



Published in final edited form as:

*Muscle Nerve*. 2024 December ; 70(6): 1140–1150. doi:10.1002/mus.28244.

## Access for ALL in ALS (ALL ALS): a large-scale, inclusive, collaborative consortium to unlock the molecular and genetic mechanisms of ALS

James D. Berry, MD<sup>\*,1</sup>, Sabrina Paganoni, MD, PhD<sup>\*,1</sup>, Matthew B. Harms, MD<sup>2</sup>, Neil Shneider, MD, PhD<sup>2</sup>, Jinsy Andrews, MD<sup>2</sup>, Timothy M. Miller, MD, PhD<sup>3</sup>, Suma Babu, MBBS<sup>1</sup>, Alex V. Sherman, MS<sup>1</sup>, Brent T. Harris, MD, PhD<sup>4</sup>, Frank A. Provenzano, PhD<sup>2</sup>,

**Correspondence to:** James D. Berry, MD, MPH, jdberry@mgh.harvard.edu.

\*Denotes equal first authorship

†Denotes equal senior authorship

### Ethical Publication Statement

The authors confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

### Conflicts of Interest

James D. Berry reports research grants from Biogen, MT Pharma of America, Alexion, Rapa Therapeutics, the ALS Association, the Muscular Dystrophy Association, ALS One, ALS Finding a Cure, Tambourine, ALS Finding a Cure, DoD, NINDS, and reports personal consulting fees from Biogen, Clene Nanomedicine, MT Pharma of America, Janssen, Projects in Knowledge, Roon, and is a paid DSMB member for Sanofi.

Sabrina Paganoni reports research grants from Amylyx Therapeutics, Revaesio Corporation, Eledon, Alector, UCB, Biohaven, Clene Nanomedicine, Prilenia, Seelos, Calico, Denali, NIH, CDC, DoD, The ALS Association, the American Academy of Neurology, ALS Finding a Cure, the Salah Foundation, the Spastic Paraplegia Foundation, the Muscular Dystrophy Association, Tambourine and reports consulting fees from Amylyx, Arrowhead, Janssen, Medscape, and Cytokinetics.

Matthew Harms Biogen, Ionis, uniQure, Amylyx, Sarepta, ALS Association, ALS United, ALS Finding a Cure, Muscular Dystrophy Association, Target ALS.

Neil Shneider reports no disclosures.

Jinsy Andrews has served as a consultant for AL-S Pharma, Amylyx, Apellis, Biogen, Clene, Cytokinetics, Denali, Neurosense, Novartis, Akava, QurAlis, Sanofi, UCB and Wave Therapeutics; Received research funding to the institution from ALS Association, Amylyx, Biogen, Novartis, Cytokinetics, Biohaven/Clene/Ra Pharma/Prilenia/Seelos/Calico/Denali MGH Foundation [ALS Platform Trial], Corcept and NIH/NINDS.

Timothy Miller reports compensation received for consulting and licensing from Ionis, consulting from Biogen and Bioio, licensing from C2N and Honorarium from Denali.

Suma Babu has received research funding from, OrphAI therapeutics, Biogen, Denali Therapeutics, Novartis, Orion, Ionis, American Academy of Neurology, AANEM Foundation and Muscular Dystrophy Association and reports consulting fees from Biogen, OrphAI therapeutics and Medscape.

Alexander Sherman has received grants and contracts for clinical research projects sponsored by NIH, FDA, The ALS Association, ALS Finding a Cure Foundation, Biogen, Mitsubishi Tanabe Pharma America, Inc., and Amylyx Pharmaceuticals.

Brent Harris reports compensation received as a consultant for Dept of Justice and HHS, President for Neuropathology Consults, LLC, Consultant for Office of the Chief Medical Examiner of DC, Medical/Scientific Board member for non-profits (Manfull Fund, Neuroimmune Foundation)

Frank Provenzano reports compensation received as a consultant for Tesarakt.

Hemali Phatnani reports no conflicts of interest

Jeremy Shefner reports compensation received as a consultant from Amylyx, Annexon, Acurastem, Eikonizo, Uniquire, NeuroSense Therapeutics, Cytokinetics, Denali Therapeutics, GSK, Mitsubishi Tanabe Pharma America, Orthogonal, RRD, SwanBio, Novartis, Sanofi, PTC, Vertex, and EMD Serono; and research support from Amylyx, Biogen, Biotie Therapies (now Acorda Therapeutics), Cytokinetics, Mitsubishi Tanabe Pharma America, Alexion, MediciNova Inc, Ionis, Alector, and Orphazyme.

Mark Garret reports research support from Biogen, uniQure, NINDS, FDA, Target ALS, ALS Finding a Cure, and ALS Association.

Shafiq Latha reports consulting fees from Amylyx, Annexon, UCB Pharma, Genentech, Sanofi, Neurosense and Rapa Therapeutics

Amy Tsou reports no conflicts of interest

Praveena Mohan reports no conflicts of interest

Courtney Igne reports no conflicts of interest.

Robert Bowser reports research grants from Target ALS, NINDS, Bristol-Myers Squibb, and reports consulting fees from MT Pharma of America, Brainstorm, Eikonizo Therapeutics, Athira Pharma, Inc., Takeda, Neurosense Therapeutics, and AcuraStem.

**Hemali P. Phatnani, PhD<sup>2</sup>, Jeremy Shefner, MD, PhD<sup>5</sup>, Mark A. Garret, MD<sup>1</sup>, Shafteeq S. Ladha, MD<sup>5</sup>, Amy Y. Tsou, MD<sup>6</sup>, Praveena Mohan, PhD<sup>5</sup>, Courtney Igne, MS<sup>1</sup>,  
The ALL ALS Consortium,  
Robert Bowser, PhD<sup>5</sup>**

<sup>1</sup>Sean M. Healey & AMG Center for ALS, Massachusetts General Hospital, Boston, MA, USA

<sup>2</sup>Neurology, Columbia University College of Physicians and Surgeons, New York City, NY, USA.

<sup>3</sup>Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA

<sup>4</sup>Department of Pathology, Georgetown University Medical Center, Washington, DC, USA

<sup>5</sup>Department of Neurology, Barrow Neurological Institute, Phoenix, USA.

<sup>6</sup>Division of Clinical Research, National Institutes of Neurological Disorders and Stroke (NINDS), Rockville, MD

## Abstract

Recent progress in therapeutics for amyotrophic lateral sclerosis (ALS) has spurred development and imbued the field of ALS with hope for more breakthroughs, yet substantial scientific gaps persist. This unmet need remains a stark reminder that innovative paradigms are needed to invigorate ALS research. To move toward more informative, targeted, and personalized drug development, the National Institutes of Health (NIH) established a national ALS clinical research consortium called Access for ALL in ALS (ALL ALS). This new consortium is a multi-institutional effort that aims to organize the ALS clinical research landscape in the US. ALL ALS is operating in partnership with several stakeholders to operationalize the recommendations of the Accelerating Access to Critical Therapies for ALS Act (ACT for ALS) Public Private Partnership. ALL ALS will provide a large-scale, centralized, and readily accessible infrastructure for the collection and storage of a wide range of data from people living with ALS (symptomatic cohort) or who may be at risk of developing ALS (asymptomatic ALS gene carriers). Importantly, ALL ALS is designed to encourage community engagement, equity, and inclusion. The consortium is prioritizing the enrollment of geographically, ethnoculturally, and socioeconomically diverse participants. Collected data include longitudinal clinical data and biofluids, genomic, and digital biomarkers that will be harmonized and linked to the central Accelerating Medicines Partnership for ALS (AMP ALS) portal for sharing with the research community. The aim of ALL ALS is to deliver a comprehensive, inclusive, open-science dataset to help researchers answer important scientific questions of clinical relevance in ALS.

## Keywords

Amyotrophic Lateral Sclerosis; ALS; Biomarkers; Observational Study; Asymptomatic Gene Carriers; natural history

## INTRODUCTION

With new treatment modalities and the identification of key disease biomarkers, drug development for neurodegenerative and neuromuscular diseases is increasingly robust. Yet,

the identification of useful biomarkers, similar to p-tau and amyloid- $\beta$  for Alzheimer's disease<sup>1</sup>, has taken concerted effort, dedicated researchers and broad collaboration across multiple disciplines and scientific approaches. In amyotrophic lateral sclerosis (ALS), neurofilament light chain (NfL) has proven to be an important biomarker in drug development, and its use is expanding tremendously<sup>2-6</sup>.

A flexible regulatory approach by the Food and Drug Administration (FDA) has led to the approval of disease modifying therapies for ALS, thus expanding therapeutic options, spurring hope, and encouraging drug development<sup>6-9</sup>. At the same time, scores of trials have not demonstrated efficacy and the field continues to grapple with clinical development programs that end in negative Phase 3 trial results after early promising clinical trial results. The key challenges even for an effective agent include the need to identify and enroll participants early in the disease to increase the chances of success, manage disease heterogeneity by enrolling relevant patient subtypes when possible, and gain early insight into target engagement<sup>10</sup>.

Clearly, additional biomarkers and clinical outcome assessments (COA) are still sorely needed to advance ALS drug development and identifying them will require additional infrastructure resources<sup>11</sup>. A large scale, coordinated effort to collect clinical information, accompanying biofluids and potentially imaging or digital data, could identify additional biomarkers, develop more effective COA and power new breakthroughs in ALS drug development. Furthermore, novel biomarkers and COA must be developed in a representative population of people living with ALS. Too often, ALS studies and trials have enrolled primarily white, non-Hispanic participants. The Access for ALL in ALS consortium (ALL ALS) has been established to address these goals and will tackle future challenges as a powerful clinical research consortium.

### **Accelerating Medicines Partnership® (AMP®) program and AMP ALS**

The Accelerating Medicines Partnership® (AMP®) program<sup>12</sup> is a public-private partnership between the National Institutes of Health (NIH), the U.S. Food and Drug Administration (FDA), multiple biopharmaceutical and life science companies, and non-profit and other organizations to transform the current model for developing new diagnostics and treatments. The AMP® program is comprised of multiple projects, each focusing on a specific disease or group of diseases, or a therapeutic modality; management support for these projects is provided by the Foundation for NIH (FNIH).

At the core of the AMP® program lies a common mission: the acceleration of novel and effective therapies to benefit patients. AMP® projects diligently strive to advance this objective through identification of clinically pertinent disease targets, refinement of patient selection criteria for optimal treatment response, discovery and validation of biomarkers<sup>13</sup> that can inform testing of novel therapeutics in early-phase clinical trials, and acceleration of development timelines for critical life-saving therapies, thereby fostering improvements in patient outcomes.

The Accelerating Access to Critical Therapies for ALS Act (ACT for ALS), which was signed into law in the US on December 23, 2021, established a US Department of Health

and Human Services (HHS) public-private partnership (PPP) for rare neurodegenerative diseases, and the AMP<sup>®</sup> program for ALS (AMP<sup>®</sup> ALS), that was launched in May, 2024.

AMP<sup>®</sup> ALS will identify priority projects such as a US national network for collection and storage of harmonized clinical, genomic, biofluid, cell, tissue, and digital data; research into the natural history of ALS (including its earliest manifestations, predictors of phenoconversion in asymptomatic ALS gene carriers, and biomarkers of phenotypic variability); and a framework for collaborations between government, industry, academia, and non-profit organizations following open science principles. AMP<sup>®</sup> ALS hopes to inform ALS drug development, taking the field one step closer toward the goal of halting, repairing, and/or preventing ALS. The ALL ALS Consortium will provide a mechanism to conduct prospective, multicenter ALS clinical research to support the AMP<sup>®</sup> ALS goals.

Here we describe the design and structure of the ALL ALS Clinical Research Consortium, comprised of two clinical coordination centers (CCC), a data coordination center (DCC), and a nationwide network of research centers funded by the National Institutes of Health/National Institute of Neurological Disorders and Stroke (NIH/NINDS) to conduct prospective, multicenter ALS clinical research (Figure 1). The first two research studies utilizing the ALL ALS Consortium structure are observational studies collecting a wide range of data and samples: 1) ASSESS ALL ALS, enrolling people living with ALS (symptomatic cohort) and controls, and 2) PREVENT ALL ALS, enrolling people who may be at risk of developing genetic forms of ALS (asymptomatic ALS gene carriers).

### ALL ALS organizational structure

The overarching goal of the ALL ALS Consortium is to prospectively collect, store and harmonize a large set of longitudinal data, which will be shared through the AMP ALS central portal, and biospecimens that will be linked to the clinical data and shared through the central biorepository for open science collaboration with the research community.

The two CCCs are the “East CCC” located at the Massachusetts General Hospital (MGH) Neurological Clinical Research Institute (NCRI) / Healey & AMG Center for ALS in Boston, MA and at the “West CCC” located at the Barrow Neurological Institute (BNI) / Gregory W. Fulton ALS Center in Phoenix, AZ. The CCC leadership team includes ten multi-Principal Investigators (mPIs) from five academic institutions (MGH, BNI, Columbia University, Washington University, and Georgetown University). The mPIs work in close collaboration with the AMP ALS Steering Committee to set research priorities for the ALL ALS Consortium and oversee experienced project management, grants and contracts, legal and communication teams at the CCCs to execute project initiatives. The CCCs manage Consortium activities, including site management, monitoring and outcomes training, investigator mentorship, marketing, outreach, and education on research methodology, data harmonization, biofluid collection and integration of data and biofluid repositories for sharing. The East and West CCCs work hand-in-hand to ensure alignment of the entire project, which shares a single institutional review board (sIRB).

Operational strengths of the ALL ALS Consortium include the use of a sIRB, execution of Master Clinical Trial Agreements with all sites, and the development of detailed standard

operating procedures (SOPs). In addition, broad ALS research community engagement and identification of synergies with existing ALS biomarker and natural history studies will maximize the utility of the ALL ALS Consortium. Consortium funding was announced in October 2023 and participant enrollment is scheduled to initiate in July 2024.

### **ALL ALS participating sites, study cohorts, data capture, and outcome measures**

There has been overwhelming interest in contributing to ALL ALS from specialized ALS centers across the US, with over 90 sites having expressed interest in participating at the time of grant proposal submissions. This interest is a testament to the vitality of the US ALS clinical research community and clinical investigators' commitment to productive collaboration. To launch ALL ALS, an initial set of 34 sites was selected by the NIH and AMP ALS Steering Committee in conjunction with ALL ALS East and West CCC leadership (Figure 2). Site selection accounted for site interest and prioritized geographic distribution and representative clinic populations across sites, with respect to geographical, ethnocultural, and socioeconomic status. To support robust enrollment and participation, sites will be funded to support a research coordinator to integrate research into ALS clinic care, interact with participants both in-person and virtually, engage with the local community, educate potential participants about the study, and enroll and retain study participants.

#### **Study 1: ASSESS ALL ALS - People with Symptomatic ALS and Controls:**

The first of the two inaugural studies being carried out across the ALL ALS Consortium, called ASSESS ALL ALS, will enroll two cohorts of participants who will contribute longitudinal data and samples. The first cohort will include symptomatic ALS participants, while the second will include control participants. This study will permit on-site and off-site participation to minimize participant burden.

**ASSESS ALL ALS: Symptomatic ALS Participants:** The study is designed to be inclusive of all people who have been diagnosed with ALS and are reasonably likely to be able to provide longitudinal data. Study visits can be conducted during routine clinical visits or as stand-alone research visits, with either a combination of on-site and off-site visits or entirely off-site visits to reach patients seen for care at the participating centers and those that are not connected to these centers and enrolled entirely remotely. This approach has been successful on a smaller scale in prior observational studies. One area of focus will be outreach from the ALL ALS Consortium sites to people living with ALS who may not be attending their center. This is intended to encourage enrollment of a more diverse and inclusive population than has previously been enrolled in ALS studies. Already, close collaborations have been established with existing ALS advocacy and community engagement organizations to this end. An ALL ALS website will be established to educate the community about ALL ALS and provide a link for individuals to self-identify their interest to participate in ALL ALS research studies.

Clinical data collected will include demographics, ALS history, family history, medical history, environmental history, current medications, and functional and cognitive COA. COA will include procedural measures, examiner-delivered functional measures, patient reported

outcomes, and digital outcome measures (Table 1). Table 2 shows the initial selection of patient reported outcomes (PROs). PROs interrogate symptomatic areas of concern for people living with ALS. The current list of PROs attempts to balance the importance of the information obtained against the burden of the scales.

Standard on-site clinical outcome measures will include the ALS Functional Rating Scale-Revised (ALSFRS-R)<sup>14</sup>, the most widely used primary outcome measure in ALS clinical trials, handheld dynamometry (HHD)<sup>15,16</sup> performed on a limited set of muscles, and vital capacity (VC), a measure of ventilatory muscle strength predictive of respiratory outcomes in ALS<sup>17</sup>. Cognitive assessment will include the Edinburgh Cognitive and Behavioral ALS Screen (ECAS)<sup>18–20</sup>. Digital outcomes can permit more frequent collection of quantitative data on-site or in the home environment<sup>21–24</sup>. While methodology to collect myriad types of digital biomarkers and COA exists and is being explored in ALS, quantitative motor speech analysis is most mature<sup>25–32</sup>. At the outset of ALL ALS, digital data collection will focus primarily on quantitative motor speech analysis through the capture of brief speech recordings on a monthly basis with hopes of expanding to additional digital outcomes in the future.

Off-site PROs will be delivered via a participant-facing, web-based data entry portal developed at the ALL ALS data coordinating center (DCC) called NeuroPRO™. This flexible, secure, and participant-friendly platform can be accessed from computer, tablet, or smartphone, has the capability of sending PRO reminders to participants via email, and can organize participant entry into more than one study. Participant-specific and overall study results can be displayed in full, filtered, or not presented. NeuroPRO is optimized for use with eye-gaze (eye-tracking) software, so research participants who utilize such tools will be enabled for easier and faster communication with the data capture platform. This powerful tool will permit the exploration of numerous PROs throughout the ALL ALS studies. The ALSFRS-R Self-Entry (ALSFRS-RSE) will act as the backbone of the PRO data collection, with additional PROs being selected. ALSFRS-RSE has been shown in numerous studies to have a high correlation to traditional ALSFRS-R with similar rate of decline, though with slightly higher scores<sup>33,21,34–36</sup>. Prior research has identified the types of symptoms most important to people living with ALS, and PROs will address these areas as well as areas of research import, including social determinants of health and quality of life (Table 2)<sup>37</sup>.

Biospecimens will be collected alongside COA to support biofluid biomarker analyses. Biospecimens will include plasma, serum, whole blood for generation of induced pluripotent stem cells (iPSCs) and DNA for whole genome sequencing, and cerebrospinal fluid (CSF). Strict collection, processing, shipping and storage SOPs will be established for this consortium, guided by prior studies<sup>38,4,39</sup>. Using a home phlebotomy vendor, a slightly restricted range of biofluids will be collected from entirely off-site participants as compared to those also seen at the study sites. This will enable study participation by individuals throughout the US.

**ASSESS ALL ALS: Control Participants:** Control participants in the ASSESS ALL ALS study must not have ALS or FTD or be known to be at risk of carrying a causative ALS/FTD gene mutation. Control participants may include spouses of ALS participants,

family members of people with ALS/FTD with a known genetic cause who have tested negative for the causative gene mutations, and members of the general US population and others encountered at ALL ALS Sites. Clinical information and biofluids collected will mimic the Symptomatic ALS cohort at baseline without disease-specific COAs. A second visit will collect follow-up medical information and biofluids 6–12 months after baseline.

**Study 2: PREVENT ALL ALS – Asymptomatic participants at risk of carrying**

**ALS causative variants:** The second study being carried out across the ALL ALS Consortium will enroll individuals at risk for carrying ALS causative gene variants. This includes known ALS gene carriers or individuals without prior genetic testing but who have a first-degree relative who carried a causative ALS gene. This study expands on a corpus of work built by the long-standing Pre-FALS study<sup>40,2</sup> as well as the existing collaboration between Columbia University, Washington University in St. Louis, and MGH called PREVENT ALS. This study will retain the PREVENT moniker and expand on these approaches. The aim of PREVENT ALL ALS is to study ALS before the onset of traditional symptoms, determine the earliest biofluid biomarker manifestations of ALS and quantify early clinical changes of the disease.

The PREVENT ALL ALS study visits will be a hybrid of on-site and off-site visits, with baseline and annual on-site visits and quarterly remote visits. On-site evaluations will include a detailed neurological evaluation for signs and symptoms of ALS and/or cognitive/behavioral impairment for frontotemporal dementia (FTD) and collection of blood and CSF. Examinations will be standardized across clinical centers and site investigator support will be offered from the PREVENT ALL ALS Cohort Principal Investigators. Demographic, social determinants of healthy, clinical, digital, epidemiological, genomic, and symptomatic data will be collected from participants (Table 3). PROs will be collected quarterly using the methods described for the Symptomatic Cohort, though the instruments will differ. Biofluid collection, storage, and analysis will accompany these data collected quarterly, as described for the Symptomatic ALS Cohort. The combination of detailed quantitative COA and biofluids will support genomic and biomarker studies that could identify genetic modifiers or herald the biochemical onset of ALS and/or FTD.

**PREVENT ALL ALS Genetic Testing Protocol:** An optional genetic testing protocol will provide confidential (identified only by study ID, not by name) genetic testing for asymptomatic people at risk of carrying ALS-causative gene variants who have enrolled in the PREVENT ALL ALS study. This genetic testing protocol, including pre- and post-test genetic counselling will be conducted via telemedicine by genetic counselors at Washington University in St. Louis, MGH and Columbia, the three original PREVENT ALS sites, who will be licensed across the US. Participants who choose not to know their genetic testing results (non-disclosure group) and those who choose to know their results (disclosure group) and are found to carry an ALS-causative mutation will continue participation in the PREVENT ALL ALS study. Those who choose to know their results and are found not to carry a known ALS causative variant may continue in the study only if their affected family members have been tested and are suspect to carry an unknown variant. Participants whose family members have a known variant and who test negative themselves can enter ASSESS

ALL ALS as a control participant if they so choose. Participants whose family members have not been tested and who test negative, themselves, will discontinue participation because of the uncertainty about whether they carry an as-yet undescribed gene or whether they are truly not ALS gene carriers.

**PREVENT ALL ALS Phenoconversion Assessment:** For a participant in PREVENT ALL ALS who is, by definition, symptom-free at study entry, the development of symptoms referable to ALS and/or FTD, referred to as “phenoconversion”, is a life-changing event signaling the need for rapid and focused evaluation. The emotional toll of phenoconversion can be substantial and people will need support. Phenoconversion also signals the need for standard symptomatic ALS or FTD therapy, including multidisciplinary care and disease modifying therapy. For SOD1 gene carriers, this includes the need to rapidly initiate treatment with tofersen. Some people may consider ALS or FTD trial entry, as well. Thus, phenoconversion must be evaluated carefully and rapidly.

PREVENT ALL ALS is designed with ad hoc Phenoconversion Visits which may be scheduled as needed to assess new symptoms reported by participants that may signal phenoconversion to clinical ALS and/or FTD. Phenoconversion study visits will allow for in-person neurologic and cognitive/behavioral evaluations and collection of both blood and CSF to help identify biomarkers of phenoconversion. Depending on clinical suspicion, additional clinical diagnostic testing outside of the study protocol may be recommended by site investigators to aid in diagnosis.

PREVENT ALL ALS will assemble a Phenoconversion Support Committee made up of FTD and ALS experts to provide site investigators with additional guidance as they evaluate and support participants in the throes of phenoconversion to FTD and/or ALS. This includes standardized definitions for phenoconversion for ALS and FTD for the purposes of this study; notably efforts will be made to standardize FTD phenoconversion definitions with those used in the ongoing ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) study <sup>41</sup>. Even with rapid evaluation, it is likely that the onset of symptoms will precede the date of phenoconversion confirmation on physical examination – these dates will all be recorded for the purposes of the study.

### **Data storage, harmonization, and sharing**

To facilitate effective sharing of data with the global ALS research community, data will be carefully collected and harmonized. ALL ALS clinical data will be collected in NeuroBANK<sup>®</sup>, a purpose-built electronic data capture system (EDC) that was designed to facilitate data collection, harmonization and sharing in accordance with all applicable legal and informed consent requirements and data use agreements, as previously described<sup>42,38</sup>. The NeuroBANK platform is compliant with Good Clinical Practice (GCP) recommendations and the 21 Code of Federal Regulations Part 11 and incorporates flexible electronic case report forms (eCRFs) that conform with Clinical Data Interchange Standards Consortium (CDISC) and Clinical Data Acquisition Standards Harmonization (CDASH) data collection approaches, NIH ALS Common Data Elements (CDEs), and existing library forms. The consortium will utilize unique research participant identifiers, called NeuroGUID

(global unique identifier), which will be created from identifiable information, which is hashed (encrypted into another number string using an encryption algorithm), sent to a secure server and used to create a unique random identifier. The NeuroGUID has been used across research fields to link information across studies from the same participant without reidentifying the participant and to harmonize and effectively share datasets <sup>43</sup>. The NeuroGUID is unique to neurology studies and has been previously used in many ALS studies and trials, including the Northeast ALS Consortium (NEALS) Biorepository <sup>44</sup>, Answer ALS <sup>38</sup>, the ALS/motor neuron disease (MND) Natural History Consortium, the Dominantly Inherited ALS (DIALS) Network, the Center for Disease Control (CDC) National ALS Registry <sup>45</sup>, and the HEALEY ALS Platform Trial <sup>46</sup>.

More recently, some ethical and legal experts have begun to consider GUIDs to be sufficiently unique that when combined with other information, that GUIDs could be used to re-identify an individual. As a result, GUIDs are sometimes considered protected health information, thereby restricting their sharing. To protect against this risk, ALL ALS will implement another layer of coding by utilizing NeuroSTAMPs. NeuroSTAMP is a unique study-specific identifier for a research participant created from the NeuroGUID that is not reidentifiable. Through the NeuroSTAMP, multi-modal clinical, genomic, and digital data will be linked across datasets, resources, platforms, and vendors, including NeuroBANK and NeuroPRO, as well as with the biofluid biorepository at BioSEND (Indiana University), and a biorepository for cell lines at Sampled (Rutgers University). NeuroSTAMP will also be used to shared data with external requestors without reidentification risk, while preserving the ability to link datasets. In these cases, the ALL ALS DCC will be the honest broker for NeuroGUID and could link datasets without releasing GUID or NeuroGUID strings to data requestors.

Data and sample collection and storage processes were carefully designed so that all data can readily flow through the central AMP ALS data portal for sharing with the worldwide research community (Figure 3).

### Partnerships and opportunities for collaboration

The design and launch of ALL ALS were facilitated by critical input from several stakeholders including people living with and/or at risk of developing ALS, caregivers, non-profit organizations, academic investigators and scientists, the Foundation for the NIH (FNIH), the Critical Path Institute, industry representatives, the AMP ALS Steering Committee, and the NIH. ALL ALS leadership is committed to continuing to work collaboratively with these partners, as well as establish new partnerships and collaborations, to ensure the Consortium can adapt to changes in the ALS landscape and continue to bring efficiency and quality to its operations and deliverables. The Northeast ALS Consortium (NEALS), the largest consortium of ALS clinical research centers <sup>47</sup>, will support ALL ALS through the use of NEALS resources for webinar education, site communication, and community engagement. People living with ALS will continue to provide input into the AMP ALS and ALL ALS projects through representation on steering committees.

ALL ALS is inextricably linked to other key ALS studies collecting prospective data and biofluids. The ALL ALS consortium will strive to harmonize with data from other

efforts so that research and participant efforts are additive, rather than duplicative. Key project alignments include Answer ALS, the Target ALS Longitudinal Biofluid Study, the ALS/MND Natural History Consortium, the NIH NeuroBioBank (post-mortem tissue), the ALS Therapy Development Institute (ALSTDI) ALS Research Consortium (ARC), PRECISION ALS<sup>48</sup>, and ALLFTD<sup>41</sup>.

The Target ALS Longitudinal Biomarker Study collects longitudinal clinical information and biofluids, including cerebrospinal fluid (CSF), from all participants. Every Target ALS Longitudinal Biomarker study site is also be site within ALL ALS. Target ALS has also developed a long-standing postmortem tissue core with ALS and control tissues linked to whole genome sequencing and bulk RNA sequencing of specific brain and spinal cord regions. ALL ALS has established a working group of experienced ALS tissue banking experts within the consortia to explore postmortem tissue collections within ALL ALS in partnership with the NIH NeuroBioBank. The ALS/MND Natural History Consortium is an ongoing effort with two closely linked studies aimed at collecting longitudinal clinical data with coordination activities conducted at MGH and University of Minnesota <sup>49</sup>. Six centers from these studies will also be part of ALL ALS, expanding participation by adding off-site participants and asymptomatic ALS mutation carriers. The CDC National ALS Registry and accompanying biorepository also use NeuroGUIDs and capture rich epidemiologic and ALS history data <sup>45</sup>. The ALSTDI ARC study is an ongoing disseminated natural history and biomarker study, and the ALL ALS team has begun conversations with the ALSTDI leads to harmonize standard operating procedures where possible. Data and biosample collection SOPs for ALL ALS and each of these studies will be harmonized, but not duplicated, in hopes that the other studies will contribute their data to the AMP ALS data portal alongside ALL ALS. The ALL FTD study is a multicenter US-based observational study enrolling participants with frontotemporal dementia (FTD) and asymptomatic gene carriers who may develop FTD. ALL FTD is occurring at 16 centers that will participate in ALL ALS, creating the possibility for additional collaboration, particularly in the asymptomatic cohort. PRECISION ALS is an analogous study to ALL ALS being conducted in Europe, opening the powerful chance to conduct cross-continent collaboration and data harmonization.

In addition, several opportunities exist for immediate harmonization with existing datasets and biorepositories that have already stored data in NeuroBANK and/or used the NeuroGUID. Answer ALS was a large scale biobanking and data generation study that now hosts the longitudinal clinical data, biofluids, whole genome sequences, and iPSC from over 1000 participants. The searchable, cloud-based Answer ALS data portal has been used by hundreds of researchers, demonstrating the clear need for this type of large resource. Additionally, the NEALS Biorepository (with its over 130,000 samples and associated clinical data), Genomic Translation for ALS Care (GTAC; [NCT02795897](#)), and scores of smaller studies whose data are already harmonized and shared from the MGH data lake could be contributed to the AMP ALS data portal. Altogether, the AMP ALS portal is expected to open the door to the largest ever data aggregation in ALS.

Finally, opportunities exist for ALL ALS to further engage with people living with ALS by collaborating with community organizations to facilitate the objective of including nearly all individuals living with ALS throughout the US in this study. Such outreach efforts and

community engagement will also generate a more robust and ethnically diverse participant group.

Conclusions

ALL ALS is designed to be a collaborative ALS consortium and to run the largest, most purposefully inclusive observational and biobanking study ever conducted in the US. Its readily accessible infrastructure for the collection and storage of prospectively collected longitudinal clinical, genomic, biofluid, cell, tissue, and digital data from people who are either living with ALS or are at high risk of developing ALS will be linked to the central AMP ALS portal for sharing. The primary aim of ALL ALS is to generate a comprehensive, multi-modal, harmonized dataset for open science that is expected to help address the most pressing scientific and clinical questions in ALS drug development, with the goal of facilitating the development of more effective and personalized treatments for all people living with ALS and those who are at high genetic risk of developing ALS.

Acknowledgments:

This research was supported by the National Institute of Neurological Disorders and Stroke, National Institutes of Health, under Agreement Numbers 1OT2NS136938–01 and 1OT2NS136939–01. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This manuscript contains information generated by the ALL ALS Consortium.

The authors wish to thank all collaborators and colleagues who have contributed to the design of this project and continue to provide invaluable feedback. A heartfelt thanks to the people with lived experience of ALS and ALS non-profits for their advocacy and support.

Appendix: ALL ALS Consortium Author List

| Author               | Institution                                |
|----------------------|--------------------------------------------|
| J. Americo Fernandes | Nebraska Medicine ALS Treatment Center     |
| Xiaoyan Li           | Duke University                            |
| Alexander V. Sherman | Massachusetts General Hospital             |
| Betul M. Gundogdu    | University of California, San Diego        |
| Bjorn Oskarsson      | Mayo Clinic, Jacksonville                  |
| Bredna Deliz Roldan  | Universidad de Puerto Rico                 |
| Brent Harris         | Georgetown University                      |
| Charles Whitaker     | Hospital for Special Care                  |
| Cindy V. Li          | Washington University in St. Louis         |
| Courtney M. Igne     | Massachusetts General Hospital             |
| Cynthia Bodkin       | Indiana University ALS Center at IU Health |
| Daragh Heitzman      | Texas Neurology                            |
| David Walk           | University of Minnesota                    |
| Dominic Ferry        | University of California, San Diego        |
| Elijah Stommel       | Dartmouth Hitchcock                        |
| Eva L. Feldman       | University of Michigan                     |
| Frank Provenzano     | Columbia University                        |

| Author                 | Institution                                  |
|------------------------|----------------------------------------------|
| Hemali Phatnani        | Columbia University                          |
| Jackie Whitesell       | Saint Alphonsus                              |
| James D. Berry         | Massachusetts General Hospital               |
| Jeffrey D. Rothstein   | Johns Hopkins University                     |
| Jeremy Shefner         | Barrow Neurological Institute                |
| Jinsy Andrews          | Columbia University                          |
| John Ravits            | University of California, San Diego          |
| Jonathan Glass         | Emory University                             |
| Kelly Gwathmey         | Virginia Commonwealth University             |
| Laura A. Foster        | University of Colorado Denver                |
| Laura Rosow            | University of California, San Francisco      |
| Laurie Guttman         | Indiana University ALS Center at IU Health   |
| Marianne Chase         | Massachusetts General Hospital               |
| Mark Bromberg          | University of Utah                           |
| Mark Garret            | Massachusetts General Hospital               |
| Matthew Harms          | Columbia University                          |
| Michael Weiss          | University of Washington                     |
| Mohamed Kazamel        | University of Alabama, Birmingham            |
| Namita A. Goyal        | University of California, Irvine             |
| Nan Jiang              | University of Alabama, Birmingham            |
| Neil Shneider          | Columbia University                          |
| Nicholas Maragakis     | Johns Hopkins University                     |
| Nicholas Olney         | Providence Brain and Spine Center            |
| Praveena Mohan         | Barrow Neurological Institute                |
| Robert Bowser          | Barrow Neurological Institute                |
| Sabrina Paganoni       | Massachusetts General Hospital               |
| Senda Ajroud-Driss     | Northwestern University                      |
| Shafeeq Ladha          | Barrow Neurological Institute                |
| Sheetal Shroff         | Houston Methodist                            |
| Stephen A. Goutman     | University of Michigan                       |
| Stephen Brierre        | Our Lady of the Lake Regional Medical Center |
| Stephen J. Kolb        | Ohio State University                        |
| Suma Babu              | Massachusetts General Hospital               |
| Terry Heiman-Patterson | Temple University                            |
| Timothy Miller         | Washington University in St. Louis           |
| Valerie Wojna          | Universidad de Puerto Rico                   |
| Xiaoyan Li             | Duke University Medical Center               |
| Ximena Arcila-Londono  | Henry Ford Health                            |
| Zachary Simmons        | Penn State Health Hershey Medical Center     |

## Abbreviations

**ALS**

amyotrophic lateral sclerosis

|                           |                                                                                                                    |
|---------------------------|--------------------------------------------------------------------------------------------------------------------|
| <b>AIMS</b>               | ALS Impairment Multidomain Scale                                                                                   |
| <b>ALSFRS-R</b>           | ALS functional rating scale-revised                                                                                |
| <b>ALSFRS-RSE</b>         | ALS Functional Rating Scale – Revised Self-Entry                                                                   |
| <b>ALS TDI</b>            | ALS Therapy Development Institute                                                                                  |
| <b>AMP ALS</b>            | Accelerating Medicines Partnership ALS                                                                             |
| <b>ARES</b>               | ALS Respiratory Symptom Scale                                                                                      |
| <b>BNI</b>                | Barrow Neurological Institute                                                                                      |
| <b>CCC</b>                | clinical coordinating center                                                                                       |
| <b>CDC</b>                | center for disease control                                                                                         |
| <b>CDE</b>                | common data element                                                                                                |
| <b>CDISK</b>              | Clinical Data Interchange Standards Consortium                                                                     |
| <b>CDASH</b>              | Clinical Data Acquisition Standards Harmonization                                                                  |
| <b>CLIA</b>               | Clinical Laboratory Improvement Amendments                                                                         |
| <b>COA</b>                | clinical outcome assessment                                                                                        |
| <b>CPIB</b>               | Communicative Participation Item Bank                                                                              |
| <b>CP-RND</b>             | Critical Path for Rare Neurodegenerative Diseases                                                                  |
| <b>CSF</b>                | cerebrospinal fluid                                                                                                |
| <b>DIALS</b>              | Dominantly Inherited ALS                                                                                           |
| <b>DNA</b>                | deoxyribonucleic acid                                                                                              |
| <b>ECAS</b>               | Edinburgh cognitive assessment scale                                                                               |
| <b>EDC</b>                | electronic data capture                                                                                            |
| <b>EMG</b>                | electromyography                                                                                                   |
| <b>EQ5D5L</b>             | European Quality of Life 5 Dimensions 5 Levels                                                                     |
| <b>FDA</b>                | Food and Drug Administration                                                                                       |
| <b>FINH</b>               | Foundation for the NIH                                                                                             |
| <b>FTD</b>                | frontotemporal dementia                                                                                            |
| <b>CDR PLUS NACC FTLD</b> | CDR Dementia Staging Instrument PLUS National Alzheimer's Coordinating Center (NACC) Behavior and Language Domains |
| <b>GCP</b>                | good clinical practice                                                                                             |

|                 |                                                           |
|-----------------|-----------------------------------------------------------|
| <b>GUID</b>     | global unique identifier                                  |
| <b>GTAC</b>     | Genomic Translation for ALS Care Study                    |
| <b>HHD</b>      | handheld dynamometry                                      |
| <b>HHS</b>      | US Department of Health and Human Services                |
| <b>IND</b>      | investigational new drug                                  |
| <b>iPSCs</b>    | induced pluripotent stem cells                            |
| <b>IRB</b>      | institutional review board                                |
| <b>MND</b>      | motor neuron disease mPIs: multi-Principal Investigators  |
| <b>NEALS</b>    | Northeast ALS Consortium                                  |
| <b>NfL</b>      | neurofilament light chain                                 |
| <b>MGH</b>      | Massachusetts General Hospital                            |
| <b>MND</b>      | motor neuron disease                                      |
| <b>mPI</b>      | multiple principal investigators                          |
| <b>NCRI</b>     | Neurological Clinical Research Institute                  |
| <b>NEALS</b>    | Northeast ALS Consortium                                  |
| <b>NIH</b>      | National Institutes of Health                             |
| <b>NINDS</b>    | National Institute of Neurological Disorders and Stroke   |
| <b>Pre-FALS</b> | Presymptomatic Familial ALS Study                         |
| <b>PPP</b>      | public private partnership; PRO: patient reported outcome |
| <b>sIRB</b>     | single institutional review board                         |
| <b>SOA</b>      | schedule of activities                                    |
| <b>SOPs</b>     | standard operating procedures                             |
| <b>US</b>       | United States (of America)                                |
| <b>VC</b>       | vital capacity                                            |

## REFERENCES:

1. Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Lancet Neurol* 2016;15(7):673–684. [PubMed: 27068280]
2. Benatar M, Wu J, Lombardi V, et al. Neurofilaments in pre-symptomatic ALS and the impact of genotype. *Amyotroph Lateral Scler Frontotemporal Degener* 2019;20(7–8):538–548. [PubMed: 31432691]

3. Benatar M, Zhang L, Wang L, et al. Validation of serum neurofilaments as prognostic and potential pharmacodynamic biomarkers for ALS. *Neurology* 2020;95(1):e59–e69. [PubMed: 32385188]
4. Huang F, Zhu Y, Hsiao-Nakamoto J, et al. Longitudinal biomarkers in amyotrophic lateral sclerosis. *Ann Clin Transl Neurol* 2020;7(7):1103–1116. [PubMed: 32515902]
5. Shefner JM, Bedlack R, Andrews JA, et al. Amyotrophic Lateral Sclerosis Clinical Trials and Interpretation of Functional End Points and Fluid Biomarkers: A Review. *JAMA Neurol* 2022;79(12):1312–1318. [PubMed: 36251310]
6. Miller TM, Cudkowicz ME, Genge A, et al. Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS. *N Engl J Med* 2022;387(12):1099–1110. [PubMed: 36129998]
7. Paganoni S, Macklin EA, Hendrix S, et al. Trial of Sodium Phenylbutyrate-Taurursodiol for Amyotrophic Lateral Sclerosis. *N Engl J Med* 2020;383(10):919–930. [PubMed: 32877582]
8. Shimizu H, Nishimura Y, Shiide Y, et al. Pharmacokinetics of Edaravone Oral Suspension in Patients With Amyotrophic Lateral Sclerosis. *Clin Ther* 2023.
9. Writing G, Edaravone ALSSG Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2017;16(7):505–512. [PubMed: 28522181]
10. Berry JD, Cudkowicz ME, Shefner JM. Predicting success: optimizing phase II ALS trials for the transition to phase III. *Amyotroph Lateral Scler Frontotemporal Degener* 2014;15(1–2):1–8.
11. Sherman AV, Gubitzi AK, Al-Chalabi A, et al. Infrastructure resources for clinical research in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 2013;14 Suppl 1:53–61. [PubMed: 23678880]
12. Accelerating Medicines Partnership. Volume 2024: Foundation for NIH.
13. Focus Area: Biomarkers. Volume 2024: FDA.
14. Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. *BDNF ALS Study Group (Phase III). J Neurol Sci* 1999;169(1–2):13–21. [PubMed: 10540002]
15. Shefner JM, Liu D, Leitner ML, et al. Quantitative strength testing in ALS clinical trials. *Neurology* 2016;87(6):617–624. [PubMed: 27385750]
16. Shefner JM. Strength Testing in Motor Neuron Diseases. *Neurotherapeutics* 2017;14(1):154–160. [PubMed: 27600518]
17. Andrews JA, Meng L, Kulke SF, et al. Association Between Decline in Slow Vital Capacity and Respiratory Insufficiency, Use of Assisted Ventilation, Tracheostomy, or Death in Patients With Amyotrophic Lateral Sclerosis. *JAMA Neurol* 2018;75(1):58–64. [PubMed: 29181534]
18. Saxon JA, Thompson JC, Harris JM, et al. The Edinburgh Cognitive and Behavioral ALS Screen (ECAS) in frontotemporal dementia. *Amyotroph Lateral Scler Frontotemporal Degener* 2020;21(7–8):606–613. [PubMed: 32811199]
19. Crockford C, Newton J, Lonergan K, et al. Measuring reliable change in cognition using the Edinburgh Cognitive and Behavioural ALS Screen (ECAS). *Amyotroph Lateral Scler Frontotemporal Degener* 2018;19(1–2):65–73. [PubMed: 29214872]
20. Gray D, Lesley R, Mayberry EJ, et al. Development, reliability, validity, and acceptability of the remote administration of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS). *Amyotroph Lateral Scler Frontotemporal Degener* 2023:1–8.
21. Berry JD, Paganoni S, Carlson K, et al. Design and results of a smartphone-based digital phenotyping study to quantify ALS progression. *Ann Clin Transl Neurol* 2019;6(5):873–881. [PubMed: 31139685]
22. Beukenhorst AL, Burke KM, Scheier Z, et al. Using Smartphones To Reduce Research Burden In A Neurodegenerative Population: Assessing Participant Adherence In Observational Study And Clinical Trial Context. *JMIR mHealth and uHealth* 2021 (in press).
23. Johnson SA, Karas M, Burke KM, et al. Wearable device and smartphone data quantify ALS progression and may provide novel outcome measures. *NPJ Digit Med* 2023;6(1):34. [PubMed: 36879025]
24. Rutkove SB, Qi K, Shelton K, et al. ALS longitudinal studies with frequent data collection at home: study design and baseline data. *Amyotroph Lateral Scler Frontotemporal Degener* 2019;20(1–2):61–67. [PubMed: 30486680]

25. Allison KM, Yunusova Y, Campbell TF, et al. The diagnostic utility of patient-report and speech-language pathologists' ratings for detecting the early onset of bulbar symptoms due to ALS. *Amyotroph Lateral Scler Frontotemporal Degener* 2017;18(5–6):358–366. [PubMed: 28355886]
26. Barnett C, Green JR, Marzouqah R, et al. Reliability and validity of speech & pause measures during passage reading in ALS. *Amyotroph Lateral Scler Frontotemporal Degener* 2020;21(1–2):42–50. [PubMed: 32138555]
27. Stipancic KL, Palmer KM, Rowe HP, et al. “You Say Severe, I Say Mild”: Toward an Empirical Classification of Dysarthria Severity. *J Speech Lang Hear Res* 2021;64(12):4718–4735. [PubMed: 34762814]
28. Eshghi M, Yunusova Y, Connaghan KP, et al. Rate of speech decline in individuals with amyotrophic lateral sclerosis. *Sci Rep* 2022;12(1):15713. [PubMed: 36127362]
29. Maffei MF, Green JR, Murton O, et al. Acoustic Measures of Dysphonia in Amyotrophic Lateral Sclerosis. *J Speech Lang Hear Res* 2023;66(3):872–887. [PubMed: 36802910]
30. Stegmann GM, Hahn S, Liss J, et al. Early detection and tracking of bulbar changes in ALS via frequent and remote speech analysis. *NPJ Digit Med* 2020;3:132. [PubMed: 33083567]
31. Stegmann GM, Hahn S, Duncan CJ, et al. Estimation of forced vital capacity using speech acoustics in patients with ALS. *Amyotroph Lateral Scler Frontotemporal Degener* 2021;22(sup1):14–21. [PubMed: 34348537]
32. Stegmann G, Charles S, Liss J, et al. A speech-based prognostic model for dysarthria progression in ALS. *Amyotroph Lateral Scler Frontotemporal Degener* 2023:1–6.
33. Johnson SA, Burke KM, Scheier ZA, et al. Longitudinal comparison of the self-entry Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-RSE) and Rasch-Built Overall Amyotrophic Lateral Sclerosis Disability Scale (ROADS) as outcome measures in people with amyotrophic lateral sclerosis. *Muscle Nerve* 2022;66(4):495–502. [PubMed: 35904151]
34. Chew S, Burke KM, Collins E, et al. Patient reported outcomes in ALS: characteristics of the self-entry ALS Functional Rating Scale-revised and the Activities-specific Balance Confidence Scale. *Amyotroph Lateral Scler Frontotemporal Degener* 2021;22(7–8):467–477. [PubMed: 33771057]
35. Bakker LA, Schroder CD, Tan HHG, et al. Development and assessment of the inter-rater and intra-rater reproducibility of a self-administration version of the ALSFRS-R. *J Neurol Neurosurg Psychiatry* 2020;91(1):75–81. [PubMed: 31558653]
36. Mehdipour A, Teshler L, Dal Bello-Haas V, et al. Assessing the Measurement Properties of the Self-Administered Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R): A Rasch Analysis. *Phys Ther* 2023;103(11).
37. Brizzi KT, Bridges JFP, Yersak J, et al. Understanding the needs of people with ALS: a national survey of patients and caregivers. *Amyotroph Lateral Scler Frontotemporal Degener* 2020;21(5–6):355–363. [PubMed: 32396393]
38. Baxi EG, Thompson T, Li J, et al. Answer ALS, a large-scale resource for sporadic and familial ALS combining clinical and multi-omics data from induced pluripotent cell lines. *Nat Neurosci* 2022;25(2):226–237. [PubMed: 35115730]
39. Otto M, Bowser R, Turner M, et al. Roadmap and standard operating procedures for biobanking and discovery of neurochemical markers in ALS. *Amyotroph Lateral Scler* 2012;13(1):1–10.
40. Benatar M, Stanislaw C, Reyes E, et al. Presymptomatic ALS genetic counseling and testing: Experience and recommendations. *Neurology* 2016;86(24):2295–2302. [PubMed: 27194384]
41. Staffaroni AM, Quintana M, Wendelberger B, et al. Temporal order of clinical and biomarker changes in familial frontotemporal dementia. *Nat Med* 2022;28(10):2194–2206. [PubMed: 36138153]
42. Mitsumoto H, Jang G, Lee I, et al. Primary lateral sclerosis natural history study - planning, designing, and early enrollment. *Amyotroph Lateral Scler Frontotemporal Degener* 2023;24(5–6):394–404. [PubMed: 36576200]
43. Johnson SB, Whitney G, McAuliffe M, et al. Using global unique identifiers to link autism collections. *J Am Med Inform Assoc* 2010;17(6):689–695. [PubMed: 20962132]
44. Bakkar N, Boehringer A, Bowser R. Use of biomarkers in ALS drug development and clinical trials. *Brain Res* 2015;1607:94–107. [PubMed: 25452025]

45. Mehta P, Raymond J, Punjani R, et al. Prevalence of amyotrophic lateral sclerosis (ALS), United States, 2016. *Amyotroph Lateral Scler Frontotemporal Degener* 2022;23(3–4):220–225. [PubMed: 34423697]
46. Quintana M, Saville BR, Vestrucci M, et al. Design and Statistical Innovations in a Platform Trial for ALS. *Ann Neurol* 2023.
47. Lincoln TC, Allen C. CLT-01 The NEALS Consortium - a collaborative research organization. *Amyotroph Lateral Scler Frontotemporal Degener* 2019;20(sup1):262–288. [PubMed: 31702475]
48. McFarlane R, Galvin M, Heverin M, et al. PRECISION ALS-an integrated pan European patient data platform for ALS. *Amyotroph Lateral Scler Frontotemporal Degener* 2023;24(5–6):389–393. [PubMed: 37221648]
49. Berger A, Locatelli M, Arcila-Londono X, et al. The natural history of ALS: Baseline characteristics from a multicenter clinical cohort. *Amyotroph Lateral Scler Frontotemporal Degener* 2023:1–9.
50. de Jongh AD, van Eijk RPA, Bakker LA, et al. Development of a Rasch-Built Amyotrophic Lateral Sclerosis Impairment Multidomain Scale to Measure Disease Progression in ALS. *Neurology* 2023;101(6):e602–e612. [PubMed: 37311649]
51. Baylor C, Burns M, Eadie T, Britton D, Yorkston K. A qualitative study of interference with communicative participation across communication disorders in adults. *Am J Speech Lang Pathol* 2011;20(4):269–287. [PubMed: 21813820]
52. Heiman-Patterson TD, Sherman MS, Yu D, et al. Use of a new ALS specific respiratory questionnaire: the ARES score. *Amyotroph Lateral Scler Frontotemporal Degener* 2021;22(sup1):48–53. [PubMed: 34348538]
53. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67(6):361–370. [PubMed: 6880820]
54. Wei QQ, Hou Y, Chen Y, et al. Health-related quality of life in amyotrophic lateral sclerosis using EQ-5D-5L. *Health Qual Life Outcomes* 2021;19(1):181. [PubMed: 34284776]
55. Antao VC, Horton DK. The National Amyotrophic Lateral Sclerosis (ALS) Registry. *J Environ Health* 2012;75(1):28–30.

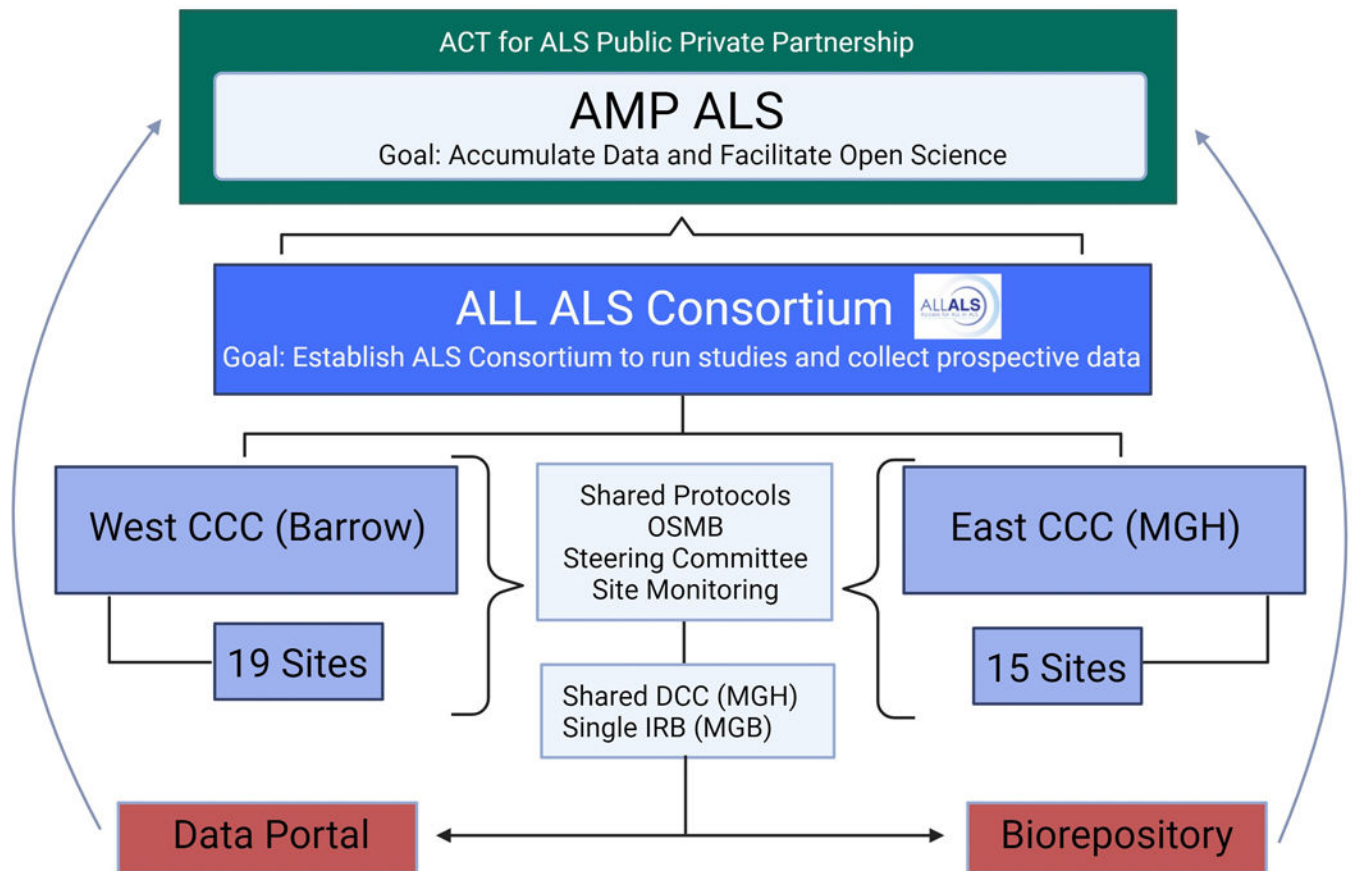


**Figure 1: ALL ALS organizational structure**

The Access for All in ALS (ALL ALS) Consortium has been established with the goal of leading multicenter prospective studies in ALS. All data and biosamples will be shared using an Open Science approach through a cloud-based portal and central biorepository to advance ALS research. The ALL ALS Consortium consists of East and West Clinical Coordinating Centers working in close coordination, sharing protocols, an observational study monitoring board (OSMB), steering committee, site monitoring, data coordinating center (DCC), and single institutional review board (IRB). Initially, 34 study sites will participate in the consortium.



**Figure 2: ALL ALS site map.**

Thirty-four U.S. sites have been selected to participate in Access for All in ALS (ALL ALS) to enroll a diverse population across a broad geographic area.

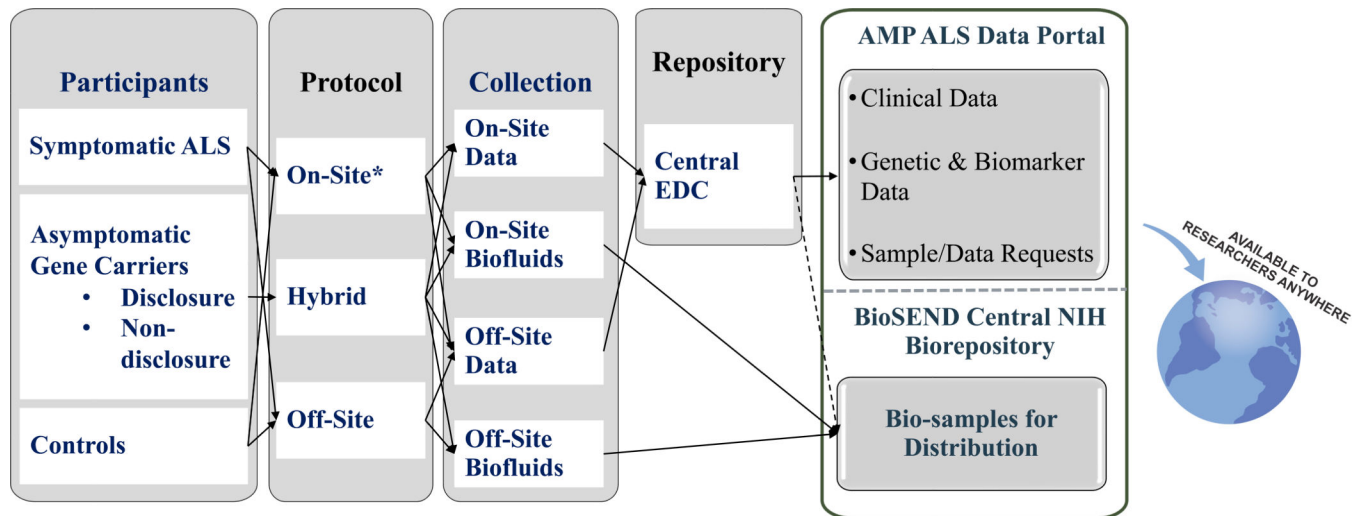


**Figure 3. Overview of data and sample collection and storage.**

Data will be collected from 1) Symptomatic ALS Participants, 2) Asymptomatic carriers of amyotrophic lateral sclerosis (ALS)-causative gene mutations, and 3) Control Participants. The protocols will incorporate on-site, off-site and/or hybrid models for participation, including collection of biosamples and data on-site (in clinic), off-site (at home) or in combination. All samples will be sent to the central repository and data will be entered into the central electronic data capture system (EDC), consisting of NeuroBANK for site-entered data and NeuroPRO for patient reported outcome (PRO) measures. Data from the EDC will be forwarded to the Accelerating Medicines Partnership for ALS (AMP ALS) portal for broad sharing.

\*On-site participants with symptomatic ALS will also complete electronic patient reported outcomes (ePROs) at home using the NeuroPRO™ system.

**Table 1.**

Assess ALL ALS study outcome measures (symptomatic ALS participants).

| <b>In Clinic/On-Site Participants</b> |                              |                       |                  |
|---------------------------------------|------------------------------|-----------------------|------------------|
| <b>Measure</b>                        | <b>Frequency</b>             | <b>Core/ Elective</b> | <b>Location</b>  |
| ECAS                                  | Every 4 Months               | Core                  | Clinic           |
| ALSFRS-R                              | Every 4 Months               | Core                  | Clinic           |
| Vital capacity                        | Every 4 Months               | Core                  | Clinic           |
| Hand-Held Dynamometry (Limited)       | Every 4 Months               | Core                  | Clinic           |
| Blood Collection                      | Every 4 Months               | Core                  | Clinic           |
| Lumbar Puncture/CSF Collection        | Baseline, 4, 8 and 12 Months | Elective              | Clinic           |
| Speech Recording                      | Monthly                      | Core                  | Home             |
| Patient Reported Outcomes (PROs)      | Monthly                      | Core                  | Home             |
| <b>Remote/ Off-Site Participants</b>  |                              |                       |                  |
| <b>Measure</b>                        | <b>Frequency</b>             | <b>Core/ Elective</b> | <b>Location</b>  |
| ECAS                                  | Every 4 Months               | Core                  | Clinic           |
| ALSFRS-R                              | Every 4 Months               | Core                  | Home (Via Video) |
| Blood Collection                      | Every 4 Months               | Core                  | Home             |
| Speech Recording                      | Monthly                      | Core                  | Home             |
| Patient Reported Outcomes (PROs)      | Monthly                      | Core                  | Home             |

AS – Edinburgh Cognitive and Behavioral ALS Screen

ALSFRS-R – ALS Functional Rating Scale – Revised

CSF – Cerebrospinal Fluid

PROs – Patient Reported Outcome Measures

**Table 2.**  
Approach to Patient Reported Outcome Measures (PROs).

| Most Concerning Symptoms for plwALS                    | Current ALL ALS PRO                                                                                                                                                                                                        |
|--------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Weakness/Physical Function                          | ALSFRS-RSE <sup>33, 21,34–36</sup><br>AIMS <sup>50</sup>                                                                                                                                                                   |
| 2. Fatigue                                             | No PRO selected                                                                                                                                                                                                            |
| 3. Dysarthria                                          | CPIB <sup>51</sup>                                                                                                                                                                                                         |
| 4. Dyspnea                                             | ARES <sup>52</sup>                                                                                                                                                                                                         |
| 5. Sleep                                               | No PRO selected                                                                                                                                                                                                            |
| 6. Depression/Anxiety/Mood Disorder/Emotional Lability | HADS <sup>53</sup>                                                                                                                                                                                                         |
| 7. Pain                                                | No PRO selected                                                                                                                                                                                                            |
| 8. Quality of Life                                     | EQ5D5L <sup>54</sup>                                                                                                                                                                                                       |
| <b>Areas of Interest for ALS Researchers</b>           |                                                                                                                                                                                                                            |
| 1. Social Determinants of Health                       | Questions pertaining to:<br>Positive and Negative Religious Coping<br>Positive and Negative Religious Coping<br>Socioeconomic Status<br>Education<br>Stress and Coping<br>Social Support<br>Loneliness/Social Interactions |
| 2. Environmental Exposures                             | Developed in consultation with the Center for Disease Control National ALS Registry <sup>55</sup>                                                                                                                          |

ALSFRS-RSE – ALS Functional Rating Scale – Revised Self-Entry

AIMS – ALS Impairment Multidomain Scale

CPIB – Communicative Participation Item Bank

ARES – ALS Respiratory Symptom Scale

HADS – Hospital Anxiety and Depression Scale

EQ5D5L – European Quality of Life 5 Dimensions 5 Levels

**Table 3.**

PREVENT ALS schedule of activities.

| Measure                                                         | Frequency                     | Core/ Elective           | Proctored/ Independent |
|-----------------------------------------------------------------|-------------------------------|--------------------------|------------------------|
| <b>In Clinic/On-Site Measures/Procedures</b>                    |                               |                          |                        |
| Neurologic Examination + Assessment for Clinically Manifest ALS | Every 12 months               | Core                     | Proctored              |
| Genetic Counseling                                              | Every 12 months and as needed | Core                     | Proctored              |
| Blood Collection (Serum, Plasma, Whole Blood, RNA)              | Every 12 months               | Core                     | Proctored              |
| Vital capacity                                                  | Every 12 months               | Core                     | Proctored              |
| Hand-Held Dynamometry (Full)                                    | Every 12 months               | Core                     | Proctored              |
| Cognitive Assessments (ECAS, CDR® PLUS NACC FTLD)               | Every 12 months               | Core                     | Proctored              |
| Lumbar Puncture/CSF Collection                                  | Every 12 months               | Elective                 | Proctored              |
| EMG/NCS                                                         | Every 12 months               | Elective (site specific) | Proctored              |
| <b>Remote/ Off-Site Measures/Procedures</b>                     |                               |                          |                        |
| Blood Collection                                                | Every 3 months                | Core                     | Proctored              |
| Digital Speech Assessment                                       | Every 3 months                | Elective                 | Independent            |
| Questionnaires: ALS symptoms questionnaire, Exposures, PROs     | Every 3 months                | Core                     | Independent            |

ECAS – Edinburgh Cognitive and Behavioral ALS Screen

CDR PLUS NACC FTLD – Clinical Dementia Rating PLUS National Alzheimer’s Disease Coordinating Center Frontotemporal Lobe Dementia

CSF – Cerebrospinal Fluid

EMG/NCS – Electromyography/Nerve Conduction Studies

PROs – Patient Reported Outcome Measures