Amyotrophic Lateral Sclerosis (ALS):

Exploring Diagnostic Criteria, Drug Development, and Clinical Trial Challenges

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Introduction

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disorder that primarily attacks motor neurons in the brain and the spinal cord.

The disease leads to the gradual deterioration and eventual death of motor neurons, which are crucial for controlling voluntary muscles. This results in increasing muscle weakness, disability, and eventually, death.

ALS was first described in 1869 by French neurologist Jean-Martin Charcot. However, it came to widespread public attention in 1939 when Lou Gehrig, a famous American baseball player, was diagnosed. Since then, ALS has been associated with his name, especially in the United States. Despite over a century of research, the exact causes of ALS remain elusive, and there is still no cure.

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iNGENū is the FDA-centric Australian CRO championing disruptive, innovative biotech firms. We are physician-led, providing access to the full spectrum of clinical and non-clinical research services.

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Australian expertise combined with direct FDA submission capabilities, offering a streamlined path for global approval.

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Expertise From the Start

Engage directly with our team of highly qualified doctors and PhD scientists from the outset.

Ready to discuss your Clinical Trial?
For further information on how iNGENū can assist you to conduct your clinical trial, book a Discovery Call with one of our Advisors.

Insights on Amyotrophic Lateral Sclerosis

Key Characteristics of ALS

- **Progressive Neurodegeneration:** ALS primarily affects the motor neurons in the brain and spinal cord, leading to their gradual degeneration and death.
- **Muscle Weakness and Atrophy:** One of the earliest signs of ALS is muscle weakness, starting typically in one part of the body and spreading, leading to severe muscle wasting (atrophy) over time.
- **Loss of Voluntary Muscle Control:** As the disease progresses, patients lose the ability to initiate and control all voluntary movement, which can include walking, speaking, swallowing, and breathing.
- **Variability in Symptom Onset and Progression:** Symptoms can start in the limbs (limb onset) or with speech/swallowing (bulbar onset) and can vary significantly from person to person in terms of progression rate.
- **Lifespan after Diagnosis:** The average life expectancy after an ALS diagnosis is three to five years, although some patients may live longer.

Influences

- **Biological Factors:** Biological factors in ALS revolve around genetic mutations and familial inheritance. Approximately 5-10% of ALS cases are familial, meaning there is a known genetic mutation passed through family members that increases the risk of developing the disease.
- **Psychological Factors:** While ALS is primarily a biological disease, the psychological impact can be significant due to its progressive and debilitating nature. This psychological stress can exacerbate physical symptoms, impact treatment outcomes, and affect quality of life.
- **Environmental Factors**
  - Smoking – There is evidence that smoking is a risk factor for ALS, particularly in women post-menopause.
  - Exposure to Environmental Toxins – Some studies suggest that exposure to lead or other substances, either in the workplace or at home, might increase ALS risk.
  - Military Service – Research indicates that individuals who have served in the military are at higher risk.

Diagnostic Criteria and Evolving Standards in ALS

ICD-11 Diagnostic Criteria and Codes

ICD-11 classifies ALS under the code 8B60.0. ALS is defined as a progressive, fatal neurologic disorder showing signs of lower motor neuron (LMN) and upper motor neuron (UMN) degeneration across various regions such as bulbar, cervical, thoracic, and lumbosacral.

It necessitates electrophysiological studies to confirm LMN degeneration and exclude other causes, with neuroimaging to rule out alternative conditions that could explain the features.

Additionally, there is an ICD-11 classification for Amyotrophic Lateral Sclerosis-Plus (ALS-Plus), identified as 8B60.5, representing a spectrum of disorders characterized by ALS motor symptoms compounded by features of other neurological dysfunctions, such as extrapyramidal, cerebellar, or cognitive impairments.

Evolution of Diagnostic Criteria

These El Escorial criteria have evolved over time, emphasizing the need for a multidisciplinary approach for a comprehensive diagnosis, incorporating clinical, electrophysiological, and imaging findings to improve sensitivity and specificity.

Diagnostic Criteria for ALS

1. **Presence of Lower Motor Neuron Degeneration** – Detected by clinical, electrophysiological, or neuropathological examination.
2. **Presence of Upper Motor Neuron Degeneration** – Determined through clinical examination.
3. **Progressive Spread of Symptoms** – Signs should extend within one region or to other regions as the disease progresses.
4. **Exclusion of Other Diseases** – Electrophysiological and neuroimaging evidence must exclude other processes that could explain LMN and UMN signs.
5. **Diagnostic Testing and History** – Medical and family history, including physical and neurological examinations.
6. **Rule-out Procedure** – ALS is often diagnosed after excluding other conditions (a "rule-out" procedure).
7. **Revised El Escorial and Awaji Criteria** – Utilized for a structured diagnostic approach; and incorporated with clinical findings and results from EMG and other tests.

Epidemiology of ALS

Incidence Rate:
ALS incidence is 1.6 to 2.7 new cases per 100,000 individuals annually worldwide. This rate can vary significantly depending on geographical and genetic factors, indicating environmental and hereditary roles in disease onset.

Prevalence:
The global prevalence of ALS is estimated to be around 4-8 per 100,000 individuals. Prevalence tends to increase with age, peaking between 55 and 75 years.

Age of Onset:
ALS commonly manifests between the ages of 40 and 70, with an average onset at approximately 55 years. However, cases can occur at much younger or older ages, denoted as early-onset and late-onset ALS, respectively.

Gender Distribution:
The disease exhibits a slight male predominance, with a male to female ratio of about 1.5:1. However, this disparity diminishes with advancing age, leading to a more balanced distribution in older populations.

Geographic Variations:
Geographical disparities in ALS incidence and prevalence have been observed, with higher rates reported in Western countries compared to Asia and Africa.

Genetic Factors:
Approximately 5-10% of ALS cases are familial, hinting at a strong genetic component. Mutations in several genes, such as C9orf72, SOD1, TARDBP, and FUS, are associated with familial ALS.

Racial and Ethnic Considerations:
While ALS affects all racial and ethnic groups, variations in incidence rates have been noted. Caucasians, particularly those of Northern European descent, tend to have higher rates compared to African, Asian, and Hispanic populations.

Environmental Factors:
Certain environmental factors, such as exposure to heavy metals, pesticides, and military service, have been associated with increased ALS risk. The role of lifestyle factors, including smoking and physical activity, remains under investigation.

FDA-Approved ALS Drugs: A Closer Look

Drug Name	Year of Approval	Sponsor	Mechanism of Action	Therapeutic Effects
Riluzole	1995	Rhone-Poulenc Rorer Pharmaceuticals, Inc (now part of Sanofi)	Inhibits glutamatergic neurotransmission to exert neuroprotective effects	Modestly prolongs survival and/or time to tracheostomy in ALS patients
Edaravone	2017	Mitsubishi Tanabe Pharma America	Scavenges free radicals to prevent oxidative stress damage to neurons	Slows down the progression of ALS in certain patient groups
Nuedexta	2010	Avanir Pharmaceuticals	Acts on sigma-1 and NMDA receptors in the brain, exact mechanism in PBA is unknown	Reduces the frequency and severity of emotional outbursts associated with pseudobulbar affect (PBA)
Tiglutik (Thickened Riluzole)	2018	ITF Pharma	It is believed to modulate glutamate neurotransmitter signaling, potentially reducing harmful neuron excitation	Tiglutik is intended to make riluzole administration easier for ALS patients who have difficulty swallowing
RELYVRIO (AMX0035)	2022	Amylyx Pharmaceuticals Inc.	Targets both the endoplasmic reticulum and mitochondria within motor neurons	Slow ALS progression by protecting motor neurons from cellular stress

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Pivotal Endpoints for ALS Clinical Trials

The determination of pivotal endpoints in ALS clinical trials presents significant challenges due to the disease's complexity, variability in progression, and multidimensional impact on patients. Endpoints in clinical trials are critical as they define what the study aims to measure to assess the efficacy of a treatment.

1. Survival Time:

The duration from when a patient starts treatment in a clinical trial to their death. It is used to determine if a treatment can extend life expectancy in ALS patients.

2. ALS Functional Rating Scale-Revised:

A clinical tool assessing motor function, including speech, swallowing, and walking, to track disease progression and response to treatment.

3. Time to Assisted Ventilation:

Tracks when patients require mechanical ventilation due to respiratory muscle weakness, indicating disease advancement.

4. Muscle Strength:

Uses objective measures like dynamometry to assess the loss of muscle strength, a key symptom of ALS progression.

5. Respiratory Function:

Often evaluated through Forced Vital Capacity (FVC) tests, measuring lung capacity and strength, crucial due to ALS's impact on respiratory muscles.

6. Quality of Life Measures:

Utilizes patient-reported outcomes to assess the impact of ALS on daily life, emotional well-being, and social interactions.

7. Biomarkers:

Involves identifying biological indicators like neurofilament light chains, which can provide insights into ALS pathology and progression.

8. Cognitive and Behavioral Function:

Assesses changes in mental health and behavior, important as ALS can affect cognitive functions.

An Overview of Previous Failures in ALS Trials

Name of Drug/ Technique	Clinical Trial Identifier	Findings
Diaphragm Pacing System	ISRCTN 53817913	• Addition of diaphragm pacing to standard care with non-invasive ventilation was associated with decreased survival in patients with ALS *Suggests it should not be used as routine treatment for patients with ALS in respiratory failure*
Mexiletine	GDCT0131777	• There were no significant differences in the ALS Functional Rating Scale-Revised (ALSFRS-R) scores between the two groups (mexiletine and riluzole) after six months of treatment • There was a significant difference in the subjective decline in total cough capacity (SDTC), favoring the mexiletine group *Suggests mexiletine may have some effects on respiratory function but does not significantly alter overall disease progression as measured by ALSFRS-R*
Nutritional interventions (gastrostomy for severe dysphagia)	ProGas study (DOI: 10.1016/S1474-4422(15)00104-0)	**Patient Recruitment and Gastrostomy Distribution** • The procedures included percutaneous endoscopic gastrostomy, radiologically inserted gastrostomy, per-oral image-guided gastrostomy, and surgical gastrostomy **Procedure Success Rates** • Approximately 6% of all attempted gastrostomy procedures were unsuccessful, with similar failure rates observed across different gastrostomy techniques *Results support the continued use of gastrostomy in managing ALS-related dysphagia and nutritional issues while emphasizing the importance of careful patient selection and procedural planning to optimize outcomes*

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Common Failure Points in ALS Clinical Trials

Clinical trials in ALS face numerous challenges and failure points that can impact their outcomes and the development of new therapies. Understanding these failure points is crucial for improving trial design, patient outcomes, and the overall success rate of ALS research.

1. Small Sample Sizes:

Small groups may not accurately reflect treatment effects, reducing the statistical power to detect significant changes.

2. High Patient Dropout Rates:

Loss of participants can bias results, especially if dropouts are related to adverse effects or lack of treatment efficacy.

3. Lack of Standardized Outcome Measures:

Inconsistent metrics across studies complicate comparisons, making it hard to consolidate findings or build upon previous research.

4. Disease Variability Among Participants:

ALS's heterogeneous nature makes it difficult to assess treatment effects uniformly across diverse patient populations.

5. Absence of Reliable Biomarkers:

Without clear biological markers, tracking ALS progression and response to treatment becomes challenging.

6. Ethical Concerns with Placebo Controls:

Using placebos raises ethical issues, particularly when effective treatments are lacking, affecting patient willingness to participate and trial fairness.

7. Inadequate Follow-up Duration:

Insufficient time to observe long-term effects or late-stage outcomes of the disease.

8. Misalignment with Patient Priorities:

Failing to focus on outcomes that matter most to patients, which can affect trial participation and relevance.

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Enhancing Clinical Trial Protocols: Towards FDA Approval

To enhance the protocol and increase the possibility of FDA approval for an ALS study, it is crucial to integrate the latest scientific insights with regulatory compliance. This involves:

Pre-trial Planning

Engage in early and continuous dialogue with the FDA through pre-IND meetings to understand regulatory expectations and obtain feedback on study design and endpoints.

Robust Study Design

Develop a clear, comprehensive protocol based on solid scientific rationale. Ensure the study design addresses FDA concerns, including patient safety, clear inclusion/exclusion criteria, and relevant endpoints.

Data Quality and Integrity

Implement stringent data management practices, including electronic data capture, to ensure data quality and integrity. Implement quality control measures throughout the trial to ensure adherence to GCP.

Patient Recruitment and Retention

Design patient-centric trials with accessible locations and minimal burden to enhance recruitment and retention. Consider using patient advocacy groups to understand patient needs and improve participation rates.

Safety Monitoring

Establish an independent data monitoring committee to oversee the safety of trial participants, ensuring that any adverse events are promptly addressed and reported to the FDA.

By integrating these strategies, clinical trials for ALS can be more effectively designed, conducted, and analyzed, leading to higher quality data and a greater likelihood of FDA approval. Ultimately, these efforts aim to accelerate the development of safe and effective therapies, addressing the unmet needs of patients and advancing the field of ALS research and treatment.

Notable Key Opinion Leaders in ALS

Name	Specialty	Designation	Location	Brief Bio
Assoc. Prof. Susan Mathers	Neurology	Clinical Director, Calvary Health Care Bethlehem	Vic, Australia	In addition to her role at Calvary Health Care Bethlehem, Associate Professor Susan Mathers is a Consultant Neurologist at Monash Medical Centre. Her professional affiliations extend to being a member of the Motor Neurone Disease Research Institute of Australia, the MND Research Tissue Bank, and a founding member of the Australian MND Register. Her primary focus lies in the management of chronic progressive neurological diseases and advancing models of care.
Dr. David W Schultz	Neurology	Assoc. Prof. at Flinders University, and Head of Neurology and Stroke at Flinders Medical Centre	SA, Australia	Dr. David W. Schultz is a distinguished neurologist with a rich background in the field. Dr. Schultz is recognized for his comprehensive approach as a general neurologist and has specific clinical and research interests in Motor Neurone Disease (MND). His commitment to MND extends to his membership on the Executive Committee for the Australian Motor Neurone Disease Registry and the Scientific Advisory Committee for the Fight MND Foundation.
Dr. Arman Sabet	Neurology	Neurologist, Gold Coast Hospital and Health Service	Qld, Australia	Dr. Arman Sabet is a respected figure in the field of neurology, with a notable tenure as the Director of Neurology at Gold Coast University Hospital, where he has served for over 15 years. His professional journey is marked by active engagement in clinical trials, particularly in areas concerning stroke treatments and neurological diseases. A notable aspect of his work includes conducting trials on the use of medicinal cannabis for early-stage motor neurone disease, showcasing his commitment to exploring innovative treatments within the neurological field.
Prof. Merrilee Needham	Neurology	Professor, Murdoch University	WA, Australia	Professor Merrilee Needham holds multiple roles including the leader of the Myositis Research Group at the Perron Institute, Director of Research at the South Metropolitan Health Service, and Consultant Neurologist and Foundation Professor of Neurology at Fiona Stanley Hospital, Murdoch University, and Notre Dame University. She is focused on myositis research and has significantly contributed to the development of a myositis biobank and the Australasian Myositis Registry
Prof. Matthew C Kiernan	Neurology	Professor, University of Sydney	NSW, Australia	Professor Matthew C. Kiernan is a distinguished figure at the University of Sydney, holding the Bushell Chair of Neurology in the Central Clinical School and serving as the Co-Director for Discovery and Translation at the Brain and Mind Centre. His research primarily focuses on neurodegenerative diseases like motor neuron disease and frontotemporal dementia.

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If you would like further information on how iNGENū CRO can assist you to conduct your clinical trial, please contact Dr Sud Agarwal or Adam Moodie:

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