These criteria recognize definite, probable, and possible MSA. Approximately 25% of patients with idiopathic late onset cerebellar ataxia can be longer. When considering cerebellar signs and symptoms, neurological features within five years, but in rare cases this interval can be longer. When levodopa responsive Parkinsonism or cerebellar ataxia. Unfortunately, lack of response to L-dopa is present in less than 50% of patients and although this response to L-dopa might be suboptimal, when present it is surprisingly sustained with a mean duration of 3 to 3.5 years, suggesting that levodopa responsiveness should be critically reconsidered as a requirement for the diagnosis of probable MSA-P. Possible MSA requires a sporadic, progressive adult onset disease including Parkinsonism or cerebellar ataxia and at least one feature suggesting autonomic dysfunction, plus one other feature that may be a clinical or a neuroimaging abnormality. Despite the acceptance of the consensus criteria over the past ten years, clinical trials have not meaningfully benefited in terms of homogeneity of patient populations or signal detection. Of note, a large series of MSA patients from the Mayo Clinic Brain Bank exhibited an unexpectedly low diagnostic accuracy, suggesting further refinement of these consensus criteria may be needed. Of 134 patients with clinically diagnosed MSA, only 83 (62%) had definite MSA confirmed at autopsy.

Outcome Measures
In addition to the diagnostic difficulties with initial misclassification, the selection of experienced investigators in MSA trials is paramount toward the successful conduct of a controlled clinical trial. This is important not only for diagnostic purposes but to ensure reliable and consistent outcome measures. Due to the disease rarity, complex disease neurobiology and clinical heterogeneity, there are only a handful of clinical research sites of excellence present across a small number of countries. In fact, one of the largest countries (the United States) is the only country close to approaching double-digit numbers of sites of excellence in MSA research. Even in such experienced sites, monitoring of strict adherence to diagnostic criteria is mandatory and we have found it useful to have an independent expert’s supervision of diagnostic procedures to ensure appropriate patient selection. Additionally, our experience across multiple orphan and ultra-orphan neurological indications support Singer et al’s reliance on an oligocentre model that selects the smallest number of very experienced and high-performing sites to ensure proper patient identification and to reduce outcome variability.

Additionally, a standardised rater training programme covering both diagnostics and assessments for site raters and clinical research monitors has been shown to reduce variability and improve signal detection via a multi-pronged training approach: assessment through audio or video recordings which must achieve at least 85-90% concordance with the score of an expert consensus panel as well as the group consensus score, applied skills assessment training through a live interview with an actor trained to portray a subject with MSA, and ongoing in-study monitoring of assessment data to ensure rater consistency utilising electronic data capture “flags” to identify scoring trends, inconsistencies, and changes in scoring that may infer rater bias or drift.

The most common efficacy outcome measure in MSA trial is the Unified Multiple System Atrophy Rating Scale (UMSARS) which allows scores ranging from 0 to 104, with higher scores indicating greater impairment. This instrument consists of four parts. The first part is the UMSARS activities of daily living subscale (range 0-48), and the second is the motor examination subscale (range 0-56). The third part is measurement of autonomic function, and the fourth is a five-grade overall clinical status, similar to Hoehn and Yahr in Parkinson’s disease. UMSARS has proven to be a reliable,
and valid scale for semi-quantitative assessments of MSA patients with known rates of change associated with natural history. These rates can be used to power models of disease progression with the caveat that changes in slope vary with length of disease with steeper declines seen earlier in the illness (thus requiring fewer patients) while plateauing later in the illness. Unlike Alzheimer’s disease, where the steepest part of the clinical decline is seen in the more moderate patients, MSA patients with the steepest declines are still in a phase of illness that is early enough to have a significant impact on disease progression.

Additionally, accelerated UMSARS progression was predicted not only by shorter symptom duration at baseline, but also by an absent levodopa response. It appears that UMSARS-related disease progression slows down as early as the second year of follow-up, which is important to consider when embarking on therapeutic trials of long duration. Of note, a minimal clinically important change using the UMSARS has not yet been established for MSA patients making it difficult to appreciate the relationship between statistical significance and clinical importance. As the scale was initially validated in Europeans, its validity and applicability across various populations requires further examination. In particular, some items regarding cutting food, handling utensils, and dressing may not apply to some rural and geographically isolated cultures. Furthermore, due to the need to design a scale that was reasonably simple, short, and user-friendly, some prominent features of MSA are not fully covered by the UMSARS and other validated scales may need to be supplemented to evaluate items not covered by the UMSARS that may have an impact on the overall function of MSA subjects, such as bradyphrenia, anhedonia, depression, sleep disorders, fatigue, and overall quality of life.

Finally, the long-term follow-up of MSA patients is restricted by the rapid neurodegenerative process resulting in reduced life expectancy. This may help explain the high rate of attrition and serious adverse events often seen in MSA trials. Given the rapid disease progression, survival rates might be considered as an outcome measure particularly when inclusion criteria are not restricted to early stages of the disease. In contrast, choosing patients earlier in the disease course should help improve attrition. Utilising the correct analysis that takes into account attrition patterns coupled with limiting the sites to those experienced investigators and demanding rigorous training on diagnostic and outcome measures which minimise error variance will help to ensure the chosen sample sizes will be able to detect treatment effects should they exist.

REFERENCES


Tomislav Babic, MD, PhD

Tomislav is Vice President of Medical and Scientific Affairs/Neuroscience Franchise at Worldwide Clinical Trials Inc. Dr Babic is a board-certified neurologist and clinical pharmacologist, with particular interest in drug development for Alzheimer’s disease, Parkinson’s, and MS. He is the author of more than 60 peer-reviewed articles and books and has been integral to the development of many approved drugs for PD. His expertise has been widely noted in neurodegenerative disorders in both industry and academia for the past 25 years.

Email: tomislav.babic@worldwide.com

Natalia E. Drosopoulou, PhD

Natalia is Executive Director of Project Management and Franchise Area Lead in Neuroscience at Worldwide Clinical Trials. She received her PhD in Biochemistry, specialised in Developmental Neurobiology from King’s College of London. With over 19 years in the clinical research industry, Dr Drosopoulou’s experience spans from small intricate Phase I studies to large global Phase III programmes with a special emphasis in neurodegenerative diseases.

Email: natalia.drosopoulou@worldwide.com

Henry J. Riordan, PhD

Henry is Executive Vice President of Medical and Scientific Affairs and Global Lead for Neuroscience at Worldwide Clinical Trials. Dr Riordan has been involved in the assessment, treatment and investigation of various CNS drugs and disorders in both industry and academia for the past 20 years. He has over 100 publications, including co-authoring two books focusing on innovative CNS clinical trials methodology.

Email: henry.riordan@worldwide.com