Multiple Sclerosis (MS):
Overcoming Clinical Trial Challenges and Enhancing Protocols

INGENŪ CRO

Introduction

Multiple Sclerosis (MS) is a complex, chronic disease affecting the central nervous system (CNS), which includes the brain, spinal cord, and optic nerves.

MS is characterized by the immune system mistakenly attacking the protective sheath (myelin) that covers nerve fibers, causing communication problems between the brain and the rest of the body. Eventually, the disease can cause permanent damage or deterioration of the nerves.

The exact cause of MS remains unknown, but it is believed to be a disease where genetic susceptibility and environmental factors interact to trigger an autoimmune response against central nervous system myelin. Key factors include genetic predisposition, viral infections, smoking, and vitamin D deficiency. The disease typically manifests in several forms, with new symptoms occurring either in discrete attacks (relapsing forms) or slowly accumulating over time (progressive forms).

iNGENŪ CRO

Book a Discovery Call to learn how iNGENū can deliver high-quality, cost-efficient, FDA-compliant research for your next clinical trial

Why Choose iNGENū CRO?

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.

Local Trials, Global Approvals

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

Disciplined, Cost-Efficient Execution

Every dollar is strategically allocated, eliminating unnecessary costs while maintaining the highest quality.

Australian Headquartered, Asia-Pacific Reach

Access high-quality trials in the Asia-Pacific region, enhancing speed and scalability.

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.

Etiology, Historical Perspectives, and Clinical Manifestations

Over the years, advancements in research have led to a better understanding of the pathophysiological mechanisms of MS, allowing for more targeted therapeutic approaches. The evolution of treatment strategies from broad immunosuppressive therapies to more specific immunomodulatory drugs reflects the growing understanding of the disease's complex nature.

Historical Perspective:

MS has been recognized as a distinct disease since the 19th century. Jean-Martin Charcot, a French neurologist, is credited with the first detailed description of the disease in 1868, including the notable triad of symptoms: nystagmus, intention tremor, and telegraphic speech. Since then, the understanding of MS has significantly advanced with developments in neurology and technology, particularly MRI imaging, which has become a critical tool in the diagnosis and understanding of the disease.

Biological Factors:

The biological underpinnings of MS include inflammation, demyelination, and neurodegeneration within the CNS. The immune system's abnormal response leads to the destruction of myelin and the formation of scar tissue (sclerosis), which disrupts the normal flow of electrical impulses along the nerves.

Psychological Impact:

Multiple Sclerosis (MS) is an autoimmune disorder characterized by immune system dysregulation leading to demyelination and neurodegeneration in the central nervous system. Genetic predispositions, particularly within the human leukocyte antigen (HLA) system, increase susceptibility to this autoimmune response.

Environmental Influences:

Epidemiological studies have shown a greater prevalence of MS in regions farther from the equator, suggesting that environmental factors such as sunlight exposure and Vitamin D levels may play a role in disease susceptibility. Vitamin D is believed to influence the immune system in a way that reduces the risk of developing autoimmune diseases like MS.

Diagnostic Criteria for Multiple Sclerosis

ICD-11 Code for Multiple Sclerosis

In the International Classification of Diseases, 11th Revision (ICD-11), MS is classified under code 8A40, which encompasses multiple sclerosis and other demyelinating diseases of the central nervous system. This classification is used globally for medical diagnosis and health management and provides a standard framework for reporting and monitoring the incidence and prevalence of diseases like MS.

Diagnostic Criteria

Diagnosis of MS involves a combination of medical history, physical exams, MRI, and sometimes spinal fluid analysis. The most widely accepted criteria for diagnosing MS are the McDonald Criteria, which have been periodically updated, with the latest revision in 2017. These criteria are designed to facilitate a more straightforward and timely diagnosis, integrating clinical assessment with MRI findings.

Key Elements of the McDonald Criteria

1. **Clinical Evidence:**
   Evidence of damage in at least two separate CNS areas.
2. **Temporal Dissemination:**
   Showing that the lesions occurred at different times.
3. **Spatial Dissemination:**
   Evidence of lesions in different CNS areas.
4. **Exclusion of Other Diagnoses:**
   No other explanations better account for symptoms.

Impact of the McDonald Criteria

By providing a clear, evidence-based framework for diagnosis, the criteria have enhanced the consistency and accuracy of MS diagnoses worldwide. This has important implications for patient care, allowing for earlier initiation of disease-modifying therapies that can slow disease progression and improve quality of life.

Epidemiology of Multiple Sclerosis

Global Prevalence and Incidence:
The prevalence of MS varies significantly by geographical location and ethnicity. The disease is most common in North America and Europe, with rates generally higher farther from the equator. This variance has led to theories regarding environmental factors, such as vitamin D deficiency due to lower sunlight exposure, contributing to the risk of developing MS.

Age and Gender Distribution:
MS is typically diagnosed in individuals between the ages of 20 and 50, although it can occur at any age. MS is more prevalent in women than in men, with recent studies indicating that the ratio can vary between 2:1 and 3:1. This discrepancy suggests that hormonal factors, genetics, or environmental exposures might influence the risk of developing MS differentially by sex.

Genetic Susceptibility:
While MS is not directly inherited, there is a higher risk among relatives of affected individuals, indicating a genetic predisposition. Siblings of an MS patient have a higher risk compared to the general population, highlighting the role of genetic factors in disease susceptibility.

Comorbidities:
The presence of other autoimmune diseases or chronic health conditions in individuals can also be an important epidemiological factor. Conditions like type 1 diabetes, thyroid disease, and inflammatory bowel disease have been found more frequently in people with MS compared to the general population. These comorbidities might share common genetic or environmental risk factors with MS.

Migration Studies:
Studies of population migration provide insights into the role of environmental factors in MS. Individuals who migrate from a high-risk area to a low-risk area before adolescence tend to adopt the lower risk of their new environment, and vice versa. This observation suggests that environmental exposures during early life play a crucial role in determining MS risk later in life.

Microbiome:
Emerging research is examining the role of the gut microbiome. The diversity and composition of gut bacteria may influence immune system functioning and has been proposed as a factor in MS development and progression.

FDA-Approved Medications for Multiple Sclerosis

Drug Name	Year of Approval	Sponsor	Mechanism of Action	Therapeutic Effects
Copaxone (Glatiramer Acetate)	1996	Teva Pharmaceuticals	Immunomodulator, alters immune processes	Reduces relapse rate in relapsing-remitting MS
Tecfidera (Dimethyl Fumarate)	2013	Biogen	Anti-inflammatory, protects against oxidative stress	Reduces relapses, delays progress
Ocrevus (Ocrelizumab)	2017	Genentech (Roche)	Targets CD20 B cells	Reduces relapse rate and slows progression in PPMS and RRMS
Rebif (Interferon beta-1a)	2002	Merck	Immunomodulator, enhances immune system	Reduces frequency of relapses
Gilenya (Fingolimod)	2010	Novartis	Sphingosine 1-phosphate receptor modulator	Reduces relapse rate and brain lesion activity

INGENŪ CRO

Pivotal Endpoints for MS Clinical Trials

Pivotal endpoints for MS clinical trials are critical for assessing the effectiveness and safety of new therapeutic agents. These endpoints are designed to measure various aspects of disease activity, progression, and the patient's quality of life. Identifying and validating these endpoints pose significant challenges due to the heterogeneity and unpredictable nature of MS.

Common Pivotal Endpoints in Multiple Sclerosis Trials

Annual Relapse Rate:

ARR is a commonly used primary endpoint in MS trials. It measures the frequency of clinical attacks or exacerbations that reflect acute inflammation in the central nervous system.

Disability Progression:

Often measured by the Expanded Disability Status Scale, which quantifies disability in 8 functional systems and provides an overall score ranging from 0 (normal neurological exam) to 10 (death due to MS).

MRI Lesions:

New or enlarging T2 lesions and gadolinium-enhancing lesions on MRI are used as surrogate markers for inflammation and disease activity.

Brain Volume Loss (or Brain Atrophy):

An important indicator of progression and neurodegeneration in MS. Measuring changes in brain volume over time can provide insights into the long-term impact of the disease and treatment efficacy.

No Evidence of Disease Activity:

NEDA status has emerged as a composite endpoint that encompasses the absence of relapses, no new or enlarging MRI lesions, and no EDSS progression.

Quality of Life:

Instruments like the MS Quality of Life-54 questionnaire assess various dimensions of QoL, but integrating these subjective measures into clinical trial design and interpreting their results can be complex.

Failed Clinical Trials to Determine Drug Efficacy to Treat Multiple Sclerosis

Drug Candidate	Clinical Trial Identifier	Reason for termination/drug failure
Opicinumab (Anti-LINGO-1)	NCT01721161	Whilst complete, the trial did not meet its primary endpoint of significantly improving optic nerve conduction velocity, as evidenced by FF-VEP latency, in the ITT population. While there was a trend towards improvement in the per-protocol population, this did not reach statistical significance. Secondary outcomes, including changes in RNFL thickness and RGCL/IPL thickness, as well as low-contrast letter acuity, did not show significant improvements with BIIB033 treatment compared to placebo.
Rituximab	NCT01212094	• Inadequate response in slowing disability progression in SPMS • Different disease mechanisms between RRMS and SPMS • Potential safety concerns and adverse effects • Possible methodological issues leading to insufficient statistical power • Incomplete understanding of SPMS pathology
Siponimod (Secondary Progressive MS)	NCT01665144	The trial met its primary endpoint of reducing the risk of three-month confirmed disability progression compared to placebo. However, the results were not as robust in all secondary endpoints, leading to mixed interpretations of the drug's overall benefit in SPMS.
Laquinimod	NCT01707992	While the trial was completed as per its protocol, the results did not robustly meet the primary efficacy endpoints to the extent required for a clear path to widespread clinical use or regulatory approval without concerns.
Amiloride, Fluoxetine, and Riluzole	NCT01910259	The MS-SMART trial, while completed, was not successful because none of the three drugs tested—amiloride, fluoxetine, and riluzole — demonstrated efficacy in significantly slowing down the progression of brain atrophy or impacting the rate of disability progression in patients with Secondary Progressive Multiple Sclerosis (SPMS).

INGENŪ CRO

Common Failure Points in Multiple Sclerosis Clinical Trials

Clinical trials in MS are essential for advancing treatment options and understanding the disease's pathophysiology. However, these trials 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 MS research.

Common Failure Points

Patient Recruitment and Retention:

MS can be a highly variable disease, with patients at different stages and with different forms of the disease. Finding enough participants who meet the specific criteria for a study can be difficult.

Heterogeneity of the Disease:

Patients can present with a wide range of symptoms and progression rates, which can vary significantly between patients. This variability makes it challenging to create a one-size-fits-all study design and can complicate the interpretation of results.

Endpoints and Outcome Measures:

Traditional endpoints like relapse rate or progression on the Expanded Disability Status Scale (EDSS) may not fully capture the benefits of a treatment, particularly for progressive forms of MS.

Statistical and Methodological Flaws:

These issues may include inadequate sample size, improper randomization, inappropriate control groups, insufficient blinding, reliance on subjective measures, and inconsistent adherence monitoring.

Biomarkers and Pathophysiological Understanding:

The absence of clear biomarkers is a significant limitation. Without these, it is challenging to measure the direct impact of treatments on the disease course.

Regulatory and Ethical Considerations:

Differences in regulatory standards and ethical expectations across countries can lead to delays, increased costs, and even trial discontinuation.

Safety Concerns and Standard of Care Treatment Options

Safety Concerns in MS Treatments

1. **Immunosuppression:** Many DMTs for MS work by suppressing or modifying the immune system. While effective in reducing relapses and slowing disease progression, this can increase susceptibility to infections.
2. **Liver Damage:** Certain MS medications can lead to elevated liver enzymes and liver damage.
3. **Infusion Reactions:** Drugs administered via infusion can cause reactions ranging from mild to severe.
4. **Cardiovascular Effects:** Some MS treatments can affect heart rate and blood pressure, necessitating baseline and periodic cardiovascular evaluations.
5. **Teratogenicity:** Many MS drugs are contraindicated during pregnancy due to risks of fetal harm. Patients of childbearing potential must use effective contraception and discuss family planning with their healthcare provider.
6. **Secondary Autoimmunity:** Some treatments may trigger other autoimmune conditions, such as thyroid disorders or type 1 diabetes, requiring ongoing vigilance and screening.

Standard of Care Treatment Options

1. **Disease-Modifying Therapies (DMTs):** The cornerstone of MS treatment, aimed at reducing disease activity and progression.
2. **Symptom Management:** Symptomatic treatments focus on improving daily functioning and quality of life.
3. **Rehabilitative Services:** Physical, occupational, and speech therapy can help manage symptoms, improve function, and maintain independence.
4. **Psychological Support:** Mental health services, including counseling or therapy, can address the psychological impacts of living with a chronic disease like MS.
5. **Lifestyle Modifications:** Diet, exercise, and smoking cessation play roles in managing MS symptoms and overall health.
6. **Regular Monitoring:** Ongoing assessment of disease activity and treatment response through clinical evaluations and MRI.
7. **Multidisciplinary Approach:** Collaborative care involving neurologists, nurses, therapists, and other healthcare professionals ensures comprehensive management.

INGENŪ CRO

Enhancing Protocol Design: Strategies for FDA Approval

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

Strategic Planning and Protocol Design

- Patient-Centric Design
- Precision Medicine Approach
- Innovative Trial Models
- Endpoint Selection

Regulatory and Ethical Considerations

- Regulatory Engagement
- Ethical Review and Approval
- Compliance and Transparency
- Ethical Recruitment and Consent

Data Management and Analysis

- Robust Data
- Collection Statistical Rigor

Operational Excellence and Collaboration

- Operational Efficiency
- Collaborative Partnerships
- Post-Market Surveillance

Patient Safety and Risk Management

- Safety Monitoring
- Patient Education

By integrating these strategies, clinical trials for MS 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 MS therapies, addressing the unmet needs of patients and advancing the field of MS research and treatment.

Notable Key Opinion Leaders in Multiple Sclerosis

Name	Specialty	Designation	Location	Brief Bio
Jason Burton	Neurology	Consultant Neurologist	WA, Australia	Dr. Jason Burton is a Consultant Neurologist at Fiona Stanley Hospital and The Perron Institute, and also practices at Nexus Neurology. He has previously worked at Sir Charles Gairdner and Fremantle Hospitals. He completed his medical degree at the University of Western Australia in 1997 and underwent specialist neurological training at Sir Charles Gairdner and Royal Perth Hospitals. His areas of specialty include multiple sclerosis, motor neuron disease, and general neurology.
Joshua Barton	Neurology	Neurologist	NSW, Australia	Dr. Joshua Barton is a neurologist currently associated with SCUH and Beach Brain, providing high-level tertiary care in Neurology. Dr. Barton completed his early neurological training in South-East Queensland and pursued further specialization with a Fellowship in Multiple Sclerosis and Neuroimmunology at the Royal Prince Alfred Hospital in Sydney. Following his fellowship, Dr. Barton worked as a consultant neurologist in the Brain and Mind Centre's Multiple Sclerosis clinic for four years. During this time, he also undertook a PhD in Multiple Sclerosis at the University of Sydney. His expertise and contributions are focused on the treatment and management of multiple sclerosis and related neurological conditions.
Mark Marriott	Neurology	Neurologist	Victoria, Australia	Dr. Mark Marriott is a distinguished neurologist affiliated with the Royal Melbourne and Box Hill Hospitals. He completed his medical degree with first class honors from Monash University in 1994 and became a neurology specialist in 2002. Dr. Marriott has contributed significantly to research in Multiple Sclerosis through his work at the Walter & Eliza Hall Institute for Medical Research and the Howard Florey Institute, culminating in a PhD from the University of Melbourne.
Katherine Buzzard	Neurology;Allergy and Immunology	Consultant Neurologist	Victoria, Australia	Dr. Katherine Buzzard is a renowned Consultant Neurologist with expertise in multiple sclerosis and neuroimmunology. She practices at Neurology Network Melbourne with consulting locations in Box Hill and Fitzroy. Dr. Katherine holds a BSc (Hons) and a PhD in cancer biology from the Peter Mac Callum Cancer Institute, and an MBBS (Hons) from The University of Melbourne. Dr. Buzzard completed her neurology specialty training at the Royal Melbourne Hospital and the Alfred Hospital and has been recognized with the ANZAN overseas fellowship at Queen Square London, UK. She leads the Multiple Sclerosis and Neuroimmunology Service at Eastern Health and holds a consultancy at The Royal Melbourne Hospital's MSNI clinic.

iNGENū CRO

The Australian CRO championing innovative biotech firms for global success.
Delivering high-quality, FDA-compliant clinical research.

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:

Dr Sud Agarwal
Chief Executive Officer
BSc (Hons), MB ChB FANZCA DDU
dr.sudhanshu@ingenucro.com

Adam Moodie
Director, Scientific Engagement
BSc
adam.moodie@ingenucro.com

Unit 22, 456 St Kilda Road, Melbourne, 3004

www.ingenuCRO.com