

**Machado-Joseph Disease (MJD/SCA-3) Workshop: Where do we stand?
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Planning and feasibility of clinical trials

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Clinical trials in Machado-Joseph disease/spinocerebellar ataxia (MJD/SCA3) with neuroprotective drugs, such as lithium, or symptomatic drugs, such as varenicline have been performed, however with negative results. In the majority of recent clinical trials in ataxia, the Scale for the Assessment and Rating of Ataxia (SARA) is used as a primary outcome measure. The SARA score is highly correlated with activities of daily living, and it is a major determinant of health-related quality of life underlining the clinical relevance of SARA. SARA progression in MJD/SCA3 is comparably slow so that neuroprotective clinical trials require large numbers of patients. Based on the 8 year longitudinal data of the EUROSCA study, we calculated that more than 500 patients will be required to detect a 30% reduction in progression of the SARA score in a trial with a power of 80%. Before embarking on such large trials, smaller proof-of-concept trials are desirable. In such trials, biomarkers are used to provide evidence of target engagement and to indicate possible efficacy. Currently, however, validated biomarkers that could be used in MJD/SCA3 trials are lacking. To overcome some of these problems, we are launching the European Spinocerebellar Ataxia Type 3/Machado-Joseph Disease Initiative (ESMI) that aims at setting up a trial ready cohort by bringing together 7 European cohorts and 1 US cohort. ESMI plans to integrate the existing data in a common database and to apply standardized and quality-controlled clinical assessment, MRI and biobanking protocols. A major part of ESMI will be the development and validation of innovative assessment instruments and disease markers, including a new highly sensitive motor test battery, ambulatory sensor-based activity measurement, automated MRI volumetric evaluation, diffusion tensor imaging (DTI), and blood as well as CSF markers based on transcript profiling and disease protein (ataxin-3) measurement.