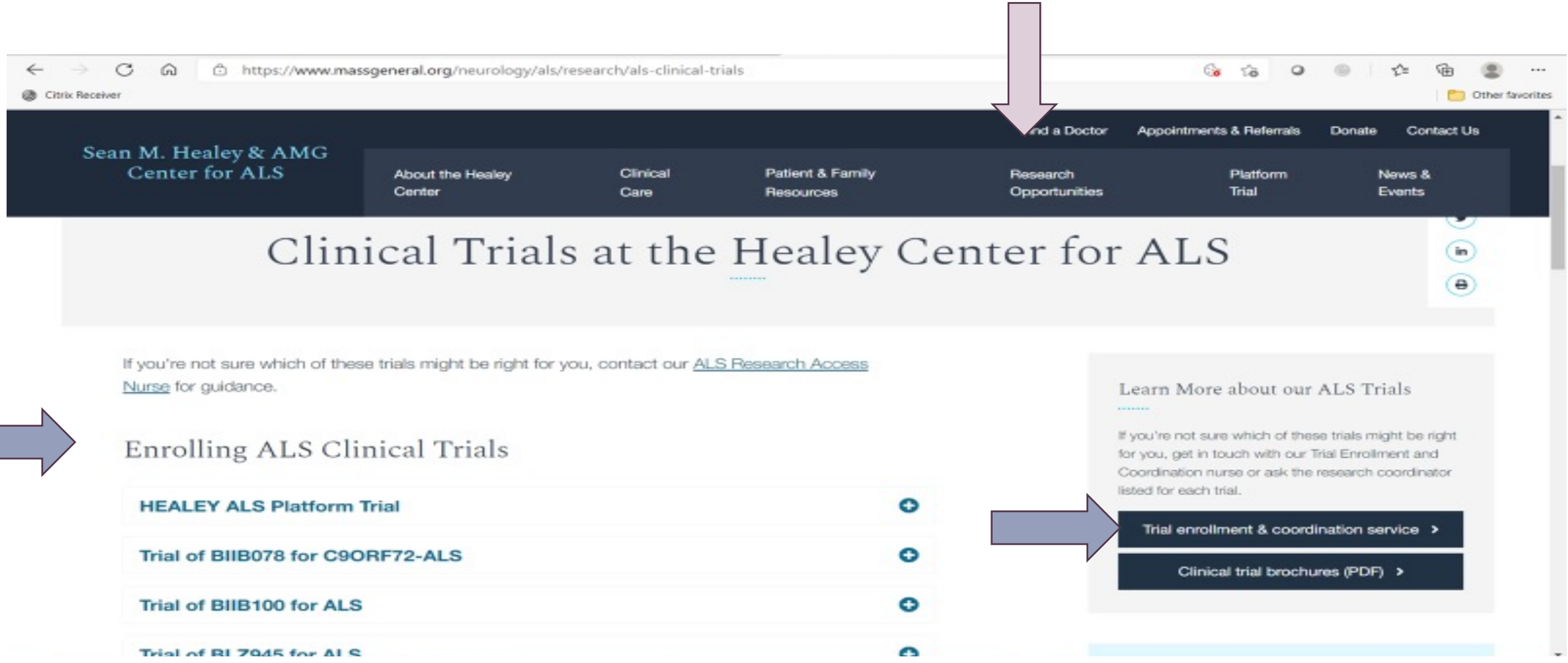
- Definite or probable ALS
- <24 months from onset
- VC > 55%

- Physical function (ALSFRS-R)
- Survival
- Respiratory function
- Time to key events (hospitalization, feeding tube, BiPAP)
- Quality of Life
- Time to transition through ALS stages
- Impact on Caregivers

ENCALS
European Network to Cure ALS

NEALS
Northeast Amyotrophic Lateral Sclerosis Consortium

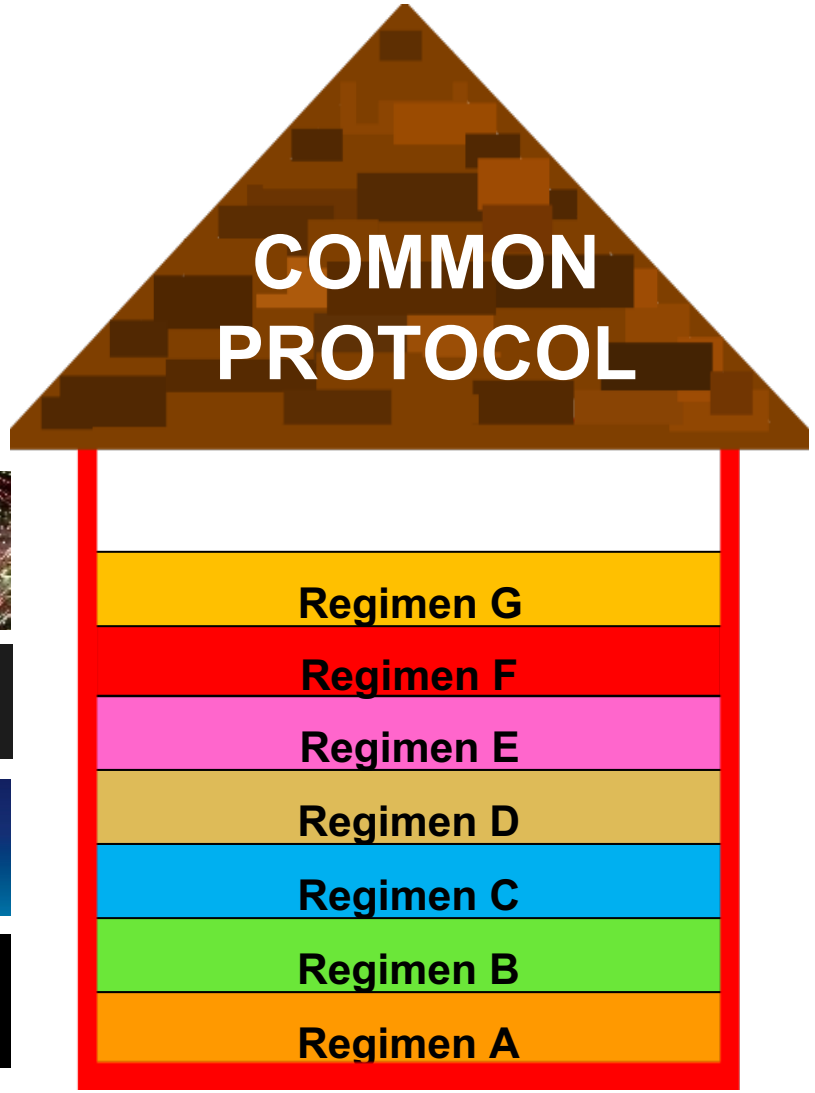
CLINICAL TRIALS AT THE HEALEY CENTER, MGH – *HTTPS://WWW.MASSGENERAL.ORG/NEUROLOGY/ALS/RESEARCH/ALS-CLINICAL-TRIALS*



THE HEALEY ALS PLATFORM TRIAL

HEALEY ALS Platform Trial- grounded in collaboration

Launched in 2020 – Continues to expand



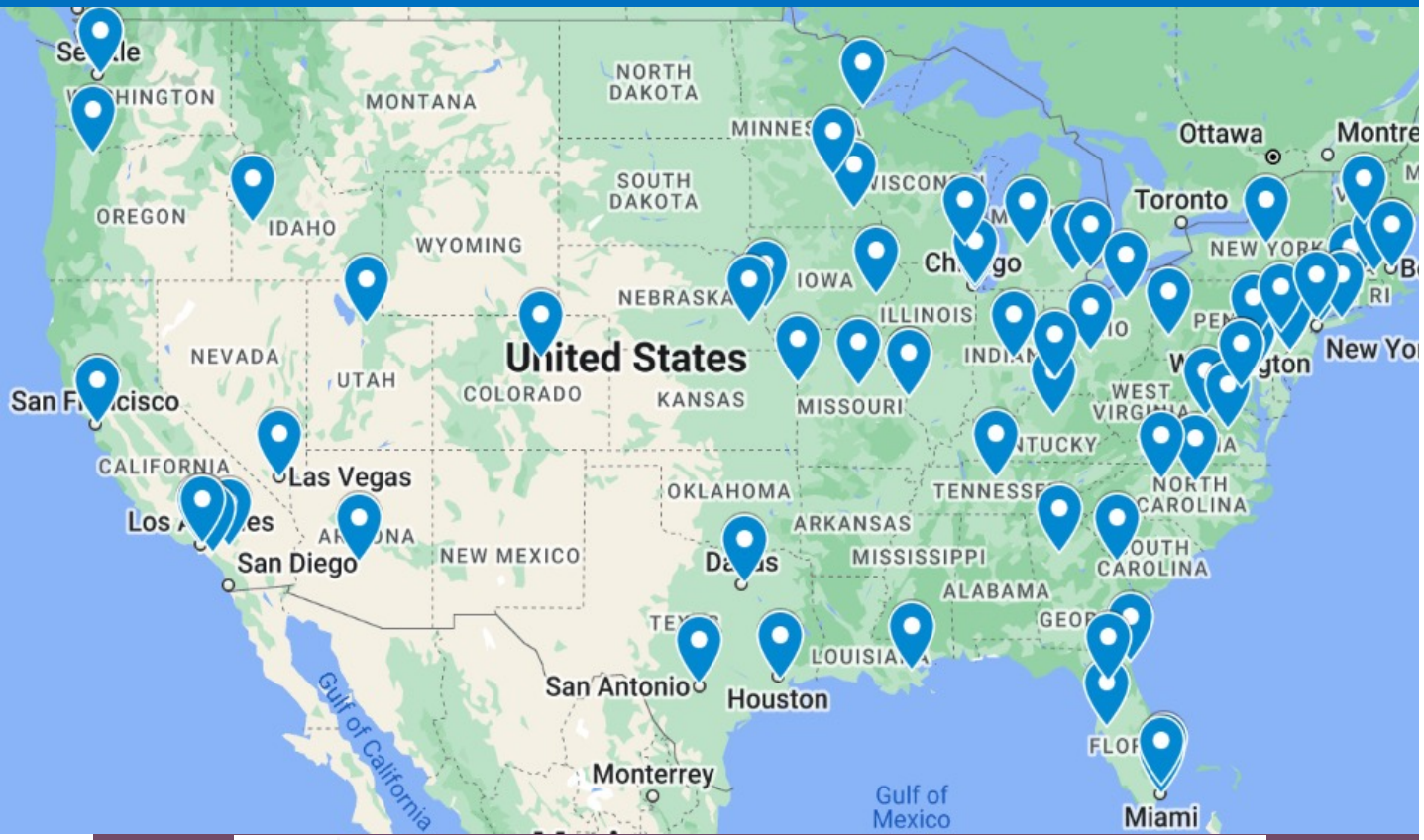
1 Protocol
(Phase 2/3)
1 single IRB
Central Governance

7 Regimens
70+ Enrolling Sites
~1300 Participants

Regimen: Active Study Drug + Matching Placebo

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

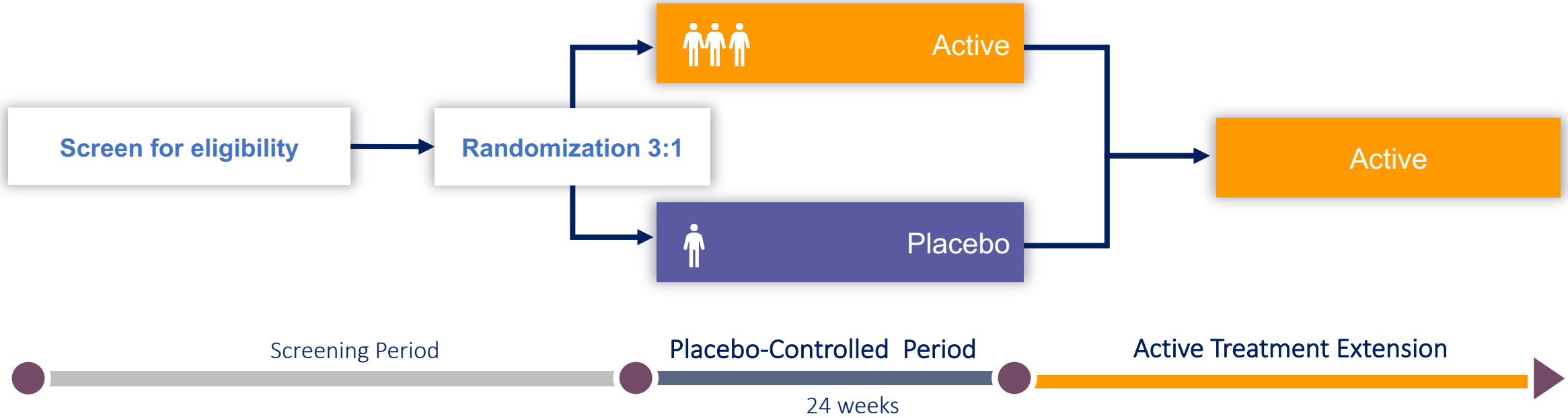
Healey ALS Platform trial is run at 70+ NEALS sites



NEALS Northeast Amyotrophic Lateral Sclerosis Consortium®

- Texas Neurology
- Mass General Hospital
- UTHSCSA
- Hospital for Special Care
- Holy Cross Hospital
- Thomas Jefferson
- Houston Methodist
- Henry Ford Health System
- Barrow Neurological Institute
- Ohio State University
- Northwestern University
- University of Chicago
- Wake Forest
- University of Nebraska
- Loma Linda University
- University of Washington
- University of Iowa
- Washington University
- University of Pennsylvania
- University of Michigan
- California Pacific Medical Cen
- Penn State Hershey
- UMass Worcester
- University of Miami
- University of Colorado
- Cedars-Sinai
- University of Florida
- University of South Florida
- Columbia University
- University of Virginia
- Emory University
- University of Maryland
- SUNY Upstate
- Beth Israel Deaconess
- Temple University
- Dartmouth-Hitchcock
- Medical College of Wisconsin
- Spectrum Health
- University of Missouri
- University of Minnesota
- Johns Hopkins University
- University of CA Irvine
- University of Kansas
- Vanderbilt University
- University of Kentucky
- Mayo Rochester
- Duke University
- Neurology Associates
- Ochsner Health System
- Mayo Clinic Florida
- St. Louis University
- Providence Brain and Spine
- Georgetown University
- University of Southern California
- Cleveland Clinic
- George Washington University
- University of California, San Francisco
- Indiana University
- Stony Brook University
- University of Pittsburgh
- University of Utah
- Augusta University
- University of Cincinnati
- Virginia Commonwealth University
- Swedish Medical Center
- Las Vegas Clinic
- Kaiser, Los Angeles
- Lehigh Valley Health Network
- St. Alphonsus Regional Medical Center
- Hackensack University
- Essentia Health
- Nova Southeastern University

This is a Phase 2 trial design with an objective to provide a go / no go decision about Phase 3 confirmatory trial candidacy for each Regimen drug



Primary Endpoint (Placebo-Controlled Period)

Change in disease severity (ALSFRS-R total score and survival) over 24 weeks of study treatment

Safety, Secondary, and Exploratory Endpoints

(respiratory function, muscle strength, survival, biomarkers + regimen-specific endpoints)

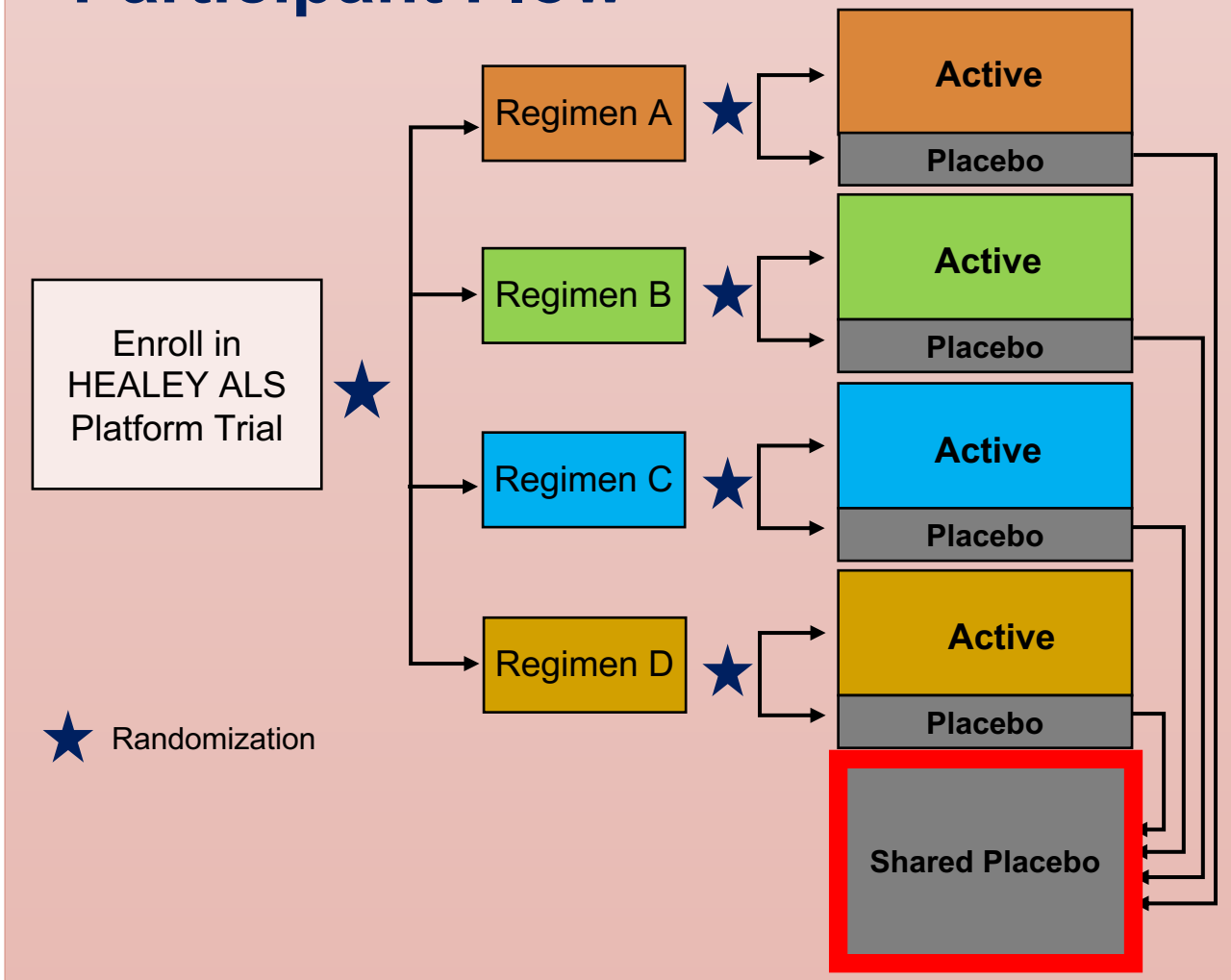
Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

BROAD AND INCLUSIVE ELIGIBILITY CRITERIA

1. Sporadic or familial ALS
   (possible, probable, lab-supported probable, or definite by revised El Escorial criteria for ALS)
2. Time since weakness onset ≤ 3 years
3. Slow vital capacity ≥ 50% of predicted
4. Able to swallow
5. Either not take or be on stable dose of riluzole for ≥ 30 days
6. Either not take or have completed at least one cycle of edaravone
7. Either not take or have started SodiumPB/TURSO ≥ 30 days prior to screening

Each regimen is compared to the shared placebo dataset
Common trial infrastructure & Shared Placebo bring trial efficiency

Participant Flow



This is a perpetual trial to provide decisive answers and direction with efficient execution (faster timelines, efficient use of resources, less placebo)

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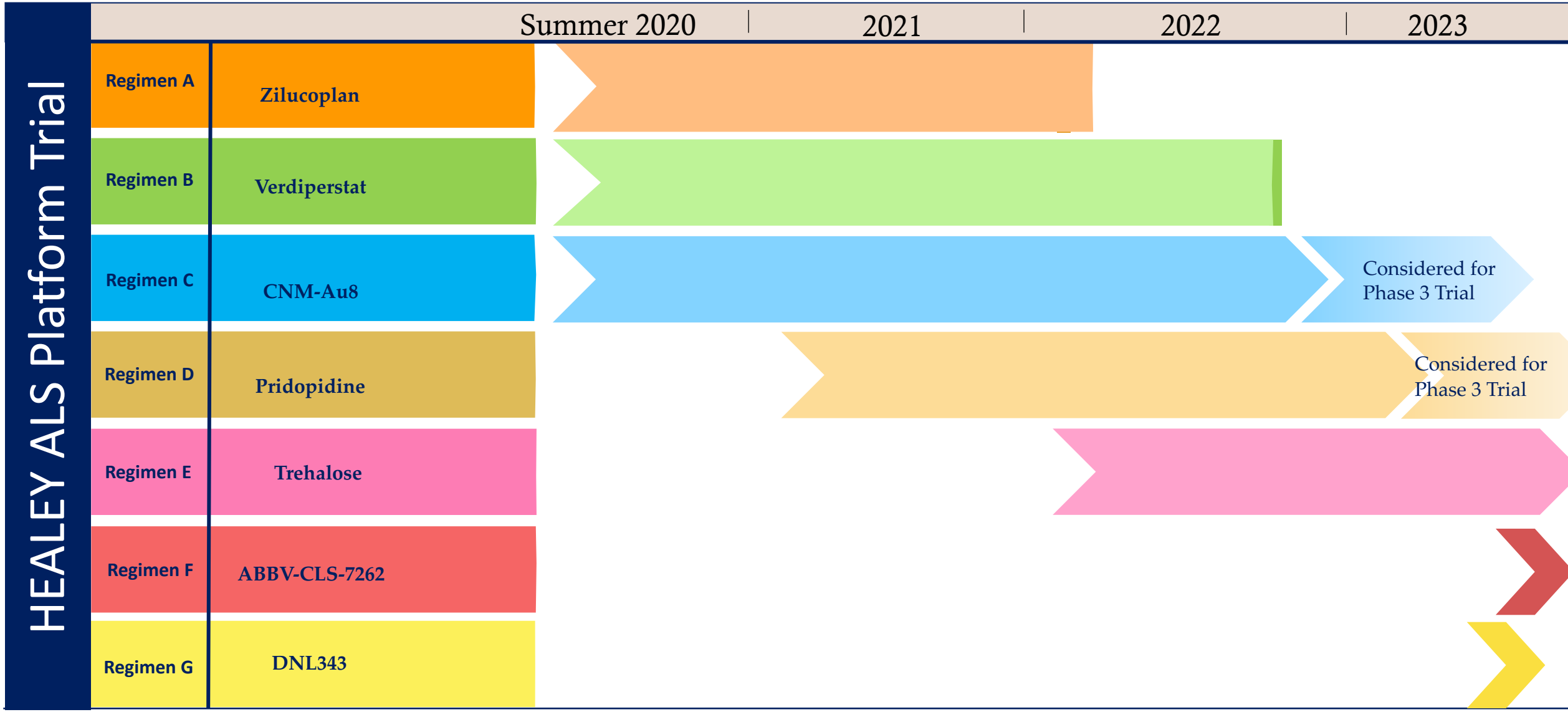
Sean M. Healey & AMG Center for ALS at Mass General

PROGRESS FROM THE TRIAL SO FAR



HEALEY ALS Platform Trial

Regimen Updates

- October 2022: **Regimen C** top line results announced

* While the primary endpoint was not met, a secondary endpoint analysis of survival demonstrated a significant reduction in risk of death or permanently assisted ventilation when adjusting for baseline risk imbalances in the CNM-Au8 regimen for the 30 mg dose

- February 2023: **Regimen D** top line results announced

* While the primary endpoint was not met, a secondary endpoint analysis of speech function demonstrated significant benefit in some speech domains and posthoc analyses showed favorable trends in early and definite ALS cohorts

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

HEALEY ALS Platform Trial

Ongoing and Upcoming Regimens

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

- **Regimen E enrollment completed & ongoing**
- **Regimens F enrolling Regimen G enrolling**
- **Additional Regimens selected** for inclusion; working on contracts

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

The Healey ALS platform trial also allows for developing novel ALS biomarkers and trial outcome measures

DNA – whole genome sequencing

Neurofilaments – for all regimens + regimen-specific biomarkers based on MOA

Home Spirometry – critical during the pandemic

Speech Analysis – emerging digital biomarker

Additional biomarkers/outcome measures for upcoming and future regimens (e.g., new patient-reported outcomes- ROADS)

Contact our patient navigators for questions regarding trial participation

Catherine Small
Patient Navigator

Allison Bulat
Community Engagement

Judi Carey, RN
Research Access Nurse

Contact the Patient Navigator

HEALEYALSPlatform@mgh.harvard.edu

833-425-8257 (HALT ALS)

https://bit.ly/3UPTzR9

THE EXPANSION OF EXPANDED ACCESS PROGRAMS (EAP) IN ALS

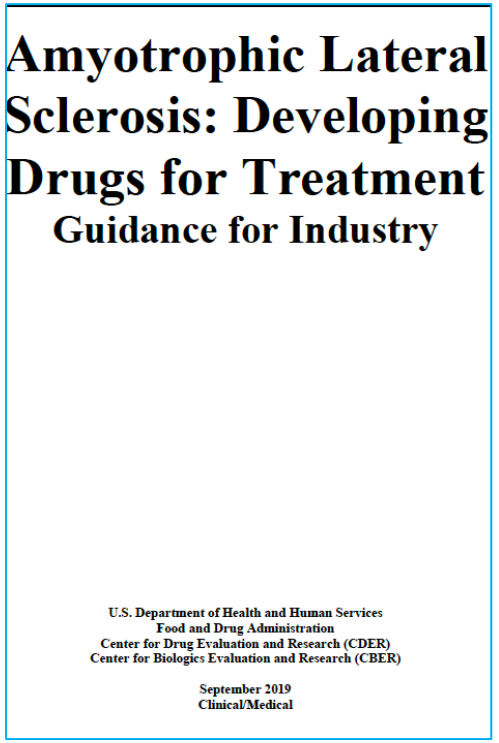
FDA ENCOURAGES OLE & EAP IN ALS CLINICAL TRIAL DESIGN

- **Long term safety data:**

"During development, sponsors should collect safety data, including data from open-label studies or expanded access programs, from patients across the spectrum of disease stages and severities, and whenever possible, data from patients who may not have been included in effectiveness studies but in whom, based on other data, the use of the drug following approval is likely." [Page 4]

- **Generalizability of safety and efficacy data:**

". There is a need to understand the safety and effectiveness of investigational drugs for ALS across disease stages….. An acceptable approach could include enrollment of a broad population with the conduct of the primary analysis in a study subset defined based on clinical characteristics and/or biomarkers, and analyses of the broader population being secondary and supportive " [Page 3]


Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment

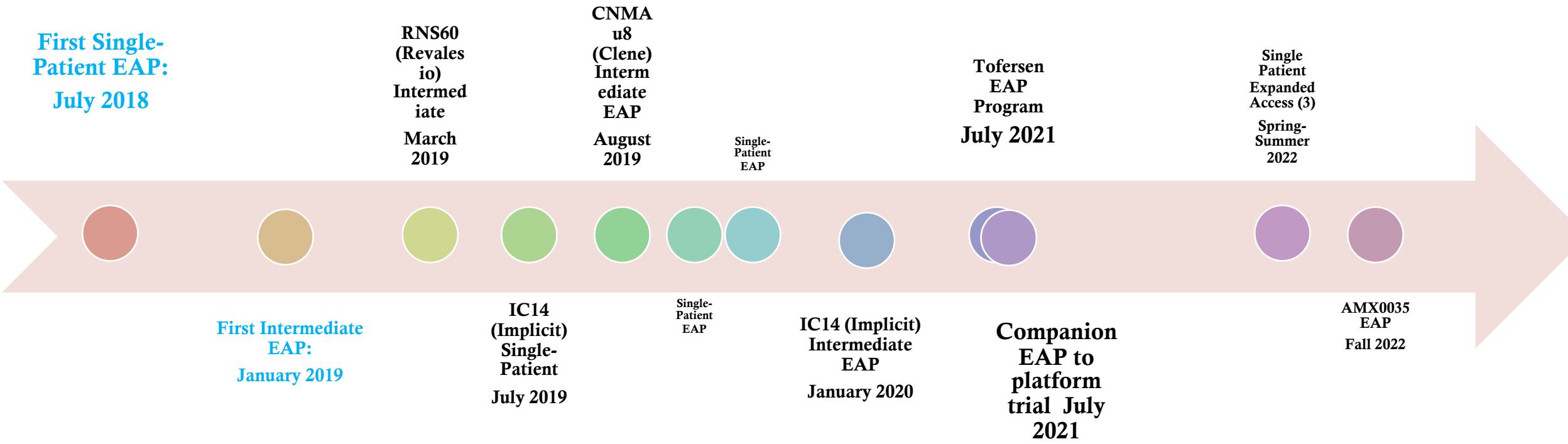
Guidance for Industry

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)

September 2019
Clinical/Medical

THE MGH EAP PROGRAM : STARTED WITH A SINGLE PATIENT AND OVER 5 YEARS, GREW TO A MULTI-PATIENT, MULTI-STUDY EAPS

- **Programs:** To date, 27 separate EAPs (under sIND and cohort-based EAPs)
  Currently, 13 active EAP protocols are active
- **Participants** ~106 active participants
  ~ 240 enrolled total since 2018



EAP PARADIGM IS AN EXTENSION OF ALS CLINICAL CARE

Extension of Clinical Care

Research Model

Aligning EAP study visits with clinical visits and and clinical labs

Aligning goals between IRB, FDA, industry sponsor, and Provider-Patient

Including clinical and research staffing resources

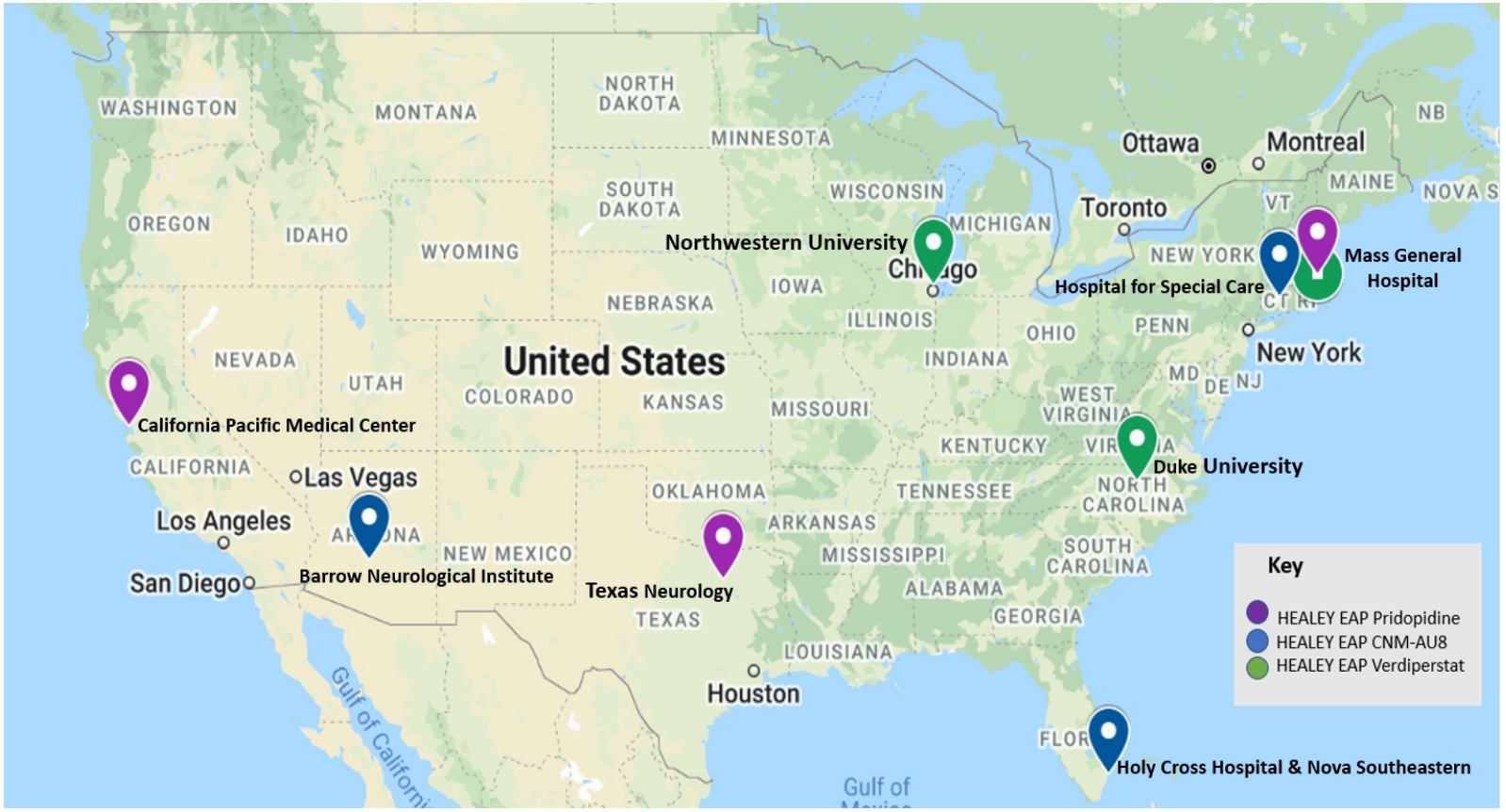
Utilizing clinic space for EAP study visits

Some institutions may use EMR for source documentation

Making sure protocol is followed for study conduct

Safety reporting (SAEs) is done in a timely and FDA/IRB compliant manner

EAP COMPANION TO HEALEY ALS PLATFORM TRIAL - FIRST MULTICENTER EAP IN ALS (SINCE JULY 2021)



81 EAP participants enrolled across 10 sites

Companies provide drug, remainder of costs covered by philanthropy and foundations

IND held by either drug manufacturer or Healey Center investigator

MGH- NCRI ARO utilized for operations given multiple sites

- Centralized operations
- Reduced site regulatory and administrative burden
- Centralized site training, regulatory reporting requirements, safety monitoring expectations, contracting, electronic data capture (NeuroREACH™)

EAP OF TOFERSEN INTRATHECAL ASO

First multi-national EAP in ALS | Ends in June 2023 in the US | 120 sites worldwide | ~300 participants enrolled

For symptomatic ALS individuals who carry the SOD1 gene mutation

Initially a single patient IND based EAP (July 2021), later expanded to intermediate cohort-based EAP (Oct 2021)

Available world wide (Canada, Europe, Asia, Australia)

Industry provides drug and protocol

All other operational costs and IRB approvals are undertaken by sites

Safety labs and study procedures may be billed to patient's insurance based on institutional practices

Only safety data provided to industry for FDA reporting, no other efficacy or biomarker data collected

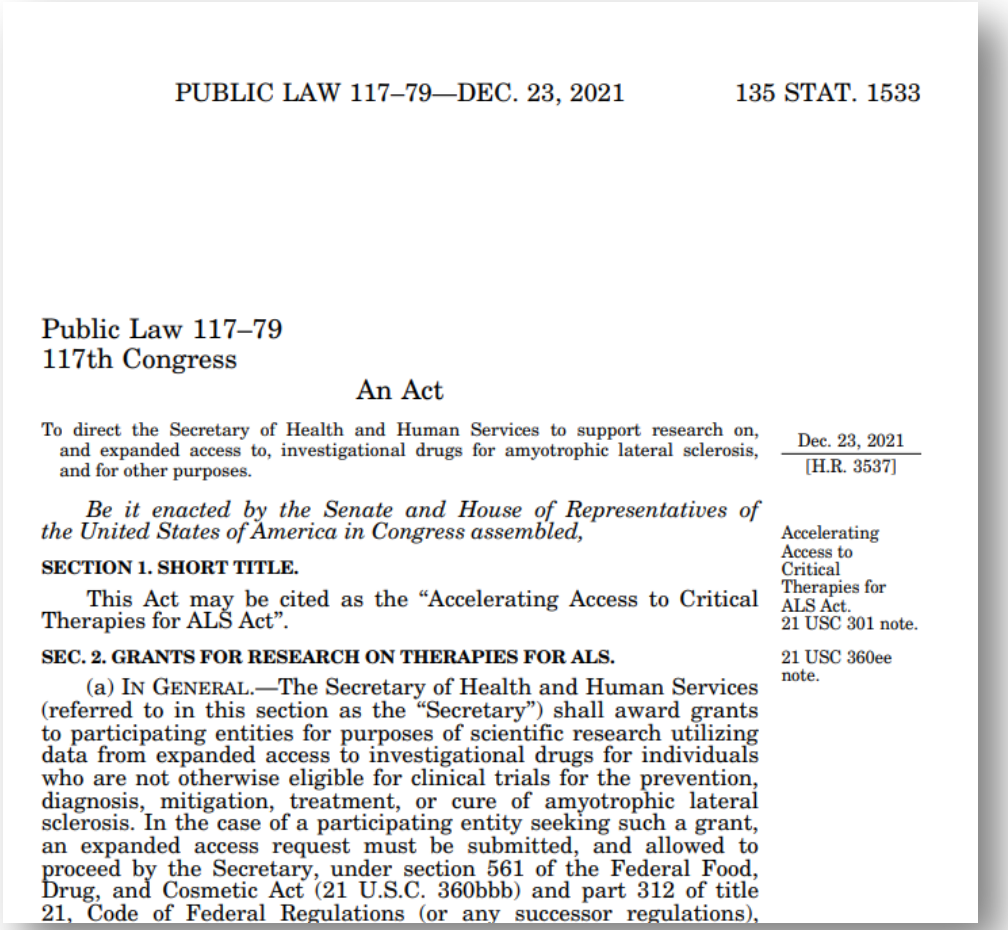
THE ACT FOR ALS –

A NEW OPPORTUNITY FOR EXPANDING ACCESS AND DRUG DEVELOPMENT RESEARCH IN PARALLEL TO ALS CLINICAL TRIALS

Signed into law on Dec 23, 2021

NIH U01 Grants for Research on Therapies via Intermediate-Size EAPs for ALS

- MGH Healey Center receives the first grant to partner with Seelos therapeutics (A small business)
- Trehalose companion EAP in startup phase, will be run in parallel to Regimen E of the HEALEY ALS Platform Trial
- MGH Multi PIs: Babu, Berry, Paganoni
- 70 ALS participants will participate in this EAP across 25 sites and will receive weekly IV infusions of experimental IV SLS-005



PUBLIC LAW 117–79—DEC. 23, 2021 135 STAT. 1533

Public Law 117–79
117th Congress

An Act

To direct the Secretary of Health and Human Services to support research on, and expanded access to, investigational drugs for amyotrophic lateral sclerosis, and for other purposes.

Dec. 23, 2021
[H.R. 3537]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

Accelerating Access to Critical Therapies for ALS Act.
21 USC 301 note.

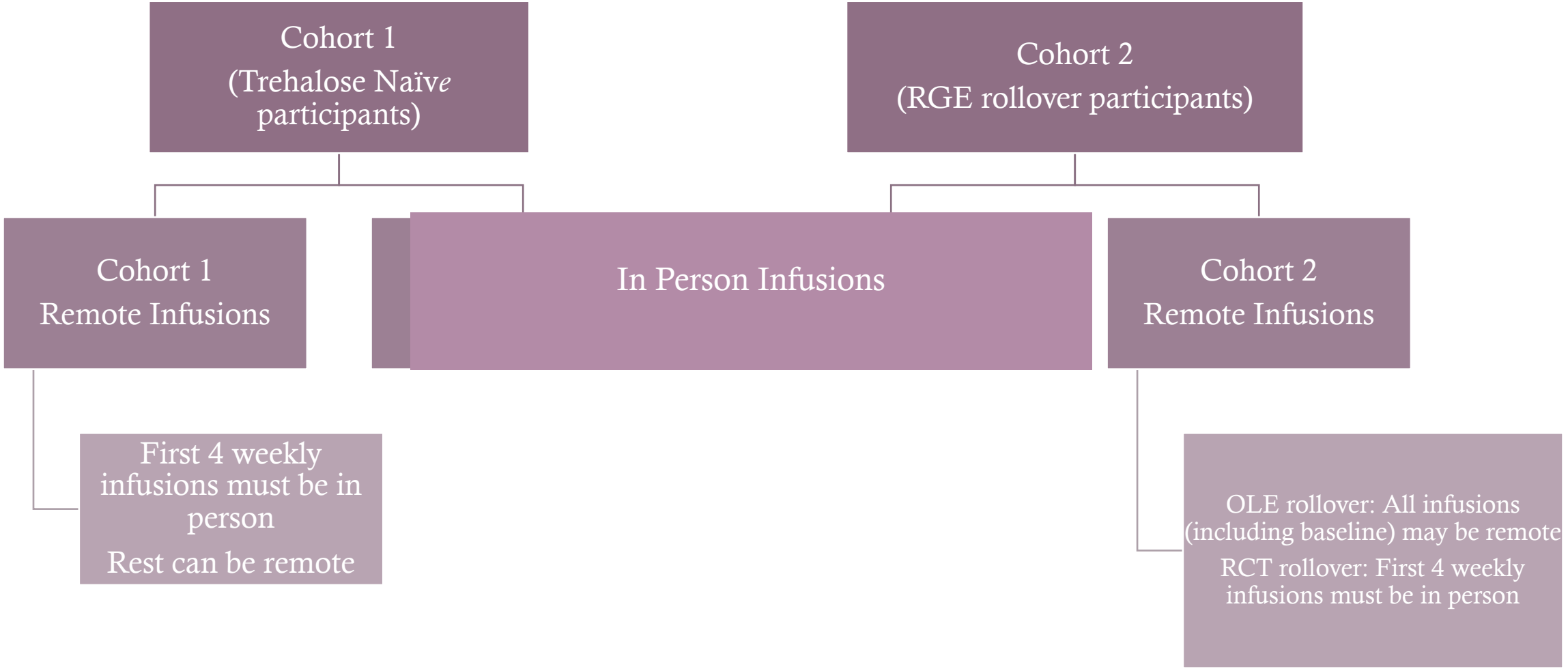
This Act may be cited as the "Accelerating Access to Critical Therapies for ALS Act".

SEC. 2. GRANTS FOR RESEARCH ON THERAPIES FOR ALS.

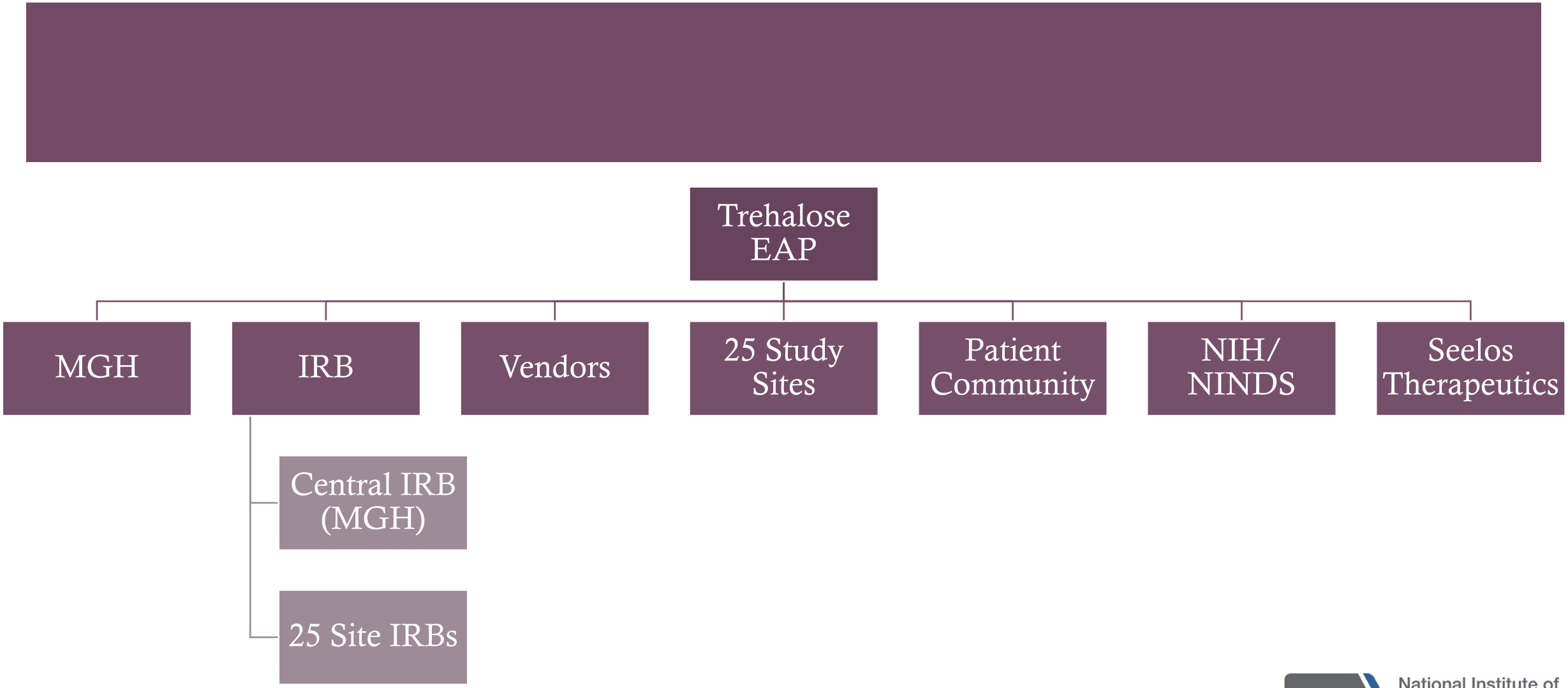
21 USC 360ee note.

(a) IN GENERAL.—The Secretary of Health and Human Services (referred to in this section as the "Secretary") shall award grants to participating entities for purposes of scientific research utilizing data from expanded access to investigational drugs for individuals who are not otherwise eligible for clinical trials for the prevention, diagnosis, mitigation, treatment, or cure of amyotrophic lateral sclerosis. In the case of a participating entity seeking such a grant, an expanded access request must be submitted, and allowed to proceed by the Secretary, under section 561 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb) and part 312 of title 21, Code of Federal Regulations (or any successor regulations),

Trehalose EAP : Run like a clinical trial– 70 participants, 6-month treatment, long term safety, efficacy assessments



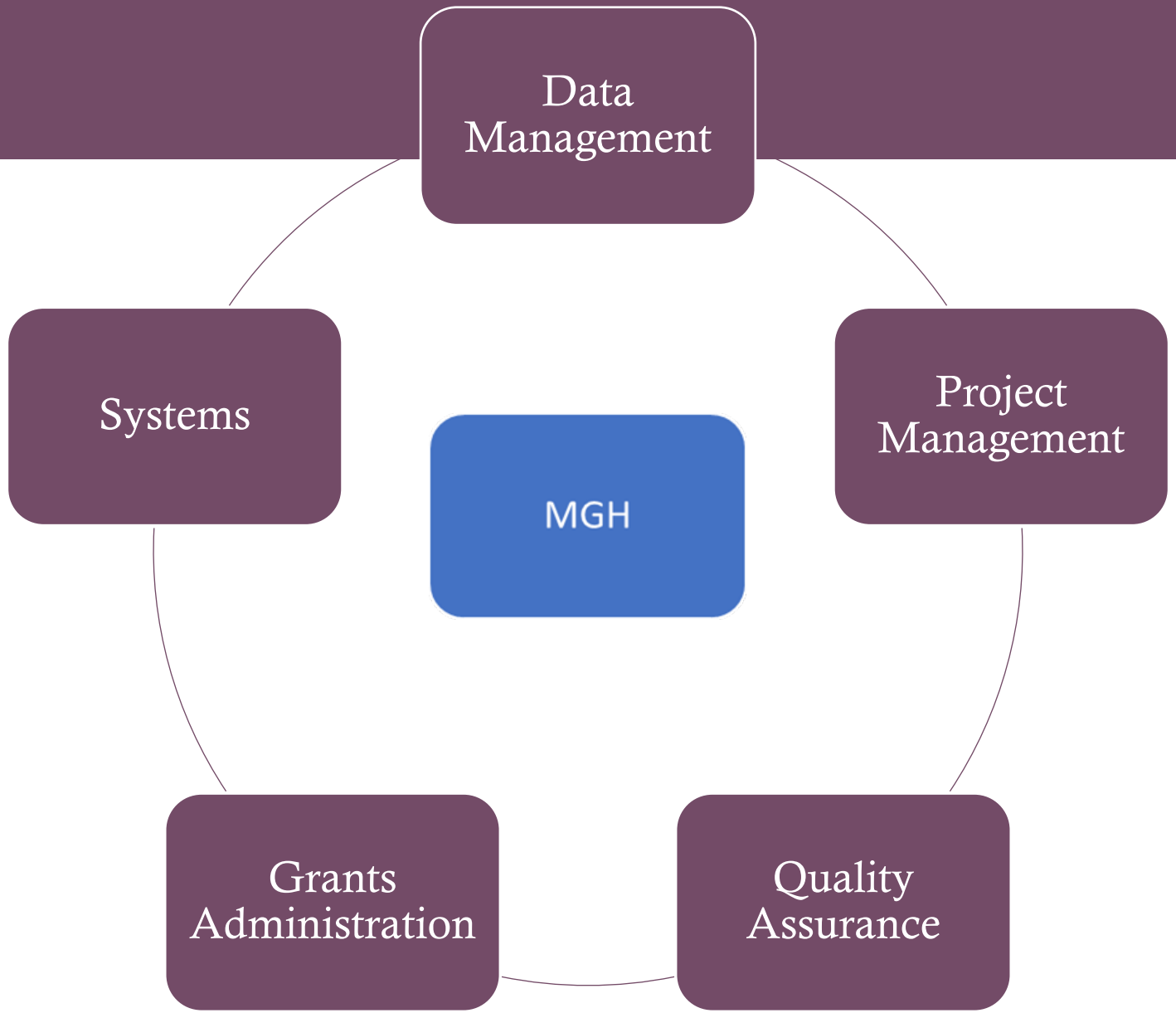
Trehalose EAP Project – large scale project with complex operations



National Institute of Neurological Disorders and Stroke

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

Trehalose EAP Project – large scale project with complex operations



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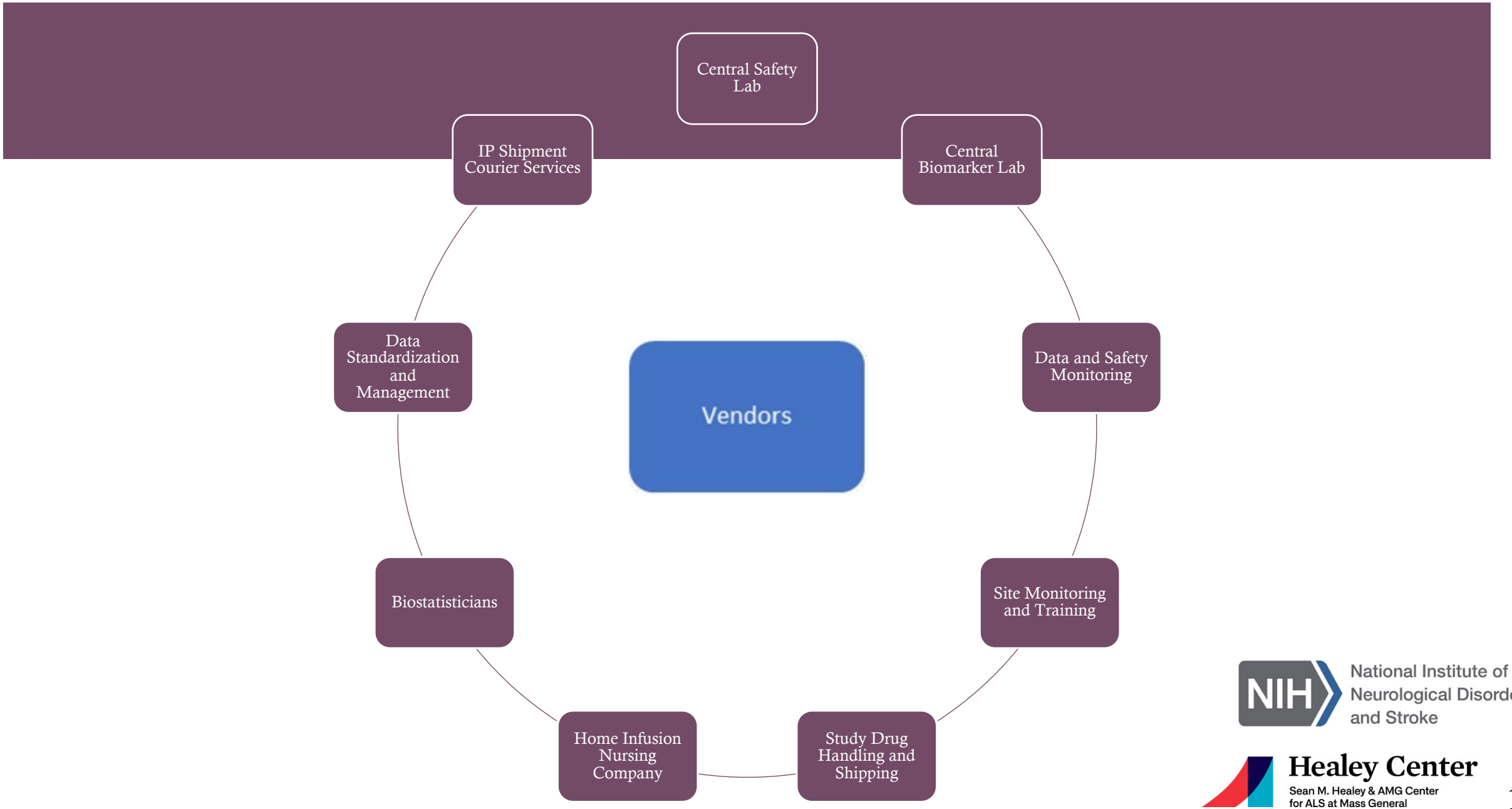

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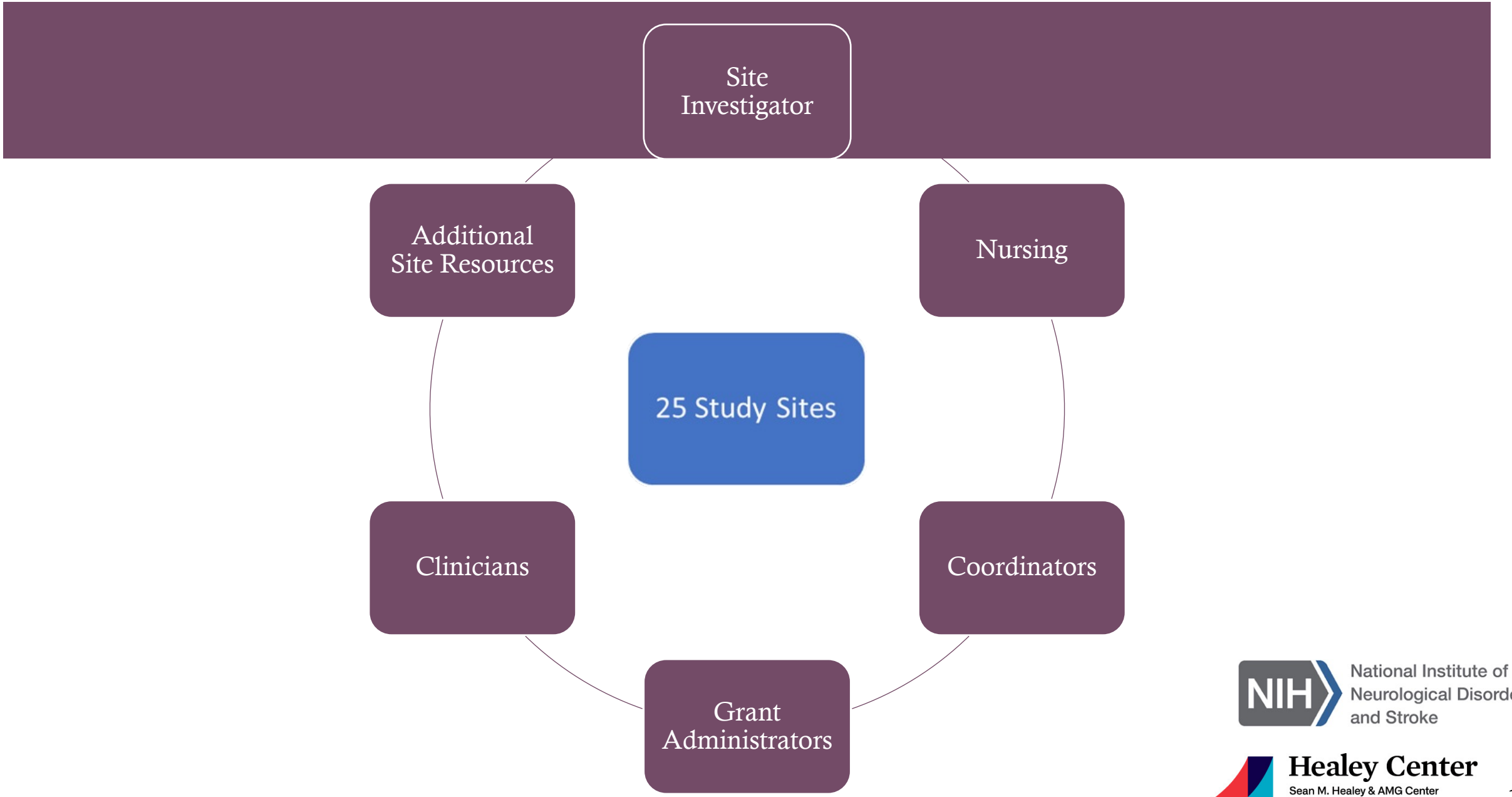
Trehalose EAP Project Overview – large scale project with complex operations



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THE MGH ALS CLINIC, THE MGH HEALEY ALS TEAM & SUPPORTING TEAMS

Bringing together a community to innovate the ALS clinical trial landscape

HARVARD MEDICAL SCHOOL

MASSACHUSETTS GENERAL HOSPITAL

NEUROLOGICAL CLINICAL RESEARCH INSTITUTE

BARROW Neurological Institute

Berry Consultants Statistical Innovation

MELIORA

Healey Center

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

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

CCALS

COMPASSIONATE CARE ALS

LEADING A NEW VISION IN ALS CARE SINCE 1998

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

ALS ASSOCIATION

MDA Muscular Dystrophy Association

SALSA For a Cure

alsFINDINGaCURE

I AM ALS

ALS ONE

TAMBOURINE

BASEBALL WINTER MEETINGS SAN DIEGO 2015

RUN2REVIVE MIND · BODY · POTENTIAL

THE ARTHUR M. BLANK FAMILY FOUNDATION

AMG The AMG Foundation

SUMMARY

It is an exciting time for ALS! There are over 160 companies developing therapies for ALS.

This calls for everyone's participation- both patients and ALS clinics!

When more clinical trials are completed in a timely and efficient manner, our knowledge advances faster and in turn, we can contribute to more treatment discoveries for patients with ALS

THANK YOU

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