# Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

***Masterthesis***

***The Impact of Goal-Oriented Inpatient Rehabilitation on Walking Ability in People with Multiple Sclerosis***

**Britt Corstjens**

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

**PROMOTOR :**
Prof. dr. Bart VAN WIJMEERSCH

**COPROMOTOR :**
Prof. dr. Peter FEYS
dr. Deborah SEVERIJNS

**BEGELEIDER :**
Mevrouw Sofie AERTS

**BEGELEIDER :**
Mevr. Eline EMMERS

2024
2025

**www.uhasselt.be**
Universiteit Hasselt
Campus Hasselt:
Martelarenlaan 42 | 3500 Hasselt
Campus Diepenbeek:
Agoralaan Gebouw D | 3590 Diepenbeek

# Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

***Masterthesis***

***The Impact of Goal-Oriented Inpatient Rehabilitation on Walking Ability in People with Multiple Sclerosis***

**Britt Corstjens**

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

**PROMOTOR :**
Prof. dr. Bart VAN WIJMEERSCH

**COPROMOTOR :**
Prof. dr. Peter FEYS
dr. Deborah SEVERIJNS

**BEGELEIDER :**
Mevrouw Sofie AERTS

**BEGELEIDER :**
Mevr. Eline EMMERS

## Acknowledgements

This master's thesis offered me the opportunity to delve deeper into the field of neurorehabilitation in people with multiple sclerosis, a subject that has deepened my understanding of evidence-based rehabilitation. I would like to express my gratitude to my promotor, Prof. dr. Bart Van Wijmeersch, for his guidance and critical insights throughout the entire research process. I also wish to thank my co-promotors, Prof. dr. Peter Feys and dr. Deborah Severijns, for their continuous support, valuable feedback, and for sharing their extensive expertise in the field. My sincere appreciation goes to my supervisors dra. Sofie Aerts and Msc. Eline Emmers for their essential contributions and their ongoing support throughout this project. Their involvement played a crucial role in the realization of this thesis.

Furthermore, I would like to acknowledge REVAL Rehabilitation Research Center of Hasselt University and Noorderhart RMSC Rehabilitation and Multiple Sclerosis Center of Pelt for providing the infrastructure and opportunities to carry out this study. Lastly, I am deeply grateful to my family, friends, and loved ones for their constant support, motivation, and patience throughout this process.

# Table of content

## List of abbreviations

2MWT = 2-Minute Walk Test
6MWT = 6-Minute Walk Test
ADL = activities of daily living
AI = artificial intelligence
BBS = Berg Balance Scale
CI = confidence interval
MIC = minimally important change
CNS = central nervous system
DWI = Distance Walked Index
EDSS = Expanded Disability Status Scale
EQ-5D = EuroQol 5D
FAC = Functional Ambulation Categories
FIM = Functional Independence Measure
GAS = Goal Attainment Scaling
HRQoL = health-related quality of life
IQR = interquartile range
MD = multidisciplinary
MI = Motricity Index
Mini-BESTest = Mini Balance Evaluation Systems Test
MS = multiple sclerosis
MSWS-12 = 12-Item Multiple Sclerosis Walking Scale
mTIS = modified Trunk Impairment Scale
PPMS = primary progressive multiple sclerosis
PwMS = people with multiple sclerosis
Q1 = first quartile
Q3 = third quartile
RMSC = rehabilitation and multiple sclerosis center
RRMS = relapsing-remitting multiple sclerosis
SD = standard deviation
SDMT = Symbol Digit Modalities Test
SMART = specific, measurable, achievable, realistic, timed
SPMS = secondary progressive multiple sclerosis
TCT = Trunk Control Test
TUG = Timed Up and Go

## Research context

The study is situated within the 'Neurorehabilitation' laboratory of Prof. dr. Bart Van Wijmeersch and Prof. dr. Peter Feys, who jointly supervise the research activities of the lab. The research context pertains to the domain of gait and balance, focusing on the impact of a structured inpatient multidisciplinary (MD) rehabilitation program on walking capacity and walking fatigability among individuals with multiple sclerosis (MS). Additionally, the study aims to compare patients whose primary rehabilitation goal was related to improving walking with those who had a non-walking-related primary goal. Given the progressive nature of MS and its impact on mobility and fatigue, optimizing rehabilitation strategies is essential for improving functional independence and overall quality of life of patients (Stevenson & Playford, 2007).

The relevance of this research lies in its potential to enhance clinical rehabilitation practices for MS patients. Fatigue and impaired walking capacity are among the most debilitating symptoms of the disease, significantly affecting daily functioning. Although rehabilitation programs commonly address these challenges, the specific contribution of structured, individualized goal setting within such programs remains unclear (Levack et al., 2006). By addressing this knowledge gap, this study may contribute to a better targeted and more effective approach to rehabilitation, potentially leading to improvements in care pathways and better outcomes for individuals with MS.

The study was conducted in a clinical setting, namely Noorderhart Rehabilitation and Multiple Sclerosis Center (RMSC) in Pelt, Belgium. RMSC offers specialized inpatient MD rehabilitation for people with MS (PwMS), providing an optimal environment to investigate the influence of personalized goal setting on walking outcomes. This retrospective study was conducted independently as part of a master's thesis within the Master of Rehabilitation Sciences and Physiotherapy at Hasselt University, under the supervision of Prof. dr. Bart Van Wijmeersch, head neurologist at RMSC.

National MS Center Melsbroek and Noorderhart RMSC have jointly agreed to assess patients using a standardized core set and extended set of outcome measures, with the intention of integrating this data into shared databases for future clinical and research use. This thesis represents a first pilot study within this larger rehabilitation context, with an additional focus on the clinical application of personalized goal setting and its effect on walking-related outcomes. Previous research efforts within this collaboration have primarily focused on neurophysiology (Aerts et al., 2023), whereas this study takes a more functional and clinically oriented approach.

This thesis was authored by Britt Corstjens. The research question was formulated in consultation with the thesis supervisor and co-supervisors. The masters' student was responsible for data collection, statistical analysis, and interpretation of the results, under the guidance of the previously mentioned supervisors.

# Abstract

Background: Multiple sclerosis (MS) is a chronic neurological disease often associated with impaired walking ability. Multidisciplinary (MD) rehabilitation plays a key role in improving mobility in people with MS (PwMS).

Objectives: This study aimed (1) to evaluate the impact of a 13-week inpatient MD rehabilitation program on walking outcomes in PwMS; (2) to determine whether having a walking-related primary goal affects outcomes; (3) to assess when the most improvements in walking capacity occur during rehabilitation; (4) to identify correlated clinical variables with change in walking capacity.

Methods: A retrospective analysis was conducted in 35 PwMS who completed the rehabilitation program. Walking outcomes were assessed using the 6-Minute Walk Test (6MWT), Distance Walked Index (DWI), 12-item MS Walking Scale (MSWS-12), and Timed Up and Go (TUG). Changes were analyzed over time and between subgroups, and correlations with clinical variables were explored.

Results: Significant improvements in walking capacity were observed after rehabilitation (6MWT mean increase: +70.89 m, $p$ = .001), with clinically meaningful gains in 65% of participants. The most substantial improvements occurred during the first half of the program. No significant differences were found between participants with and without a walking-related primary goal. Better balance at baseline and younger age were associated with greater improvements.

Conclusion: Inpatient MD rehabilitation led to clinically meaningful improvements in walking capacity in PwMS, especially early in the program. Goal setting showed no measurable effect, but baseline characteristics such as balance and age appear to influence outcomes.


Keywords: multiple sclerosis, rehabilitation, walking capacity, goal setting

## Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease affecting the central nervous system (CNS), characterized by inflammation, demyelination, gliosis, and neuronal loss. Worldwide, approximately 2.3 million people are affected by MS, with a higher prevalence in women than in men. MS is typically diagnosed between the ages of 20 and 50 (Haki et al., 2024) and is commonly classified into relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). However, recent insights suggest that MS should be viewed as a continuum rather than distinct subtypes (Niedziela et al., 2024). People with MS (PwMS) experience various symptoms, according to lesion location and severity. The symptoms that are experienced most are, among others, fatigue, heat sensitivity, bladder dysfunction, pain, and cognitive dysfunction (Hauser & Cree, 2020). Impairments in walking and mobility are also among the most significant concerns for PwMS, and as the disease progresses, most patients will eventually require assistance to walk. Walking is an essential component of physical functioning and is crucial for performing activities of daily living (ADL) (Kieseier & Pozzilli, 2012).

Rehabilitation for PwMS is generally regarded as effective, especially in improving physical capacities and overall walking, as assessed by various outcome measures (Amatya et al., 2019; Khan et al., 2007). PwMS who have more complex functional impairments or disabilities are appropriate candidates for multidisciplinary (MD) rehabilitation. MD rehabilitation is specialized rehabilitation with continuous care in hospital wards or specialized rehabilitation units offering more intensive MS management. The strongest evidence for the effectiveness of MD rehabilitation exists for people with progressive MS. However, those with RRMS can also benefit, especially after acute relapses with incomplete recovery (Beer et al., 2012).

During rehabilitation programs, it is important to select appropriate assessment tools that align with the individual's functional capacity and disease severity. Long walking tests, such as the 6-Minute Walk Test (6MWT), are mainly suitable for evaluating walking fatigability, maximum walking distance limitations, and functional capacity. Longer tests are minorly affected by floor effects and offer great precision in identifying disability differences in patients with mild disease. However, these tests can be more challenging for patients with significant disability (e.g., Expanded Disability Status Scale (EDSS) > 6). The 2-Minute Walk Test (2MWT), with a shorter duration, could serve as a viable alternative to the 6MWT (Kieseier & Pozzilli, 2012). Walking fatigability can be quantified using the Distance Walked Index (DWI), calculated as the percentage change in distance walked after the second minute of the 6MWT (Leone et al., 2016; Van Geel et al., 2020).

Objective assessments of walking disability demonstrate high reliability and have been validated against various other outcome measures, such as the 12-Item Multiple Sclerosis Walking Scale (MSWS-12). Patient-reported measures, like the MSWS-12, specifically designed for walking disability in MS, can be used alongside objective outcomes of walking ability to evaluate different dimensions of walking. Importantly, the MSWS-12 is considered more responsive to change than the EDSS (Kieseier & Pozzilli, 2012).

Literature indicates that goal setting at the start of rehabilitation may influence outcomes both during and after rehabilitation (Kalron et al., 2019). However, its impact on walking ability after MD rehabilitation for PwMS remains unclear. Goal setting refers to the collaborative process of establishing clear and measurable objectives, typically involving the patient and other relevant stakeholders. This process often includes defining goals at multiple levels and across different time frames to guide therapy and assess progress (Wade, 1998). Most physiotherapists establish one to three goals per patient; however, the strategies and frameworks may differ significantly. Some examples of tools that are used for goal setting are the SMART (specific, measurable, achievable, realistic, timed) criteria to formulate the goals, and the Goal Attainment Scaling (GAS) to establish the treatment goal, which is evaluated afterward to assess the extent to which the goal has been achieved (Rasova et al., 2020). So far, studies examining MD rehabilitation and exercise programs have poorly described whether included patients had set goals, through collaborative goal setting, to improve walking capacity. Only one study, using a convenience sample in multiple European MS centers, showed that changes were greater if the goal was to improve balance or walking compared to having other goals in the social or cognitive domain (Kalron et al., 2019).

Given the importance of MD rehabilitation for improving walking ability in PwMS, the primary objective of this study is to investigate the differential impact of a 13-week inpatient MD rehabilitation program on walking capacity and walking fatigability among PwMS. Additionally, this study wants to compare different subgroups, such as those who had a primary goal related to improving walking during their rehabilitation with those who had a non-walking-related primary goal. Furthermore, this study aims to determine at which stage of the rehabilitation process walking capacity improves the most, whether this improvement occurs primarily at the beginning, the end, or gradually throughout the rehabilitation, and identify the point at which this improvement is maximal. Lastly, this study wants to identify the clinical factors, such as balance and trunk control, that may be correlated with change in walking capacity after rehabilitation.

## Methods

Study design

This observational, single-center, retrospective study was conducted at Noorderhart Rehabilitation and Multiple Sclerosis Center (RMSC) in Pelt, Belgium. The study analyzed the medical records of all patients who participated in the 13-week inpatient MD rehabilitation program between May 2023 and December 2024.

Participants

Patients were eligible for inclusion if they (1) were diagnosed with MS according to the McDonald Criteria (2017), confirmed by a neurologist; (2) completed the 13-week inpatient MD rehabilitation at the study center; (3) had an EDSS score of 7.0 or less; (4) had available results of either the 6MWT or the 2MWT at a minimum of two of the following time points: pre-rehabilitation (baseline), mid-rehabilitation (6 weeks) and post-rehabilitation (13 weeks).

Patients were excluded if they (1) had incomplete documentation of primary outcome measures necessary for statistical analysis; (2) experienced a relapse during the rehabilitation period; (3) had concurrent medical conditions that could significantly affect rehabilitation outcomes, such as major surgeries (e.g., total hip replacement), or acute conditions requiring medical intervention. Mild musculoskeletal injuries, like minor overuse injuries, were managed within the rehabilitation program and did not lead to exclusion.

Eligible patients were categorized into two groups. The first group was defined as those who had a primary goal related to improving walking. These walking-related goals were subdivided into three categories. The first category includes goals related to safe and independent walking, with or without assistive devices, minimizing fall incidents. The second category encompasses goals focused on the ability to walk a specific distance, which was defined as short-, middle, or long-distance walking, and optimizing the use of walking aids. The third category includes goals aimed at improving cardiorespiratory and muscular endurance to support long-distance walking. The second group consisted of patients who had other primary goals than those related to improving walking abilities, which included all goals other than those listed above.

Given the exploratory nature of this study, sample size calculations were not conducted. Instead, the medical files of all patients who participated in the 13-week inpatient MD rehabilitation at Noorderhart RMSC were screened based on the inclusion and exclusion criteria. The latest data extraction was done in December 2024.

Procedure

**Multidisciplinary Rehabilitation Program**

All patients in both groups participated in the inpatient MD rehabilitation program. The program spanned a duration of three months, during which the primary aim was to address the individual expectations and specific needs of the participants to the fullest extent possible. After intake, a personalized rehabilitation plan was developed, tailored to the unique goals and requirements of each patient. Participants engaged in rehabilitation activities individually or in group sessions, supplemented by independent exercises, for a minimum of two hours per weekday.

Therapies were provided by a MD team, which could include physiotherapists, occupational therapists, speech therapists, psychologists, social workers and/or dietitians. Every two weeks, an interdisciplinary meeting was held. During these meetings, all professionals involved in the rehabilitation process convened to discuss various aspects, including test results, rehabilitation and treatment goals, ongoing therapy, and discharge planning. Additionally, a neurologist was responsible for the medical follow-up of the patient. This provided an opportunity for patients to address any questions or concerns regarding their treatment.

**Outcome Measures**

Descriptive data were collected for all patients, including demographic characteristics (date of birth, sex), MS-related parameters (date of MS diagnosis, type of MS, EDSS score, type of MS medication), and description of physical functioning, such as usage of assistive devices and/or orthoses. For each patient, both primary and secondary goals set during the rehabilitation program were examined. Then, specifically, the primary goals were reviewed to determine whether they were related to improving walking.

To answer the primary objective of this study, walking capacity, walking fatigability, patient-reported walking ability, and functional mobility were analyzed, assessed by the 6MWT or the 2MWT, the DWI, the MSWS-12, and the Timed Up and Go (TUG), respectively. To evaluate these outcomes, data were collected from multiple measures, as described below.

Walking capacity was measured with either the 6MWT (Goldman et al., 2008) or, in case the patient could not perform the 6MWT, the 2MWT (Valet et al., 2019). During these tests, the maximum distance a patient could walk in six or two minutes, respectively, was assessed. The course was set at 20 meters. Patients were allowed to use walking aids and/or orthoses during the test. For the 6MWT, the minimally important change (MIC) is deemed to be an improvement of 19.7 meters (Oosterveer et al., 2022), while for the 2MWT, an improvement of 9.6 meters is considered to be clinically meaningful (Baert et al., 2014). These tests were performed at the start of the rehabilitation program, after six weeks, and at the end of the program. Walking fatigability was calculated using the DWI (Van Geel et al., 2020) by comparing the distance walked at minute six with that walked at minute one during the 6MWT. Equation 1 demonstrates how the DWI is expressed as a percentage of the distance walked at minute one. The DWI was automatically computed based on the results of the 6MWT.

**Equation 1**

*Calculation of the DWI*

$$DWI_{6-1} = \left(\frac{\text{distance walked at minute 6} - \text{distance walked at minute 1}}{\text{distance walked at minute 1}}\right) \times 100$$

Patient-reported walking ability was measured with the MSWS-12 (McGuigan & Hutchinson, 2004), which is a 12-item self-report instrument developed to measure the impact of MS on a person's ability to walk. The scale consists of 12 questions. The scores of the 12 items were summed to obtain a total score, which was then converted to a percentage (0-100%). A reduction of 8 points is considered to be clinically meaningful (Mehta et al., 2015). This test was filled in at the start and at the end of the rehabilitation program. The TUG (Sebastiao et al., 2016) was used to assess functional mobility by measuring the time required for a patient to stand up from a chair, walk three meters, turn, return, and sit down again. This test was performed at the start and end of rehabilitation. A score of more than 14 seconds on the TUG indicates an increased risk of falling.

For the secondary objectives, balance, trunk control, and muscle strength were assessed in all participants, while additional outcome measures, such as walking independence, functional independence in ADL, cognitive processing speed, and health-related quality of life (HRQoL), were included if available. Below, the acquisition protocols for these secondary outcome measures are described.

Balance was evaluated using the Mini Balance Evaluation Systems Test (Mini-BESTest) (Potter et al., 2019) and/or the Berg Balance Scale (BBS) (Tyson & Connell, 2009). The Mini-BESTest assesses postural control and balance maintenance through 14 different tasks, each scored on a 3-point scale (0-2), leading to a total score between 0 and 28. The BBS focuses on balance during standing and transferring tasks, consisting of 14 items rated on a 5-point scale (0-4), resulting in a total score ranging from 0 to 56. Both tests were conducted at baseline, after six weeks, and at the end of the rehabilitation program.

Trunk control was assessed with the Trunk Control Test (TCT) (Parlak Demir & Yildirim, 2015) and the modified Trunk Impairment Scale (mTIS) (Verheyden et al., 2006). The TCT, designed to evaluate trunk stability, includes four tasks scored from 0 to 25, with the total score expressed as a percentage (0-100%). Similarly, the mTIS is used to assess trunk stability in neurological patients, with individual items scored on an ordinal scale (0-2 or 0-3), summed to obtain a total score. These tests were performed at the start of the rehabilitation program, after six weeks, and at the end of the program.

To measure muscle strength, the Motricity Index (MI) (Cameron & Bohannon, 2000) was used, focusing on motor deficits in the upper and lower limbs by assessing voluntary movement and maximum isometric strength. Each item was scored on a 33-point scale, with the total score expressed as a percentage (0-100%). For this study, only the scores for the lower extremities were included. Measurements were performed at the beginning of rehabilitation, after six weeks, and at program completion.

When available, walking independence was evaluated using the Functional Ambulation Categories (FAC) (Viosca et al., 2005), a six-level scale assessing performance in four walking tasks. To evaluate the level of a patient's disability and the assistance required for ADL, the Functional Independence Measure (FIM) (Dodds et al., 1993) was used. This tool consists of 18 items across motor and cognitive domains, rated on a 7-point ordinal scale (1 = total assistance, 7 = complete independence), and was completed three times during interdisciplinary meetings throughout rehabilitation.

Lastly, if available, cognitive and HRQoL measures were considered. Cognitive processing speed was assessed using the Symbol Digit Modalities Test (SDMT) (Strober et al., 2019), in which patients match symbols with corresponding numbers based on a reference key, with the final score representing the number of correct responses within a set time frame. This test was administered during the second week of rehabilitation.

The EuroQol 5D (EQ-5D) (Feng et al., 2021) was used to measure HRQoL, a standardized instrument evaluating five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses were recorded on a 3-point scale, forming a five-digit health profile (e.g., 12323), which could be converted into an overall score. The EQ-5D was completed once at baseline.

Statistical analysis

Data was analyzed using IBM SPSS Statistics (IBM Corp. (2022). *IBM SPSS Statistics for Macintosh, Version 29.0.* Armonk, NY: IBM Corp.) and JMP Pro (SAS Institute Inc. (2023). *JMP® Pro, Version 17.* Cary, NC: SAS Institute Inc.). The normal distribution of the continuous variables was assessed using the Shapiro-Wilk test and visual inspection of histograms and Q-Q plots. Categorical variables were presented as percentages and continuous variables as mean ± standard deviation (SD) or as median with interquartile range (IQR), in case the data were not normally distributed. Missing values were handled through the pairwise deletion method. A $p$-value ≤ 0.05 was anticipated as statistically significant for all tests.

To analyze whether there were significant differences for age, disease duration, and rehabilitation duration between the groups with and without a walking-related primary goal, a two-sample $t$-test was used. In case data were not normally distributed, the non-parametric Wilcoxon rank-sum test was performed (Appendix 1). Differences in sex, type of MS, EDSS, and type of MS medication between the same two groups were assessed using the Pearson's chi-squared test or, when expected cell counts were less than five, and thus the assumptions for using Pearson's chi-squared test were not met, the Fisher's exact test (Appendix 2).

To evaluate the effect of the rehabilitation program, various outcome measures were examined at baseline compared to post-rehabilitation. This included walking capacity (6MWT and 2MWT), walking fatigability (DWI), patient-reported walking ability (MSWS-12), and functional mobility (TUG). The appropriate statistical test was selected for each outcome based on a decision tree for continuous data (Appendix 3). This was either a one-sample $t$-test or the Wilcoxon signed-rank test. Cohen's $d$ was used to calculate the effect size.

To explore potential differences in rehabilitation outcomes between clinically relevant subgroups, separate analyses were conducted for each outcome measure. The same measures as in the previous analysis were used. For each test, a new variable (delta) was calculated by subtracting the post-rehabilitation result from the baseline result.

The subgroups included: (1) participants with vs. without a primary walking-related rehabilitation goal; (2) participants with vs. without walking fatigability at baseline; and (3) participants with EDSS ≤ 6 vs. EDSS ≥ 6.5. Walking fatigability was defined as a DWI of -10% or lower at baseline (Santinelli et al., 2025). For each comparison, the appropriate statistical test was selected using a decision tree for continuous data (Appendix 1). This was either an independent samples *t*-test or the non-parametric Wilcoxon rank-sum test. The effect size was again calculated using Cohen's *d*.

To analyze the evolution of walking capacity and walking fatigability throughout the rehabilitation program, the 6MWT, 2MWT, and DWI were assessed at three distinct time points: pre-, mid-, and post-rehabilitation. If data were normally distributed across all three time points, a repeated measures ANOVA was performed. In case Mauchly's test indicated that the assumption of sphericity was violated, the Greenhouse-Geisser correction was applied. If there proved to be a statistically significant difference across time points, a post-hoc Bonferroni multiple comparisons test was conducted to further investigate when during the rehabilitation program these changes occurred, and at which point they became maximal. The Friedman test was used if data were not normally distributed across all three time points.

To investigate which clinical factors may be correlated with the difference in walking capacity after rehabilitation, a correlation analysis was performed between the delta score of the 6MWT and a set of predefined variables: age, sex, disease duration, type of MS, EDSS score, type of MS medication, walking-related primary rehabilitation goal (yes/no), walking fatigability at baseline (yes/no), FAC level, SDMT score, EQ-5D score, and the baseline scores of the Mini-BESTest, BBS, TCT, mTIS, MI, and FIM. Pearson's correlation coefficient (*r*) was used for normally distributed variables; otherwise, Spearman's rank-order correlation ($\rho$) was applied.

<u>Ethical approval</u>

This study was approved by the ethics committee of Noorderhart VZW and the medical ethics committee of Hasselt University on 03/07/2024 (CME2024/034). Patient informed consent was not deemed necessary in accordance with Belgian legislation and ethical guidelines. Approval from the institutions was obtained to permit the secondary use of patient data for the purposes of this research.

Use of Artificial Intelligence tools

In the context of this master's thesis, artificial intelligence (AI) tools were used to support the formulation and refinement of written content (e.g., for language clarity and structure) as well as for guidance in statistical analysis and result interpretation. Specifically, OpenAI’s ChatGPT (free version, GPT-3.5) was consulted. The input prompts and AI-generated suggestions were critically reviewed and adapted by the author to ensure scientific accuracy and academic integrity.

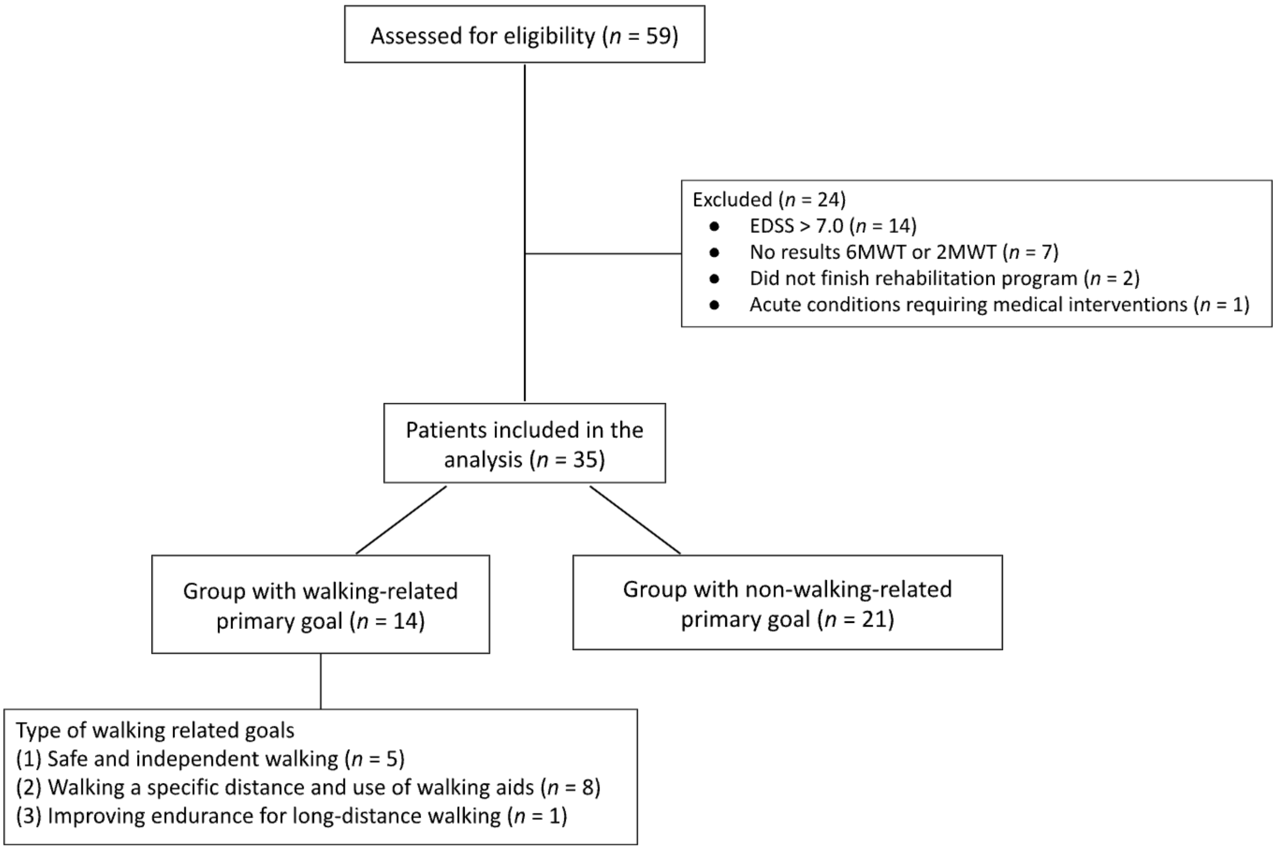
The use of AI was limited to support purposes and did not replace any part of the research process, including data collection, analysis, or final interpretation. The responsibility for all content and conclusions presented in this thesis remains entirely with the author.

## Results

In total, 59 patients participated in the 13-week inpatient MD rehabilitation program between May 2023 and December 2024. Twenty-four participants were excluded: 14 due to an EDSS score > 7, seven because of insufficient available data from either the 6MWT or the 2MWT, two for not completing all 13 weeks of the rehabilitation program, and one due to concurrent medical conditions that could significantly affect rehabilitation outcomes. Consequently, 35 patients were included in the final analysis, of which 14 had a primary goal related to improving walking and 21 had a non-walking-related primary goal. Figure 1 presents the CONSORT Flow Diagram.

**Figure 1**

*CONSORT Flow Diagram*




*Note.* EDSS = Expanded Disability Status Scale; 6MWT = 6-minute Walk Test; 2MWT = 2-minute Walk Test.

No statistically significant differences between groups were observed for age, sex, type of MS, disease duration, EDSS score, rehabilitation duration, and type of MS medication (Table 1). The mean duration of the rehabilitation program was 86 days.

**Table 1**

*Characteristics of the Study Sample*

| Variable | Total group (*n* = 35) | Group with walking-related primary goal (*n* = 14) | Group with non-walking-related primary goal (*n* = 21) | Group difference (*p*-value) |
|---|---|---|---|---|
| Age (years), mean ± SD | 53.69 ± 11.32 | 53.57 ± 8.61 | 53.76 ± 13.03 | .959 (a)(b) |
| Sex, *n* (%) | | | | .268 (c) |
| Female | 19 (54) | 6 (43) | 13 (62) | |
| Male | 16 (46) | 8 (57) | 8 (38) | |
| Type of MS, *n* (%) | | | | .896 (d) |
| RRMS | 15 (43) | 6 (43) | 9 (43) | |
| PPMS | 4 (11) | 1 (7) | 3 (14) | |
| SPMS | 16 (46) | 7 (50) | 9 (43) | |
| Disease duration (years), median [Q1,Q3] | 13 [3,21] | 10 [5.25,21.25] | 13 [2,21.50] | .987 (a) |
| EDSS, median [Q1,Q3] | 6 [4,6] | 6 [6,6.50] | 6 [4,6] | .382 (d) |
| EDSS (2.5 – 4), *n* (%) | 9 (26) | 1 (7) | 8 (38) | |
| EDSS (4.5 – 5.5), *n* (%) | 3 (8) | 1 (7) | 2 (10) | |
| EDSS (6 – 7), *n* (%) | 23 (66) | 12 (86) | 11 (52) | |
| Rehabilitation duration (days), median [Q1,Q3] | 88 [87,88] | 88 [87.75,88] | 88 [85.50,88] | .224 (a) |
| Type of MS medication, *n* (%) | | | | .895 (d) |
| None | 3 (9) | 2 (14) | 1 (5) | |
| Ocrelizumab (Ocrevus) | 10 (28) | 3 (21) | 7 (33) | |
| Interferon beta-1a (Rebif) | 1 (3) | 0 (0) | 1 (5) | |
| Natalizumab (Tysabri) | 4 (10) | 2 (14) | 2 (9) | |
| Teriflunomide (Aubagio) | 3 (9) | 2 (14) | 1 (5) | |
| Ofatumumab (Kesimpta) | 3 (9) | 1 (8) | 2 (9) | |
| Glatiramer acetate (Copaxone) | 1 (3) | 0 (0) | 1 (5) | |
| Cladribine (Mavenclad) | 7 (20) | 3 (21) | 4 (19) | |
| Fingolimod (Gilenya) | 1 (3) | 1 (8) | 0 (0) | |
| Cyclophosphamide (Endoxan) | 1 (3) | 0 (0) | 1 (5) | |
| Alemtuzumab (Lemtrada) | 1 (3) | 0 (0) | 1 (5) | |

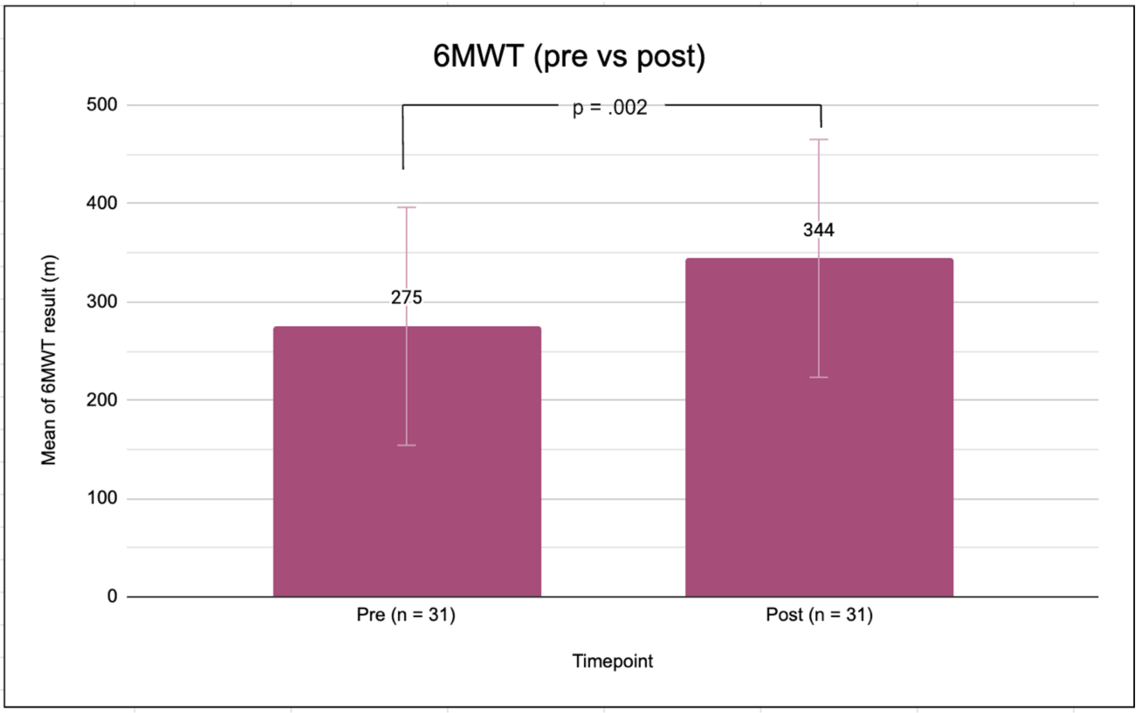
*Note.* MS = Multiple Sclerosis; EDSS = Expanded Disability Status Scale; RRMS = Relapsing-Remitting Multiple Sclerosis; PPMS = Primary Progressive Multiple Sclerosis; SPMS = Secondary Progressive Multiple Sclerosis; SD = standard deviation; Q1 = first quartile; Q3 = third quartile. The *p*-values were calculated using the following tests: (a) Wilcoxon rank-sum test, (b) 2-sample *t*-test, (c) Pearson's chi-squared test, and (d) Fisher's exact test. For all parametric tests, the mean and SD are reported. For non-parametric tests, the median and interquartile range are reported. See Appendices 1 and 2 for the statistical decision trees used.

**Difference in walking capacity and walking fatigability after rehabilitation**

An overview of the results for walking capacity and walking fatigability can be found in table 2. A one-sample *t*-test showed a statistically significant improvement on the 6MWT following the rehabilitation program ($p$ = .002), indicating a higher distance walked post-intervention (Figure 2). In Appendix 4, an additional figure can be found that displays the line plots of all 31 participants, illustrating the individual evolution on the 6MWT from pre- to post-rehabilitation (Figure 6).

**Figure 2**

*Improvement in 6MWT Result Pre vs Post-Rehabilitation*




*Note.* 6MWT = 6-Minute Walk Test. Each error bar is constructed using one standard deviation from the mean.

In 20 out of the 31 PwMS for whom data on the 6MWT were available, this improvement was greater than the MIC (≥ 19.7 m), indicating that the walking capacity improved significantly after a 13-week inpatient MD rehabilitation program. There were three participants who were not able to perform a 6MWT before the start of the rehabilitation. No statistically significant difference was found on the 2MWT after rehabilitation (*t*-test, $p$ = .416), and none of the three participants with available difference scores reached the threshold for MIC (≥ 9.6 m), indicating no relevant change in short-duration walking capacity. There were no statistically significant differences between DWI before and after rehabilitation (*t*-test, $p$ = .668). For the MSWS-12, the result approached statistical significance but did not reach the conventional threshold (Wilcoxon, $p$ = .055), suggesting a trend toward improvement in perceived walking ability.

However, 11 out of 22 participants showed a clinically meaningful improvement on the MSWS-12 after rehabilitation (reduction of eight points or more). A statistically significant improvement was found for the TUG after the rehabilitation program (Wilcoxon, $p$ = .003), indicating enhanced functional mobility for PwMS. Out of 28 participants with both pre- and post-assessments of the TUG available, 16 initially scored above 14 seconds, indicating an increased fall risk. Four of these 16 PwMS improved to a score of 14 seconds or less after the program, suggesting a reduced fall risk after rehabilitation.

**Table 2**

*Difference in Walking Capacity, Walking Fatigability, and Perceived Walking Ability After Rehabilitation*

| Measure | Pre Mean ± SD / Median [Q1,Q3] | Post Mean ± SD / Median [Q1,Q3] | *p*-value | Cohen's *d* | MIC* / fall risk reduction** |
|---|---|---|---|---|---|
| 6MWT (m) | 275.19 ± 103.84 | 344.26 ± 138.43 | .002 (a) | 0.49 | 20 out of 31 ≥ 19.7 m* |
| 2MWT (m) | 19.50 ± 13.81 | 15.67 ± 9.07 | .416 (a) | 0.01 | 0 out of 3 ≥ 9.6 m* |
| DWI (%) | -2.85 ± 13.01 | -2.02 ± 15.97 | .668 (a) | 0.32 | – |
| MSWS-12 (total /60) | 44.50 [35.75,52.75] | 39 [31.75,46.25] | .055 (b) | 2.68 | 11 out of 22 ≥ 8-point reduction* |
| TUG (sec) | 15 [10,24.50] | 13 [8,17.75] | .003 (b) | 0.64 | 4 out of 16 improved to ≤ 14 sec** |

*Note.* SD = standard deviation; Q1 = first quartile; Q3 = third quartile; MIC = minimally important change; 6MWT = 6-Minute Walk Test; 2MWT = 2-Minute Walk Test; DWI = Distance Walked Index; MSWS-12 = Multiple Sclerosis Walking Scale-12; TUG = Timed Up and Go. The *p*-values were calculated using the following tests: (a) one-sample *t*-test, and (b) Wilcoxon signed-rank test. A $p$-value ≤ 0.05 was anticipated as statistically significant. For all parametric tests, the mean and SD are reported. For non-parametric tests, the median and interquartile range are reported. See Appendix 3 for the statistical decision tree used.

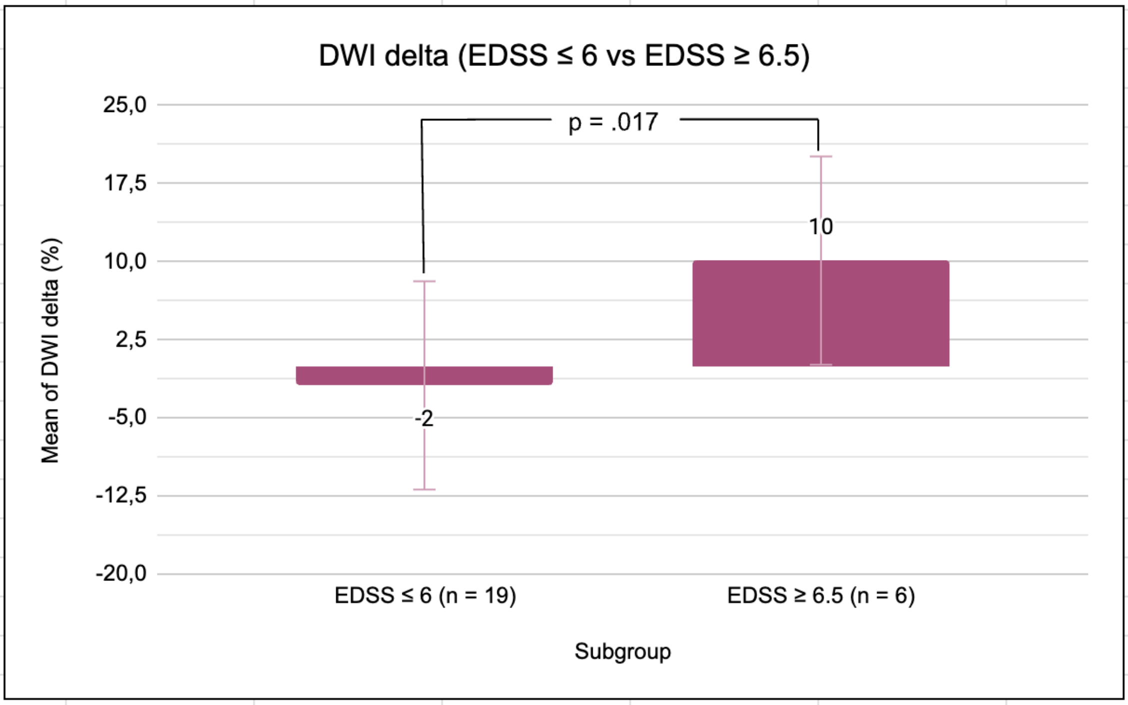
**Difference in change after rehabilitation between subgroups (walking-related primary goal; walking fatigability at baseline; overall disability at baseline)**

No significant differences were found in 6MWT results between participants with and without a walking-related primary goal (Wilcoxon, $p$ = .139), between those with and without walking fatigability at baseline (Wilcoxon, $p$ = .273), or between the EDSS subgroups (Wilcoxon, $p$ = .620). Regarding the 2MWT, the sample sizes per group were too small to adequately assess normality, and therefore, no valid statistical comparisons could be performed for these subgroups. As such, 2MWT results were excluded from this part of the analysis. For the DWI, no significant differences were observed between participants with and without a walking-related primary goal ($t$-test, $p$ = .281), nor between those with or without walking fatigability at baseline ($t$-test, $p$ = .192).

However, an independent samples *t*-test comparing the delta score of the DWI between participants with EDSS ≤ 6 and those with EDSS ≥ 6.5 revealed a statistically significant difference between the two groups ($p$ = .017) (Figure 3). This suggests that participants with higher disability levels (EDSS ≥ 6.5) experienced a greater improvement in DWI. Although this is an important finding, it should be interpreted with caution due to the small sample size.

**Figure 3**

*Difference in DWI Delta Scores Between EDSS Subgroups*




*Note.* DWI = Distance Walked Index; EDSS = Expanded Disability Status Scale. Each error bar is constructed using one standard deviation from the mean.

No significant differences were found in MSWS-12 delta scores between participants with and without a walking primary goal (Wilcoxon, $p$ = .391), with and without walking fatigability at baseline (Wilcoxon, $p$ = .488), or between the EDSS subgroups (Wilcoxon, $p$ = .196). Lastly, the Wilcoxon rank-sum test revealed no significant differences in improvement on the TUG between participants with and without a walking-related primary goal ($p$ = .365), with and without walking fatigability at baseline ($p$ = .766), or between EDSS ≤ 6 and EDSS ≥ 6.5 ($p$ = .739). Table 3 provides a summary of the key findings.

**Table 3**

*Difference in Change After Rehabilitation Between Subgroups*

| Measure | Group | Subgroup | Mean ± SD / Median [Q1,Q3] | *p*-value | Cohen's *d* |
|---|---|---|---|---|---|
| 6MWT (m) | Primary walking-related rehabilitation goal | Yes | 49 [26,113.50] | .139 (a) | 0.25 |
| | | No | 20.50 [9.25,66.75] | | |
| | Walking fatigability at baseline | Yes | 24.50 [5.25,57.75] | .273 (a) | 0.47 |
| | | No | 40 [14.25,115.50] | | |
| | EDSS score | EDSS ≤ 6 | 42 [11.50,111.75] | .620 (a) | 0.30 |
| | | EDSS ≥ 6.5 | 38 [3,68] | | |
| 2MWT (m) | Primary walking-related rehabilitation goal | Yes | – | – | – |
| | | No | – | | |
| | Walking fatigability at baseline | Yes | – | – | – |
| | | No | – | | |
| | EDSS score | EDSS ≤ 6 | – | – | – |
| | | EDSS ≥ 6.5 | – | | |
| DWI (%) | Primary walking-related rehabilitation goal | Yes | 3.78 ± 10.15 | .281 (b) | 0.23 |
| | | No | -1.19 ± 12.32 | | |
| | Walking fatigability at baseline | Yes | 7.08 ± 12.27 | .192 (b) | 0.07 |
| | | No | -0.92 ± 10.83 | | |
| | EDSS score | EDSS ≤ 6 | -1.88 ± 10.91 | .017 (b) | 0.20 |
| | | EDSS ≥ 6.5 | 10.11 ± 8.45 | | |
| MSWS-12 (total /60) | Primary walking-related rehabilitation goal | Yes | -5 [-11.25,8] | .391 (a) | 0.45 |
| | | No | -7.50 [-12.25,-4] | | |
| | Walking fatigability at baseline | Yes | -4 [-8,8] | .488 (a) | 0.01 |
| | | No | -7.50 [-12.25,1.25] | | |
| | EDSS score | EDSS ≤ 6 | -5 [-10,2.50] | .196 (a) | 0.15 |
| | | EDSS ≥ 6.5 | -12 [-17,8.50] | | |
| TUG (sec) | Primary walking-related rehabilitation goal | Yes | -2 [-5,-0.50] | .365 (a) | 0.06 |
| | | No | -4 [-6,-1] | | |
| | Walking fatigability at baseline | Yes | -2 [-6.50,-1] | .766 (a) | 0.07 |
| | | No | -3 [-5,-1.25] | | |
| | EDSS score | EDSS ≤ 6 | -3 [-5,-1] | .739 (a) | 0 |
| | | EDSS ≥ 6.5 | -2.50 [-5.75,0.50] | | |

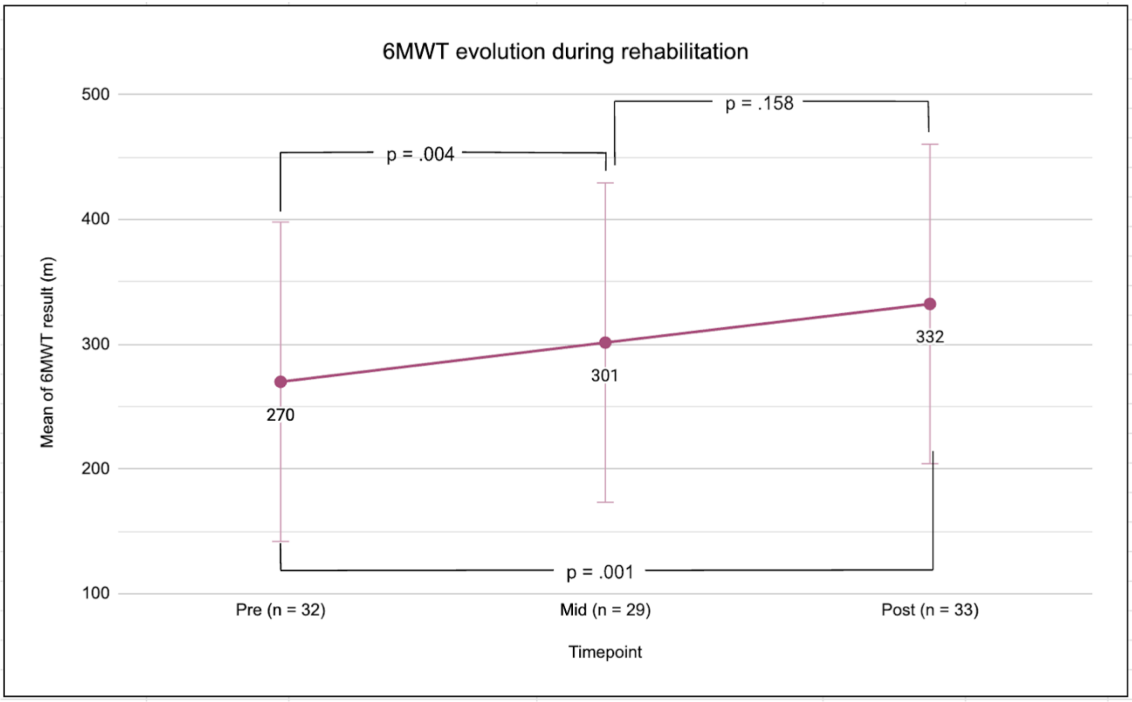
*Note.* SD = standard deviation; Q1 = first quartile; Q3 = third quartile; 6MWT = 6-Minute Walk Test; 2MWT = 2-Minute Walk Test; DWI = Distance Walked Index; MSWS-12 = Multiple Sclerosis Walking Scale-12; TUG = Timed Up and Go; EDSS = Expanded Disability Status Scale. The *p*-values were calculated using the following tests: (a) Wilcoxon rank-sum test, and (b) two-sample *t*-test. A *p*-value ≤ 0.05 was anticipated as statistically significant. For all parametric tests, the mean and SD are reported. For non-parametric tests, the median and interquartile range are reported. See Appendix 1 for the statistical decision tree used.

**Walking capacity and walking fatigability improvement at different stages during rehabilitation**

A repeated measures ANOVA revealed a statistically significant difference for the 6MWT across time points ($p$ < .001), indicating changes in walking capacity throughout the rehabilitation process. A post-hoc Bonferroni multiple comparisons test showed a significant improvement from pre- to mid-rehabilitation (mean difference = +49.731 m, $p$ = .004; 95% confidence interval (CI): [14.385,85.076]) and from pre- to post-rehabilitation (mean difference = +70.885 m, $p$ = .001; 95% CI: [25.405,116.364]). However, the difference between mid- and post-rehabilitation did not reach statistical significance (mean difference = +21.154 m, $p$ = .158; 95% CI: [−5.514,47.822]) (Figure 4).

**Figure 4**

*Evolution of 6MWT Result During Rehabilitation*




*Note.* 6MWT = 6-Minute Walk Test. Each error bar is constructed using one standard deviation from the mean.

Due to insufficient data, no valid statistical analysis could be performed for the 2MWT across time points. For the DWI, the Friedman test revealed no significant difference between time points ($p$ = .684), indicating that walking fatigability, as expressed by the DWI, did not significantly change throughout the rehabilitation period. Table 4 shows the most important findings.

**Table 4**

*Walking Capacity and Walking Fatigability Improvement at Different Stages During Rehabilitation*

| Measure | Pre Mean ± SD / Median [Q1,Q3] | Mid Mean ± SD / Median [Q1,Q3] | Post Mean ± SD / Median [Q1,Q3] | Mean difference | 95% CI | *p*-value |
|---|---|---|---|---|---|---|
| 6MWT (m) | 269.91 ± 106.44 | 301.31 ± 134.02 | 332.29 ± 143.09 | | | < .001 (a) |
| Pre → mid | | | | +49.731 m | [14.385,85.076] | .004 (b) |
| Mid → post | | | | +21.154 m | [−5.514,47.822] | .158 (b) |
| Pre → post | | | | +70.885 m | [25.405,116.364] | .001 (b) |
| 2MWT (m) | 20.50 [10.13,32.75] | 55 [43,111] | 19 [9.75,36.50] | | | – |
| DWI (%) | -4.05 [-11.69,4] | -6.18 [-11.78,3.90] | -2.50 [-13.45,3.23] | | | .684 (c) |

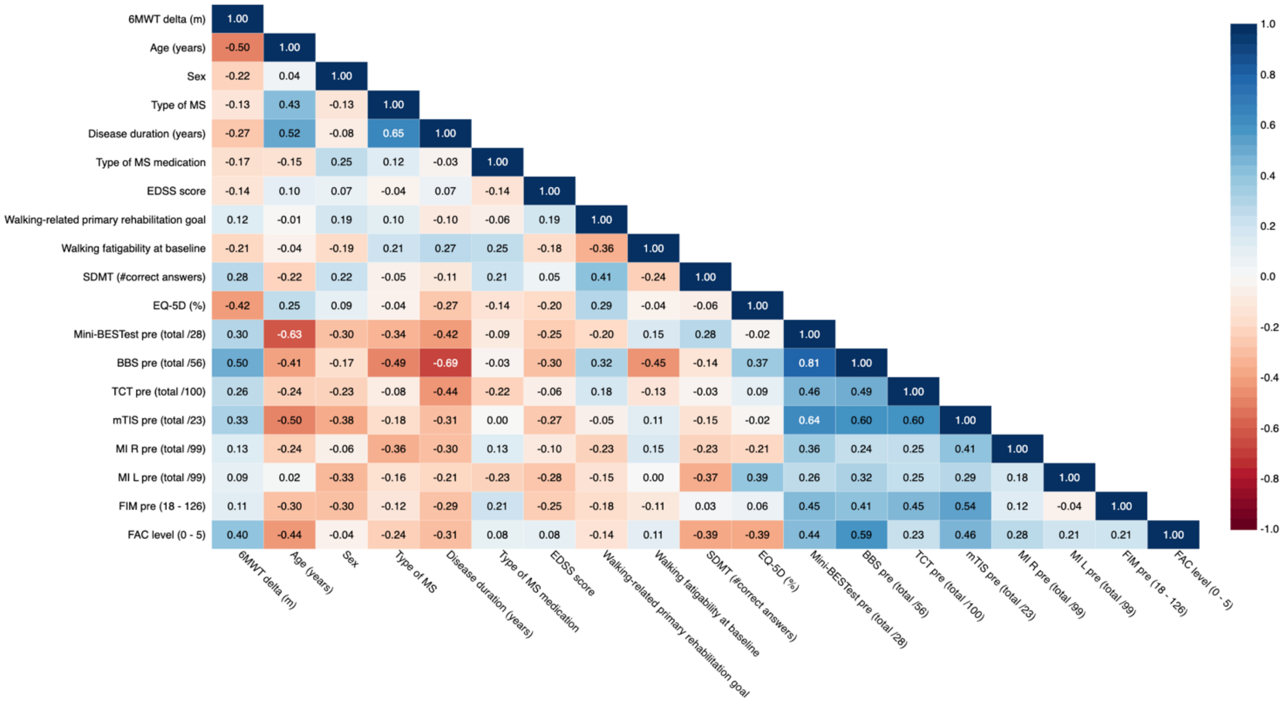
*Note.* SD = standard deviation; Q1 = first quartile; Q3 = third quartile; CI = confidence interval; 6MWT = 6-Minute Walk Test; 2MWT = 2-Minute Walk Test; DWI = Distance Walked Index. The three timepoints are: pre = pre-rehabilitation (baseline); mid = mid-rehabilitation (6 weeks); and post = post-rehabilitation (13 weeks). The *p*-values were calculated using the following tests: (a) repeated measures ANOVA, (b) post-hoc Bonferroni multiple comparisons test, and (c) Friedman test. A *p*-value ≤ 0.05 was anticipated as statistically significant. For all parametric tests, the mean and SD are reported. For non-parametric tests, the median and interquartile range are reported.

## Correlation of clinical factors with changes in walking capacity

A correlation analysis was conducted to explore the relationship between (baseline values of) various clinical and demographic variables and changes in walking capacity, as measured by the 6MWT delta score. Age showed a moderate negative correlation (Spearman's $\rho$ = -0.50, $p$ = .003), indicating that younger individuals tend to improve more during the rehabilitation program. The BBS was moderately positively correlated with the change in walking capacity (Spearman's $\rho$ = 0.50, $p$ = .044), suggesting that PwMS with better baseline balance experienced greater improvements in walking performance. However, other variables related to mobility and motor impairment, such as the Mini-BESTest, TCT, and mTIS baseline scores, showed weak positive trends but were not significantly correlated. Similarly, FIM and SDMT scores showed no significant associations with changes in walking capacity. Interestingly, a positive trend was observed for the FAC level at baseline (Spearman’s $\rho$ = 0.40, $p$ = .051), suggesting that individuals with better initial ambulatory function tended to show greater improvements in walking capacity. Type of MS, sex, EDSS score, MS medication type, and walking-related primary rehabilitation goal did not show significant correlations. Figure 5 presents the full correlation matrix.

**Figure 5**

*Correlation Matrix*




*Note.* 6MWT = 6-Minute Walk Test; MS = multiple sclerosis; EDSS = Expanded Disability Status Scale; SDMT = Symbol Digit Modalities Test; EQ-5D = EuroQol 5D; Mini-BESTest = Mini Balance Evaluation Systems Test; BBS = Berg Balance Scale; TCT = Trunk Control Test; mTIS = modified Trunk Impairment Scale; MI = Motricity Index; R = right; L = left; FIM = Functional Independence Measure; FAC = Functional Ambulation Categories. Spearman's rank correlation coefficients ($\rho$) are presented. Positive values indicate a direct relationship between variables, while negative values indicate an inverse relationship. The color scale represents the strength and direction of the correlations: blue for positive and red for negative associations.

## Discussion

This study investigated the effects of a 13-week inpatient MD rehabilitation program on walking capacity and walking fatigability in PwMS, with an additional focus on the added value of goal setting. The findings highlight that intensive rehabilitation in a real-world clinical setting can result in clinically meaningful improvements in walking capacity. While the results on some outcomes aligned with previous literature, others deviated, offering important insights into rehabilitation outcomes in PwMS.

A significant overall improvement in walking capacity, as measured by the 6MWT, was observed following the rehabilitation program. Importantly, the majority of participants exceeded the MIC threshold, indicating that these gains were not only statistically relevant but also clinically meaningful. This aligns with previous results reported by Amatya et al. (2019), who found significant improvements in functional mobility following structured inpatient rehabilitation. The average improvement on the 6MWT in this study was approximately 71 meters. This is notably greater than the mean improvement of 36 meters reported in the multicenter study by Kalron et al. (2019), which included a sample of PwMS undergoing rehabilitation programs lasting between three and 12 weeks. Similarly, Hvid et al. (2021) reported a mean improvement of 22 meters on the 6MWT following a four-week personalized inpatient MD rehabilitation program, which also exceeded the threshold for clinical relevance. However, this result was considerably smaller than the improvement observed in the present cohort. These findings suggest that the longer duration of the 13-week inpatient rehabilitation program in this study may have contributed to a more pronounced enhancement in walking capacity compared to shorter interventions.

In some cases, the 6MWT could not be performed because the duration of the test exceeded the patients' walking abilities. As suggested by Gijbels et al. (2010), the 2MWT can serve as a suitable alternative in such cases, as it has been shown to reflect similar aspects of walking performance while placing less physical demand on participants with more severe limitations. However, in our sample, improvements in walking fatigability and short-duration walking capacity were not significant, the latter possibly due to a small sample size, limiting statistical power. Alternatively, the 6MWT is more demanding than the 2MWT and may therefore be more susceptible to interventions.

Regarding perceived walking ability, as measured by the MSWS-12, the findings suggest a possible positive effect of the rehabilitation program. The observation that a substantial number of participants experienced a MIC implies that changes in subjective walking perception may occur independently of clear group-level statistical effects. It is possible that improvements in functional mobility and endurance during the program contributed to greater confidence or reduced perceived walking limitations in daily life. Moreover, these results may reflect the broader, holistic benefits of MD rehabilitation, which often extend beyond what is captured by objective performance measures alone.

Interestingly, goal setting did not appear to influence rehabilitation outcomes in this study, contrasting with previous findings that suggest patient-centered goal setting may enhance mobility outcomes (Iodice et al., 2023). This discrepancy could stem from methodological limitations, notably the analysis being based solely on the primary goal, without taking into account the secondary goals. As therapy sessions typically address both primary and secondary goals, the actual content of therapy sessions likely extended beyond what was reflected by the primary goal alone. As Kalron et al. (2019) noted, secondary goals often remain undocumented despite influencing motivation and outcomes. Additionally, the mixed evidence surrounding goal setting in the literature (Levack et al., 2006; Wade, 1998) suggests that its effectiveness is highly dependent on implementation and patient involvement. In the current study, goals were well defined and documented; however, future research with larger sample sizes should consider stratifying participants based on the presence of walking-related primary and/or secondary goals. This may offer a more nuanced understanding of how different types of goals contribute to rehabilitation outcomes. Ultimately, a more comprehensive evaluation of goal setting, beyond the primary goal alone, may be essential to fully capture its impact on patient progress.

A noteworthy and somewhat unexpected finding was that participants with higher disability levels (EDSS $\geq$ 6.5) showed greater reductions in walking fatigability, as reflected by the DWI. However, this group did not exhibit significantly greater improvements in walking capacity compared to those with lower EDSS scores. This suggests that the observed reduction in walking fatigability in the more disabled group may not be directly linked to changes in endurance, but could reflect other factors such as altered pacing strategies, or increased therapy intensity tailored to individual needs. These findings underline the multifaceted nature of rehabilitation outcomes and emphasize that different constructs (e.g., walking capacity vs. fatigability) may respond differently to the same intervention. Further studies are needed to clarify the mechanisms underlying these differential responses.

The analysis of the different measurement points of the 6MWT during the rehabilitation program revealed that the most substantial improvements in walking capacity occurred in the first half of the intervention period. This suggests that the initial stages of rehabilitation may be particularly effective, and that a plateau tends to emerge during the later stages. This finding aligns with meta-analytic evidence indicating that exercise interventions shorter than three months showed a statistically significant effect on walking mobility, whereas longer interventions did not yield a significant overall effect (Snook & Motl, 2009). However, the authors caution against concluding that longer programs are less effective, as this result may have been influenced by factors such as reduced compliance, loss of motivation, or limited reporting on adherence. It is possible that longer interventions lead to the maintenance of early improvements rather than to their further enhancement. Therefore, it may be beneficial to adjust rehabilitation content or intensity in the later stages of a rehabilitation program to sustain engagement and optimize long-term outcomes.

Regarding variables correlated with improvement in walking capacity, the findings from the correlation analysis suggest that younger participants, those with better balance at baseline, and better functional ambulation tend to experience greater improvements in walking capacity following an inpatient rehabilitation program. This indicates that patients who begin rehabilitation with a certain functional foundation may have more potential for meaningful gains. Clinically, this underscores the importance of carefully assessing a patient's initial functional status, particularly balance and mobility, to set realistic goals and tailor rehabilitation interventions accordingly. The lack of significant associations with variables such as cognitive function and trunk control suggests that improvements in walking capacity in this context may rely more heavily on motor-related baseline abilities rather than cognitive or broad functional status.

This study also presents several important limitations. Firstly, the use of real-world clinical data introduced variability in assessment timing. The 6MWT was not always performed at consistent time points across participants, potentially leading to fluctuating performance due to factors such as daily fatigue, recent therapy sessions, or external circumstances. Additionally, the 6MWT is a single-time-point measure focused on distance, without capturing gait quality or perceived exertion. Manual data entry further increased the risk of human error.

Another limitation lies in the lack of systematic documentation regarding the use of orthoses or walking aids during the 6MWT and the 2MWT. This variability complicates the interpretation of results and may have confounded observed changes. Furthermore, the composition of the therapeutic team, as well as the specific therapists assigned to individual patients, likely varied across participants. As a result, the content and delivery of therapy may not have been entirely uniform, potentially contributing to differences in individual outcomes.

Despite these limitations, this study's key strength lies in its use of real-world data from a specialized rehabilitation center. This enhances the generalizability and practical relevance of the findings for clinical settings. The results support previous Cochrane reviews and expert consensus, emphasizing the value of inpatient MD rehabilitation for improving functional outcomes in PwMS (Amatya et al., 2019; Beer et al., 2012; Khan et al., 2007). Moreover, the results affirm the importance of individualized, MD care, which is central to current best practices in MS rehabilitation (Iodice et al., 2023).

Future research should strive for greater standardization in the timing and conditions of functional assessments to minimize variability and enhance data reliability. Incorporating complementary measures that assess gait quality, fatigue, and the use of assistive devices would offer a more comprehensive picture of patient progress. In addition, longitudinal follow-up after discharge could provide valuable insights into the durability of the improvements achieved during inpatient rehabilitation. Finally, larger prospective studies should aim to identify which patient characteristics best predict responsiveness to rehabilitation, thereby supporting more personalized care planning and efficient resource allocation.

**Conclusion**

In summary, this study confirms that a 13-week inpatient MD rehabilitation program can lead to clinically meaningful improvements in walking capacity in PwMS, with the most substantial gains occurring during the early stages of the program. Although goal setting did not show a statistically measurable effect in this context, this may reflect methodological limitations rather than a true lack of benefit. The findings also highlight the importance of individual baseline characteristics, such as age, balance, and ambulation level, in shaping rehabilitation outcomes. To optimize clinical results, future rehabilitation efforts should consider increasing therapy intensity or adapting treatment content towards the end of a rehabilitation program, analyzing both primary and secondary goals to better understand their impact, and tailoring interventions to the initial functional status and rehabilitation potential of each patient.

## Reference list


Aerts, S., Khan, H., Severijns, D., Popescu, V., Peeters, L. M., & Van Wijmeersch, B. (2023). Safety and effectiveness of cladribine tablets for multiple sclerosis: Results from a single-center real-world cohort. *Mult Scler Relat Disord*, *75*, 104735. https://doi.org/10.1016/j.msard.2023.104735

Amatya, B., Khan, F., & Galea, M. (2019). Rehabilitation for people with multiple sclerosis: an overview of Cochrane Reviews. *Cochrane Database Syst Rev*, *1*(1), CD012732. https://doi.org/10.1002/14651858.CD012732.pub2

Baert, I., Freeman, J., Smedal, T., Dalgas, U., Romberg, A., Kalron, A., Conyers, H., Elorriaga, I., Gebara, B., Gumse, J., Heric, A., Jensen, E., Jones, K., Knuts, K., Maertens de Noordhout, B., Martic, A., Normann, B., Eijnde, B. O., Rasova, K., . . . Feys, P. (2014). Responsiveness and clinically meaningful improvement, according to disability level, of five walking measures after rehabilitation in multiple sclerosis: a European multicenter study. *Neurorehabil Neural Repair*, *28*(7), 621-631. https://doi.org/10.1177/1545968314521010

Beer, S., Khan, F., & Kesselring, J. (2012). Rehabilitation interventions in multiple sclerosis: an overview. *J Neurol*, *259*(9), 1994-2008. https://doi.org/10.1007/s00415-012-6577-4

Cameron, D., & Bohannon, R. W. (2000). Criterion validity of lower extremity Motricity Index scores. *Clin Rehabil*, *14*(2), 208-211. https://doi.org/10.1191/026921500675786655

Dodds, T. A., Martin, D. P., Stolov, W. C., & Deyo, R. A. (1993). A validation of the functional independence measurement and its performance among rehabilitation inpatients. *Arch Phys Med Rehabil*, *74*(5), 531-536. https://doi.org/10.1016/0003-9993(93)90119-u

Feng, Y. S., Kohlmann, T., Janssen, M. F., & Buchholz, I. (2021). Psychometric properties of the EQ-5D-5L: a systematic review of the literature. *Qual Life Res*, *30*(3), 647-673. https://doi.org/10.1007/s11136-020-02688-y

Gijbels, D., Alders, G., Van Hoof, E., Charlier, C., Roelants, M., Broekmans, T., Eijnde, B. O., & Feys, P. (2010). Predicting habitual walking performance in multiple sclerosis: relevance of capacity and self-report measures. *Mult Scler*, *16*(5), 618-626. https://doi.org/10.1177/1352458510361357

Goldman, M. D., Marrie, R. A., & Cohen, J. A. (2008). Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. *Mult Scler*, *14*(3), 383-390. https://doi.org/10.1177/1352458507082607

Haki, M., Al-Biati, H. A., Al-Tameemi, Z. S., Ali, I. S., & Al-Hussaniy, H. A. (2024). Review of multiple sclerosis: Epidemiology, etiology, pathophysiology, and treatment. *Medicine (Baltimore)*, *103*(8), e37297. https://doi.org/10.1097/MD.0000000000037297

Hauser, S. L., & Cree, B. A. C. (2020). Treatment of Multiple Sclerosis: A Review. *Am J Med*, *133*(12), 1380-1390 e1382. https://doi.org/10.1016/j.amjmed.2020.05.049

Hvid, L. G., Gaemelke, T., Dalgas, U., Slipsager, M. K., Rasmussen, P. V., Petersen, T., Norgaard, M., Skjerbaek, A. G., & Boesen, F. (2021). Personalised inpatient multidisciplinary rehabilitation elicits clinically relevant improvements in physical function in patients with multiple sclerosis - The Danish MS Hospitals Rehabilitation Study. *Mult Scler J Exp Transl Clin*, *7*(1), 2055217321989384. https://doi.org/10.1177/2055217321989384

Iodice, R., Aceto, G., Ruggiero, L., Cassano, E., Manganelli, F., & Dubbioso, R. (2023). A review of current rehabilitation practices and their benefits in patients with multiple sclerosis. *Mult Scler Relat Disord*, *69*, 104460. https://doi.org/10.1016/j.msard.2022.104460

Kalron, A., Feys, P., Dalgas, U., Smedal, T., Freeman, J., Romberg, A., Conyers, H., Elorriaga, I., Gebara, B., Merilainen, J., Heric-Mansrud, A., Jensen, E., Jones, K., Knuts, K., Maertens de Noordhout, B., Martic, A., Normann, B., B, O. E., Rasova, K., . . . Baert, I. (2019). Searching for the "Active Ingredients" in Physical Rehabilitation Programs Across Europe, Necessary to

Improve Mobility in People With Multiple Sclerosis: A Multicenter Study. *Neurorehabil Neural Repair*, *33*(4), 260-270. https://doi.org/10.1177/1545968319834893
Khan, F., Turner-Stokes, L., Ng, L., & Kilpatrick, T. (2007). Multidisciplinary rehabilitation for adults with multiple sclerosis. *Cochrane Database Syst Rev*, *2007*(2), CD006036. https://doi.org/10.1002/14651858.CD006036.pub2
Kieseier, B. C., & Pozzilli, C. (2012). Assessing walking disability in multiple sclerosis. *Mult Scler*, *18*(7), 914-924. https://doi.org/10.1177/1352458512444498
Leone, C., Severijns, D., Dolezalova, V., Baert, I., Dalgas, U., Romberg, A., Bethoux, F., Gebara, B., Santoyo Medina, C., Maamagi, H., Rasova, K., Maertens de Noordhout, B., Knuts, K., Skjerbaek, A., Jensen, E., Wagner, J. M., & Feys, P. (2016). Prevalence of Walking-Related Motor Fatigue in Persons With Multiple Sclerosis: Decline in Walking Distance Induced by the 6-Minute Walk Test. *Neurorehabil Neural Repair*, *30*(4), 373-383. https://doi.org/10.1177/1545968315597070
Levack, W. M., Taylor, K., Siegert, R. J., Dean, S. G., McPherson, K. M., & Weatherall, M. (2006). Is goal planning in rehabilitation effective? A systematic review. *Clin Rehabil*, *20*(9), 739-755. https://doi.org/10.1177/0269215506070791
McGuigan, C., & Hutchinson, M. (2004). Confirming the validity and responsiveness of the Multiple Sclerosis Walking Scale-12 (MSWS-12). *Neurology*, *62*(11), 2103-2105. https://doi.org/10.1212/01.wnl.0000127604.84575.0d
Mehta, L., McNeill, M., Hobart, J., Wyrwich, K. W., Poon, J. L., Auguste, P., Zhong, J., & Elkins, J. (2015). Identifying an important change estimate for the Multiple Sclerosis Walking Scale-12 (MSWS-12v1) for interpreting clinical trial results. *Mult Scler J Exp Transl Clin*, *1*, 2055217315596993. https://doi.org/10.1177/2055217315596993
Niedziela, N., Kalinowska, A., Kulakowska, A., Mirowska-Guzel, D., Rejdak, K., Siger, M., Stasiolek, M., & Adamczyk-Sowa, M. (2024). Clinical and therapeutic challenges of smouldering multiple sclerosis. *Neurol Neurochir Pol*, *58*(3), 245-255. https://doi.org/10.5603/pjnns.98592
Oosterveer, D. M., van den Berg, C., Volker, G., Wouda, N. C., Terluin, B., & Hoitsma, E. (2022). Determining the minimal important change of the 6-minute walking test in Multiple Sclerosis patients using a predictive modelling anchor-based method. *Mult Scler Relat Disord*, *57*, 103438. https://doi.org/10.1016/j.msard.2021.103438
Parlak Demir, Y., & Yildirim, S. A. (2015). Reliability and validity of Trunk Control Test in patients with neuromuscular diseases. *Physiother Theory Pract*, *31*(1), 39-44. https://doi.org/10.3109/09593985.2014.945673
Potter, K., Bowling, R., Kavanagh, L., Stone, A., Witt, B., & Wooldridge, A. (2019). Reliability, Validity, and Responsiveness of the Mini-Balance Evaluation Systems Test in Ambulatory Individuals with Multiple Sclerosis. *Physiother Can*, *71*(4), 327-334. https://doi.org/10.3138/ptc-2018-0071
Rasova, K., Martinkova, P., Soler, B., Freeman, J., Cattaneo, D., Jonsdottir, J., Smedal, T., Romberg, A., Henze, T., Santoyo-Medina, C., & Feys, P. (2020). Real-World Goal Setting and Use of Outcome Measures According to the International Classification of Functioning, Disability and Health: A European Survey of Physical Therapy Practice in Multiple Sclerosis. *Int J Environ Res Public Health*, *17*(13). https://doi.org/10.3390/ijerph17134774
Santinelli, F. B., Abasiyanik, Z., Dalgas, U., Ozakbas, S., Severijns, D., Gebara, B., Maamagi, H., Romberg, A., Rasova, K., Santoyo-Medina, C., Ramari, C., Leone, C., & Feys, P. (2025). Prevalence of distance walking fatigability in multiple sclerosis according to MS phenotype, disability severity and walking speed. *Ann Phys Rehabil Med*, *68*(1), 101887. https://doi.org/10.1016/j.rehab.2024.101887

Sebastiao, E., Sandroff, B. M., Learmonth, Y. C., & Motl, R. W. (2016). Validity of the Timed Up and Go Test as a Measure of Functional Mobility in Persons With Multiple Sclerosis. *Arch Phys Med Rehabil*, *97*(7), 1072-1077. https://doi.org/10.1016/j.apmr.2015.12.031

Snook, E. M., & Motl, R. W. (2009). Effect of exercise training on walking mobility in multiple sclerosis: a meta-analysis. *Neurorehabil Neural Repair*, *23*(2), 108-116. https://doi.org/10.1177/1545968308320641

Stevenson, V. L., & Playford, E. D. (2007). Rehabilitation and MS. *International MS journal*, *14*.

Strober, L., DeLuca, J., Benedict, R. H., Jacobs, A., Cohen, J. A., Chiaravalloti, N., Hudson, L. D., Rudick, R. A., LaRocca, N. G., & Multiple Sclerosis Outcome Assessments, C. (2019). Symbol Digit Modalities Test: A valid clinical trial endpoint for measuring cognition in multiple sclerosis. *Mult Scler*, *25*(13), 1781-1790. https://doi.org/10.1177/1352458518808204

Thompson, A. J., Banwell, B. L., Barkhof, F., Carroll, W. M., Coetzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M. S., Fujihara, K., Galetta, S. L., Hartung, H. P., Kappos, L., Lublin, F. D., Marrie, R. A., Miller, A. E., Miller, D. H., Montalban, X., . . . Cohen, J. A. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*, *17*(2), 162-173. https://doi.org/10.1016/S1474-4422(17)30470-2

Tyson, S. F., & Connell, L. A. (2009). How to measure balance in clinical practice. A systematic review of the psychometrics and clinical utility of measures of balance activity for neurological conditions. *Clin Rehabil*, *23*(9), 824-840. https://doi.org/10.1177/0269215509335018

Valet, M., Lejeune, T., Devis, M., van Pesch, V., El Sankari, S., & Stoquart, G. (2019). Timed Up-and-Go and 2-Minute Walk Test in patients with multiple sclerosis with mild disability: reliability, responsiveness and link with perceived fatigue. *Eur J Phys Rehabil Med*, *55*(4), 450-455. https://doi.org/10.23736/S1973-9087.18.05366-2

Van Geel, F., Veldkamp, R., Severijns, D., Dalgas, U., & Feys, P. (2020). Day-to-day reliability, agreement and discriminative validity of measuring walking-related performance fatigability in persons with multiple sclerosis. *Mult Scler*, *26*(13), 1785-1789. https://doi.org/10.1177/1352458519872465

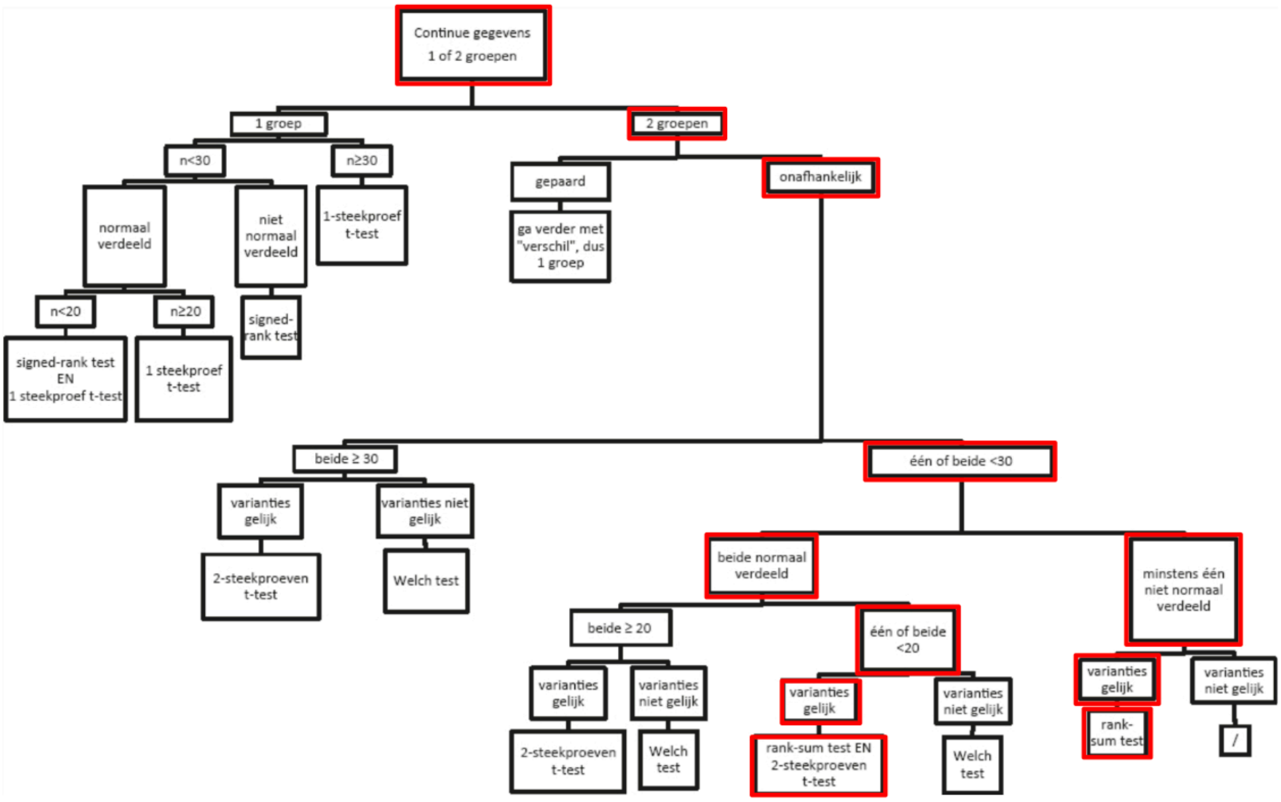
Verheyden, G., Nuyens, G., Nieuwboer, A., Van Asch, P., Ketelaer, P., & De Weerdt, W. (2006). Reliability and validity of trunk assessment for people with multiple sclerosis. *Phys Ther*, *86*(1), 66-76. https://doi.org/10.1093/ptj/86.1.66

Viosca, E., Martinez, J. L., Almagro, P. L., Gracia, A., & Gonzalez, C. (2005). Proposal and validation of a new functional ambulation classification scale for clinical use. *Arch Phys Med Rehabil*, *86*(6), 1234-1238. https://doi.org/10.1016/j.apmr.2004.11.016

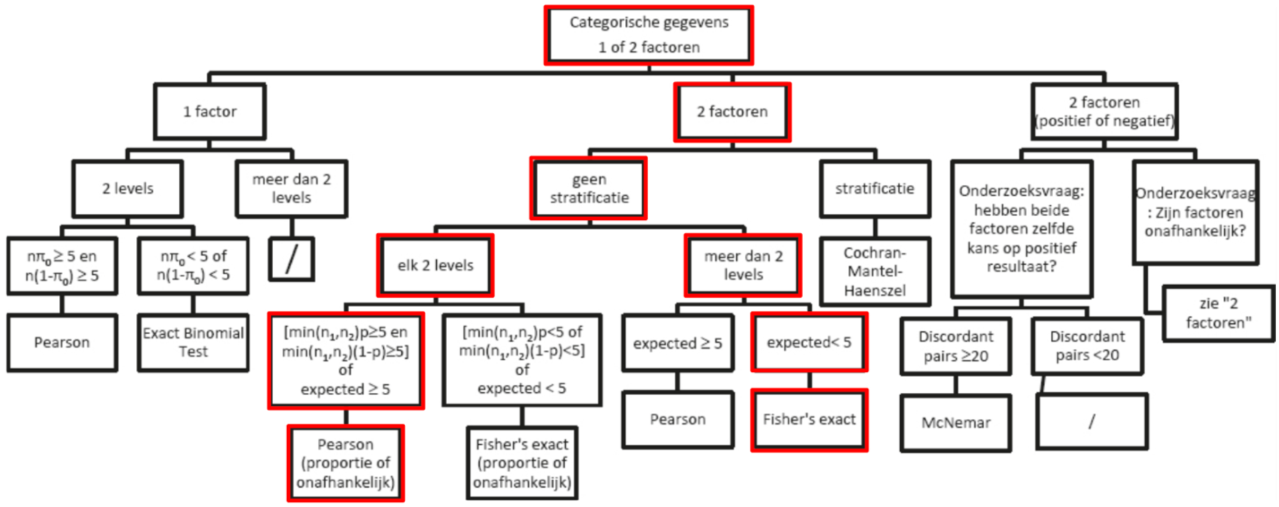
Wade, D. T. (1998). Evidence relating to goal planning in rehabilitation. *Clin Rehabil*, *12*(4), 273-275. https://doi.org/10.1191/026921598678166365

# Appendix

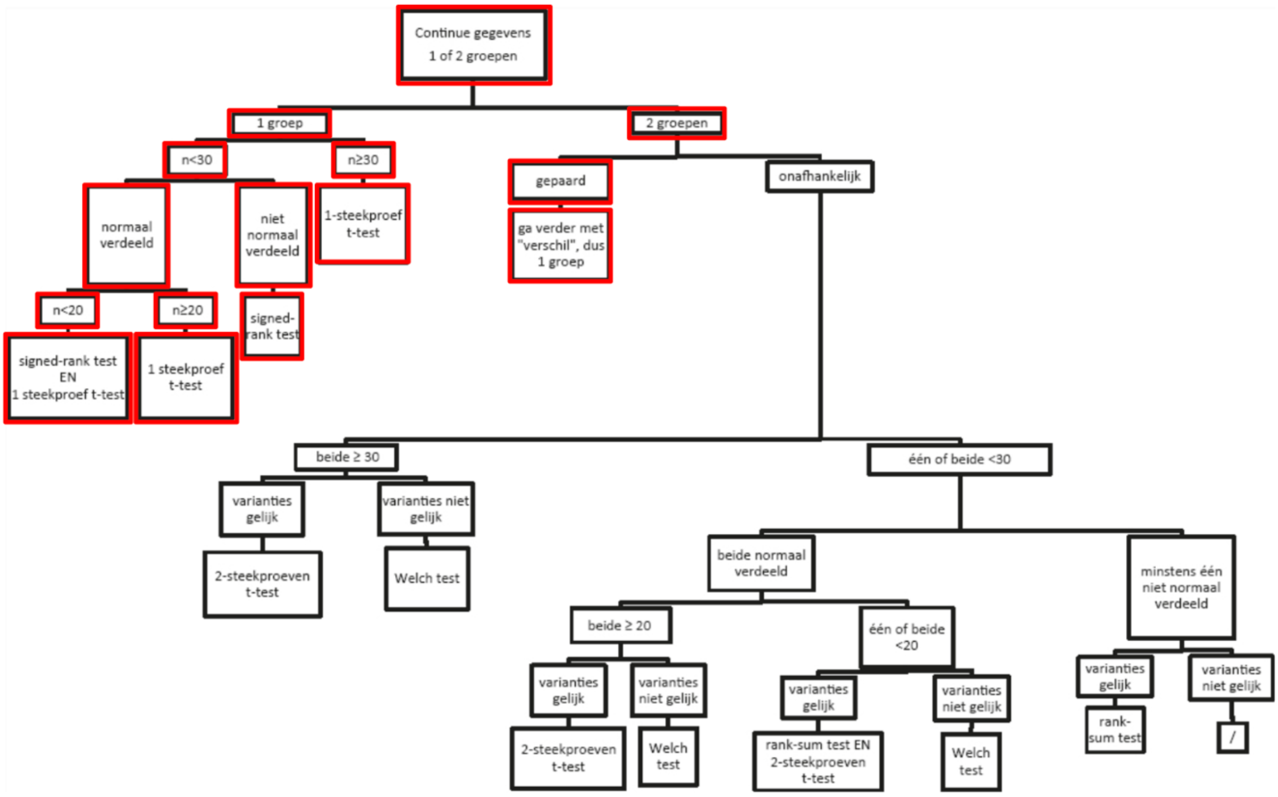
## Appendix 1




## Appendix 2



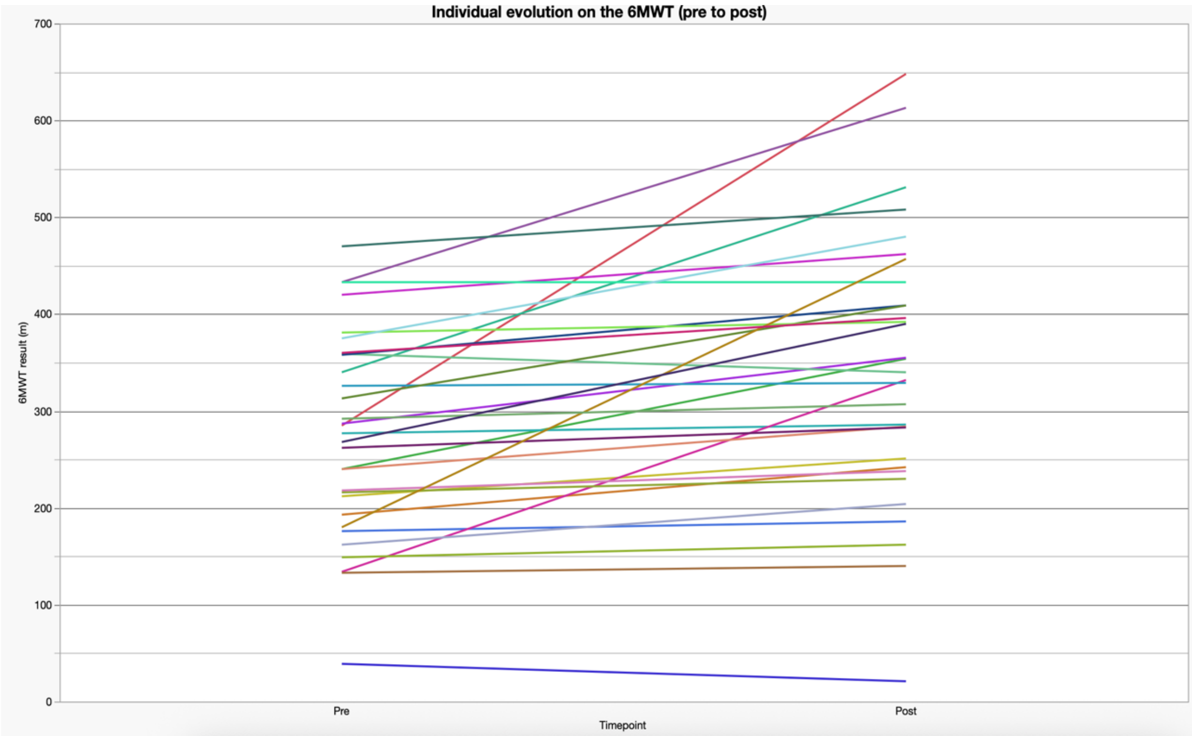
Appendix 3




Appendix 4

**Figure 6**

*Individual Evolution on the 6MWT from Pre to Post-Rehabilitation*




*Note.* 6MWT = 6-Minute Walk Test. Each line represents an individual participant, illustrating their change in 6MWT distance from pre- to post-rehabilitation ($n$ = 31).