Protocol and statistical plan

Validity and Reliability of the 6-minute Walk Test Over a Distance of 6 Metres in People With Multiple Sclerosis

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Study Title	Validity and Reliability of the 6-minute Walk Test Over a Distance of 6 Metres in People With Multiple Sclerosis
Short Title / Study ID	VTM6M6m, CERVD-2019-01864
Study Registration	Clinicaltrial.gov : NCT04228328 Swiss National Clinical Trial Portal : SNCTP000003657
Study Category and Rationale	Minimum risks (A category) The tests are current and usual tests in the normal care of people with multiple sclerosis. Participants only have to walk for 6 minutes and to turn around. This turn will be timed.
Background and Rationale	The 6-minute walk test is used by physiotherapists to monitor the walking endurance of patients with multiple sclerosis. The protocol for this test calls for a distance of 30 meters (6MWT30) to be walked. However, this distance is not always available in practices and at patients' homes. The aim of this study is to validate a shorter version over a distance of 6 meters (6MWT6) and to evaluate its intra-rater reliability and the reliability of the instrument.
Risk / Benefit Assessment	The risks are a temporary increase in fatigue and the risk of falling. The direct benefits go beyond the knowledge of the performance of the tests. The participants will have feedback on their walking abilities and will use these data for their phyisotherapeutic follow-up. Performing the tests will contribute to their training in walking and physical activity recommended in their situation. The indirect benefits are the satisfaction of being able to help research on the disease that impacts them directly. Indeed, if there is a good correlation and concordance between the 6MWT6 and the 6MWT30, the use of the 6-minute test over 6 meters could be generalized.
Objective(s)	The main objective is to validate a different version of the 6MWT, the 6MWT6. The secondary objectives are to verify the reliability of this new version (of the instrument and of the rater) and to analyze the possible differences between the 6MWT6 and the 6MWT30 (according to the speed at the half-turn and other parameters: age, gender, height, EDSS score, type of disease, time since last relapse)
Endpoint(s)	6-minute walk test over 6 meters: meters walked 6-minute walk test over 30 meters: meters walked 360 Degree Turn Test: time in seconds and number of steps
Study Design	Non-randomized validation study
Statistical Considerations	The primary objective is to validate a new version of the 6MWT over a distance of 6 m, so it is necessary to prove that there is an excellent correlation with the 6MWT30, the current reference. To do this, the data will be first presented, as means and standard deviations for normally distributed variables, and as medians and interquartile ranges for non-normally distributed variables. The differences between the 6MWT6 and 6MWT30 will be

	plotted (absolute and relative values) and a test of comparison of means will be performed with Student's ttest. Than, a Pearson or Kendall coefficient (depending on the distribution of the data) will be used. Analysis of the degree of agreement according to the method described by Taffé (bias and precision plot) will supplement the Bland and Altmann plot (Taffé, 2018; Taffé et al., 2020). The secondary objective, reliability, will be assessed using the Intra Class Coefficient (ICC), according to the model: two-way mixed-effects as recommended by Koo (2016), as repeated measures cannot be considered as random sampling and absolute agreement, as agreement between repeated measures is sought (Koo & Li, 2016). The 6MWT6 data at Day1 will be compared to the same data at Day2 to assess intrarater reliability. These data will be compared to the post hoc count based on the video performed at Day1 and Day2 for instrument reliability. For the last objective, analysis of explanatory factors for the differences between 6MWT6 and 6MWT30, correlation analyses will be performed between the continuous variable of these differences and the 360DTT. Multiple linear regressions will then be performed between this dependent variable "6MWT30 - 6MWT6" and the continuous and categorical variables: 360 DTT (time), age, gender, height, time since last relapse, type of MS, and assistive device. All analyses will be performed using STATA software, v.15.1. (StataCorp LLC, College Station, TX, USA).
Inclusion- / Exclusion Criteria	The project focuses on the population of walking patients with MS. Inclusion: adults, confirmed diagnosis of MS, Expanded Disability Status Scale (EDSS) score 3 to 6.5, or be able to walk 30 metres with or without aids, good understanding of French, have already completed a 6-minute walking test, be able to give consent by signature. Exclusion: Lung disease, heart disease, co-morbidity preventing 6minWT, relapse in the last 3 months, chronic fatigue ≥ at 8 (Visual Analog Score-Fatigue).
Number of Participants with Rationale	21 participants will be needed to obtain a good correlation coefficient, which is the objective of the validation of the new version of the 6MWT. The alpha was set at 0.01, the power at 0.9 for a correlation of 0.8
Study Intervention	Test under study: People have to walk for 6 minutes without stopping when possible.
Control Intervention	No control intervention.
Study procedures	Eligible patients will be recruited by their treating physiotherapist or through the presentation of the project to the regional groups of the Swiss MS Society. The patients will be interns at the Institution or will come to the Institution of Lavigny for 2 times 1 hour and 20 minutes of testing at one week intervals. On the first day (Day1), they will perform the 6MWT6, followed by a 15-45 minutes lying down break, then they will perform the 360 Degree Turn Test. On the second day (Day2), they will perform the 6MWT30 and then the 6MWT6, interspersed with a 15-45 minutes break.
Study Duration and Schedule	March to November 2020
Investigator(s)	Sylvie Ferchichi-Barbey, physical therapist Bsc, student in Master of Sciences. 21 years of experience with multiple sclerosis patients
Study Center(s)	Insitution de Lavigny, Rte du Vignoble 60 - 1175 Lavigny Tél. 021 821 46 17 Switzerland

Ethical consideration	1. The results of this study would be generalized to the population of MS walkers with an EDSS between 3 and 6.5. They will allow the use of a valuable tool, the 6MWT6, in previously impossible contexts, i.e. in the practices and at patients' homes. Participants will benefit directly from feedback on their abilities, be able to compare these results to previous results and use this data for their phyisotherapeutic follow-up. Performing the tests will contribute to their training in walking and in the physical activity recommended for their situation. The indirect benefits are the satisfaction of being able to help research on the disease that impacts them directly. The main risk is a temporary increase in fatigue. 2. The proposed methodology is ethical because, in order to evaluate the reliability and validity of a test, while excluding the fatigue bias, it would be necessary to call the patient 3 times at a few days interval. In this context, it was attempted to do it in 2 days rather than 3 and the impact of fatigue was minimized through the systematization of the breaks in lying position with adjustable duration according to the patient's condition.
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements. A clinical trial covered by ClinO Chapter 4 may be conducted in accordance with other rules than ICH-GCP guidelines, provided that such rules are recognised in the specialty in question and the protection of participants and data quality and security are guaranteed (ClinO Art. 5, Abs 2). If the clinical trial is not conducted according to ICH-GCP guidelines, the paragraph above must be adapted accordingly.