Motor Neuron disease (MND) is the overarching description of the devastating neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) or Lou Gehrig’s disease, that attack motor neurons. What is the state of play in this rare disease in terms of clinical therapies and what are the challenges faced in designing a clinical trial in this area?

ALS is the most common form of MND and is known as Lou Gehrig’s disease in the US, after the great American baseball player whose career was ended by the disease. It affects both upper and lower motor neurons and limb weakness and wasting is a key symptom. Other types of MND that have recently been characterised are

- Progressive bulbar palsy
- Progressive muscular atrophy
- Primary lateral sclerosis (PLS, sub-types being ascending, multifocal, and sporadic paraparesis (PLS-A, PLS-M or PLS-SP))
- Kennedy’s disease

Current Therapy

These disorders are rare, and treatments even rarer. There is one drug approved for the treatment of ALS – Riluzole (Rilutek in the US), developed by Rhone Poulenc Rorer (now Sanofi) and approved in 1995. It was shown to delay disease progression in clinical studies and in 2012 sales reached $64 million before generics were introduced in 2013.

Progression and Aetiology

Age of onset is generally in the late middle-ages, but in rare cases can affect people in their early twenties. Progression varies, with ALS generally leading to death in two to four years, although a small number of ALS cases have had an essentially normal lifespan albeit with severe disability. The eminent British scientist Stephen Hawking was diagnosed in his twenties with ALS and he is now in his 70s...
although completely paralysed. With PLS the life span is also essentially normal but with severe disability.

What is known about the causes of MND? As with most neurodegenerative disorders the cause is unknown. There is increasing work looking at the role of genetics in ALS. It has also been noticed that MND seems to affect more male, fit sportsmen, such as Lou Gehrig and more recently the Dutch footballer Fernando Ricksen. Various reviews have investigated this, but no definitive conclusions have been reached \cite{1,2}. However, this has led to a lot of research looking at energy metabolism.

**Challenges in Clinical Trials**

Let’s have a look at the major challenges ahead for drug developers when they are planning their phase II and crucially the phase III trials.

- **Patient selection.** There are many types of MND and the knowledge of each type is evolving, it is crucial that the correct patients are included from what is a very heterogeneous disease. The inclusion/exclusion criteria may need to go beyond the typical diagnosis in order to achieve this.

- **End point selection** - The current gold standard is the ALS functional rating scale (ALSFRS). The advantage of this scale is that it measures the progression of disability and, therefore, meets the clinically relevant hurdle. The disadvantage is that it is a composite score covering multiple symptoms and domains, such as limb and bulbar dysfunction as well as dyspnea, orthopnea, and the need for ventilatory support. As such, the slope of decline is not consistently linear and statistical assumptions based on a linear model may be incorrect.

Other endpoints have been the traditional survival/time to death, meaning that patients are included in the study whilst in the midst of a rapid decline in their condition. This is a highly clinically relevant endpoint but presents a challenge to demonstrate an effective product. The primary endpoint in the recent large (973 patients) phase III ALS study, named Empower from Biogen, used a combined assessment of function and survival, based on changes in ALSFRS total scores and time to death up to 12 months.

**Top tips to help you through the mine field**

In aiming for a homogenous population additional inclusion/exclusion criteria could be used to supplement the traditional diagnosis (e.g. the revised El Escoral criteria).

Cognitive and behavioural impairment are now recognised features of
ALS, however, they are often not measured in clinical trials and are not part of the ALSFRS. Importantly cognitive dysfunction particularly in executive function may predict those patients with reduced survival \(^3,^4\).

Additional outcome measures such as the Neurophysiological Index (NI) could be included. The NI has good intra-rater reliability and has been shown to be sensitive to change in ALS, its inclusion may allow for shorter studies \(^5\).

Inclusion of biomarkers in clinical trials of MND. Work is on-going in this area such as the NIH/NINDS and ALS associations funded study of validation of biomarkers in ALS and NINDS funded study of screening and natural history of PLS and related disorders (see http://1.usa.gov/1mdA9yA). It is clear that future trials must routinely incorporate candidate biomarkers if the historical reliance on survival as the primary outcome measure is to be overcome.

Ideally we would like to see patients being offered, as soon as they are diagnosed, immediate entry into a short clinical trial, with a biomarker outcome, modelling the clinical trial pathway of people with a cancer diagnosis. With the increased research that has taken place over the last decade this may just be possible.