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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

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Hanne Van Marcke
Floris Van Thienen

Eerste deel van het scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

PROMOTOR :
Prof. dr. Bart VAN WIJMEERSCH

COPROMOTOR :
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2018
2019

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The therapy content effects of inpatient and outpatient multidisciplinary rehabilitation programs in people with multiple sclerosis

Hanne Van Marcke (1541234)

Floris Van Thienen (1436686)

“A multidisciplinary approach in MS is recommended since the disease presents itself in a multifaceted way with different impairments and disability”

“Because almost every intervention was individualized in terms of intervention content and therapy dosage. Forming conclusions about therapy dosage and intensity was difficult.”

“Specific multidisciplinary rehabilitation programs like an aquatic program could be used to improve certain items like balance, gait, transfers, …“

” Individualized multidisciplinary rehabilitation programs are effective on the perception of the patient about their own disability status without improvements on other objective measures..

Research context

This research fits within the domain of neurological rehabilitation, to be precise in the domain: rehabilitation of people with multiple sclerosis (pwMS). Multiple sclerosis (MS) is a progressive disease of the central nervous system with inflammatory and neurodegenerative components, which affect the axons and myelin sheats. MS has a heterogeneous and unpredictable clinical course and causes impairments and disabilities in the different levels of the International Classification of Functioning, Disability and Health (ICF) *(Nedeljkovic et al., 2016; Storr, Sorensen, & Ravnborg, 2006*). Frequently reported MS impairments such as coordination, fatigue, muscle weakness, spasticity, bladder and bowel dysfunction, sexual dysfunction and memory loss can have an impact on activity level (e.g. household, gait, transfers, mobility) and participation level (e.g. social activities, family, financial state) *(Khan, Turner-Stokes, Ng, & Kilpatrick, 2008; Onat, Delialioglu, Ozisler, & Ozel, 2015)*.

In this master thesis, a literature study was performed to investigate the contents and effects of multidisciplinary rehabilitation programs in pwMS. The second part of this research will be in collaboration with the Rehabilitation and MS centrum Overpelt.

This thesis is written by two students, Hanne Van Marcke and Floris Van Thienen. A central format was used in the making of this thesis. Prof. Dr. Bart Van Wijmeersch and Ilse Lamers were the additional research members of the UHasselt. The research question and the literature search strategy were assembled in conjunction with Prof. Dr. Bart Van Wijmeersch Dr. Ilse Lamers. Both students executed the literature search together. The Quality assessment and data-extraction were done by both students separately.

The protocol for the second part of the master thesis was already in place, but the two students had to give a critical appraisal in function of their own research questions. The data for part two has already been collected and will be processed in part two.

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PART I: OVERVIEW OF THE LITERATURE

1 Abstract

Background:

Aim of the study: The aim of this systematic review was to provide an overview of the therapy content and dosage of multidisciplinary rehabilitation programs in persons with multiple sclerosis (pwMS) and to discuss their clinical effects. This review aims to provide more insights in what type of rehabilitation is more suitable for every phase that occurs or returns during the course of multiple sclerosis (MS).

Methods: Literature was gathered by using two databases, Web of Science (WoS) and Pubmed. Only studies investigating multidisciplinary rehabilitation in persons with MS were included. Articles were excluded when the study was a case study, the only intervention was use of medication or surgery, the article was a review or a cross-sectional study and when the article was older than 25 years.

Results: Twenty-three articles were included for analysis. Most interventions were multidisciplinary rehabilitation programs individualized on the patients needs. Some were specific programs like for example an aquatic exercise program which could be used to improve certain items gait, balance, transfers, Statistical significant improvements were found in the categories of General Health State, Quality of Life, Coping with MS, Physical measurements and the psychological aspects of the impact of MS on daily life.

Discussion and conclusion: Individualized multidisciplinary rehabilitation programs are effective on the perception of the patient about their own disability status without improvements on objective measures. Because almost every intervention was individualized, forming conclusions about therapy dosage and intensity was difficult.

Operationalisation: This review is part of a preparation for a research project for the Rehabilitation and MS Clinic Overpelt under the guidance of Prof. Dr. Bart Van Wijmeersch and Dr. Ilse Lamers.

Most important key words: Multiple sclerosis, multidisciplinary, interdisciplinary, rehabilitation, inpatient, outpatient

2 Introduction

Multiple sclerosis (MS) is a progressive disease of the central nervous system characterized by inflammatory and neurodegenerative components, which affect the axons and myelin sheats. MS has a heterogeneous and an unpredictable clinical course and causes impairments and disabilities in the different levels of the International Classification of Functioning, Disability and Health (ICF) *(Nedeljkovic et al., 2016; Storr, Sorensen, & Ravnborg, 2006).* Frequently reported MS impairments such as coordination, fatigue, muscle weakness, spasticity, bladder and bowel dysfunction, sexual dysfunction and memory loss can have an impact on activity level (e.g. household, gait, transfers, mobility) and participation level (e.g. social activities, family, financial state) *(Khan, Turner-Stokes, Ng, & Kilpatrick, 2008; Onat, Delialioglu, Ozisler, & Ozel, 2015)*. According to Khan et al "About 50% of persons require a walking aid and 10% a wheelchair within 15 years of onset, and 90% will have significant functional limitation 25 years after onset" *(Khan et al., 2008).* The use of modern disease-modifying treatments has been proven to reduce the inflammatory component of MS. However, there is no medication available to cure MS and the medication for progressive MS is scarce. The long-term benefits on the consequences of MS have not yet been proven. Because of this, continuous rehabilitation plays an important part in the standard treatment in MS. *(Storr, Sorensen, & Ravnborg, 2006)*. The continuous rehabilitation is important in the treatment of MS because it reduces the burden of the disease on the affected individuals and their environment as well as the socioeconomic impact *(Beer, Khan, & Kesselring, 2012).*

A recently published systematic review by Khan and Amatya suggests that there is strong evidence for physical therapy modalities, such as physical activities and exercises, for improving outcome measures (mobility, muscle strength and aerobic capacity) and reducing fatigue and improved QoL *(Khan & Amatya, 2017).* In addition, there was strong evidence for comprehensive fatigue management programs related to reported fatigue in patients. Moderate evidence was found for multidisciplinary rehabilitation concerning gains in activity and participation levels in the long run. Cognitive behavior therapy for the treatment of depression also had moderate evidence *(Khan & Amatya, 2017).* The evidence concerning other interventions and programs about rehabilitation in MS were found to be inconclusive (dietary interventions, hippotherapy and electrical stimulation) or low (psychological interventions, specific MS-related spasticity programs, exercise therapy concerning balance

and cognitive symptoms, Whole-body vibration, hyperbaric oxygen therapy, upper-limb programs, telerehabilitation, vocational rehabilitation and occupational therapy strategies) *(Khan & Amatya, 2017).*

The importance of multidisciplinary rehabilitation should not be underestimated in pwMS. Because MS is a multifaceted disease and has consequences that can be found in all aspects of the ICF-model. MS has an impact on both physical and psychological elements, which are stated earlier in this paper. This should be approached with a multidisciplinary view to tackle as much of the influences it has on the pwMS to ease the burden on their activities of daily life (ADL). The goal of this review was to summarize the therapy content and effects of multidisciplinary rehabilitation so that it will become clearer which interventions are more effective and needed in which type of patients. Because MS has an unpredictable course and different phases it goes through, it could be possible that every phase should be approached differently to be more effective. For example, someone who is having a relapse will not be treated the same way as someone who is in a remitting phase. Also, it could be interesting to know if an inpatient or outpatient approach is more effective in different stadia of the disease or depending on the disabilities that the pwMS experiences.

3 Methods

3.1 Research question

The aim of this paper was to summarize the different contents and effects of multidisciplinary rehabiitation in persons with multiple sclerosis (pwMS).

3.2 Literature search

The databases Web of Science (WoS) and Pubmed were searched using the following MeSH terms and keywords: Multiple sclerosis (Topic), multidisciplinary (Topic), interdisciplinary (Topic), Multiple sclerosis (Title/Abstract), interdisciplinary (Title/Abstract), multidisciplinary (Title/Abstract) and multi-disciplinary (Title/Abstract). An overview of the literature search strategy can be found in table 1. All the keywords and terms used were combined with the use of Boolean operators 'AND' or 'OR'. In WoS this led to the following search strategy: "Multiple sclerosis (Topic) AND (Multidisciplinary (Topic) OR Interdisciplinary (Topic))". In Pubmed this led to the following search strategy: "((multiple sclerosis [Title/Abstract])) AND (((interdisciplinary [Title/Abstract]) OR (multidisciplinary [Title/Abstract])) OR multi-disciplinary [Title/Abstract]). For the search in Pubmed, 'multi-disciplinary' was added because it was noticed that some authors weren't found with only the use of 'multidisciplinary'. All duplicates were removed, and every article got screened based on title/abstract. After this, all relevant articles were screened based on full text.

3.3 Selection criteria

Articles were included when 1) there were at least two disciplines involved, 2) there were at least 5 participants with MS included. Articles were excluded when 1) the article was a case study, 2) medication or drug therapy 3) only intervention was surgery, 4) the article was a review 6) when the article was older than 25 years.

3.4 Quality assessment

The level of evidence of each included article was determined by the standards of the Center for Evidence-Based Management (CEBM). For each article, the appropriate checklist (Cochrane randomized controlled trial checklist, checklist for pilot studies, STROBE-checklist for observational studies) was used and was reviewed by two researchers individually (HVM and FVT). In case of disagreement, both assessors sat together to until consensus was reached.

3.5 Data-extraction

In function of the research questions, all relevant information (patient characteristics, therapy parameters and outcome parameters) was extracted from the included articles. The patient characteristics and aim of the studies involves the aim of the studies, the design of the studies, the number of dropouts, the EDSS score, type of MS, age, gender and whether the study was inpatient, outpatient or both. Beside patient characteristics also the aim and the design of the studies was extracted. The extracted therapy parameters contains the group type, if the intervention used was individual or group therapy, the disciplines used, the types of training, the duration of the intervention in weeks, how many days per week, the duration of one session in minutes and the total time trained in minutes. The outcome parameters contains a summary of every outcome measure that was encountered in the analyzing of the articles for this review.

Relevant outcome measures used for interpretation included pre-post measures and level of significance determined with p-value. Effect sizes (Hedges' g) were calculated by dividing the standardized mean difference between post and pre-measurements by pooled standard deviation. Afterwards, multiplication was performed with a factor, to correct for small sample sizes (<20). All data were extracted by two independent reviewers (FVT and HVM).

4 Results

4.1 Results literature search

The search strategy that was applied resulted in the identification of 946 potentially relevant articles. When all duplicates were removed, 669 articles remained. All these articles were screened, based on title/abstract. The total amount of articles that were excluded based on title/abstract was 641. They were excluded for the following reasons: based on population (n=196), the study design (n=238), the publication year (n=5), the intervention used in the study (n=202) and the design of the study (n=238). The 28 articles that remained were screened based on full text. After the screening of the full text, 23 relevant studies were included in the quality assessment. The reasons for exclusion based on full text were: based on design (n=2), the intervention (n=2) and because not being able to retrieve the full text (n=9). To obtain the full texts, several university databases were consulted as well as after trying to contact the authors via mail and on research gate. An overview can be found in the flowchart (figure 1).

4.2 Results quality assessment

An overview of the quality assessment can be found in table 2a, 2b, 2c and 2d. A detailed overview of strengths and weaknesses of the articles is presented in table 3. To assess the quality of the studies with different study designs, four types of checklists were used. The checklist for randomized, controlled trials (n=14), the checklist for prognosis articles (n=5), the checklist for pilot studies (n=2) and the Strengthening the Reporting of Observational Studies (STROBE) checklist (n=3).

There were 14 randomized, controlled trials (RCT's) included in this paper. For these articles the checklist for RCT's was used. All RCT's used randomization except one because of the following reason. Voluntering participants were put on a waiting list. The intervention group was chosen in chronological order of application. First half of the waiting list received the intervention, the second half remained on the waiting list as control group. Blinding of the randomization was not present in two articles. Blinding of the participants was not present in 12 articles and blinding of the practice was not present in 11 articles. Blinding of the practice or participants was not reported in one article. Blinding of the effect rater was not present in

five articles and was not reported in two articles. Loss to follow-up was reported in all 14 articles as well as the intention to treat. Based on the results of the checklist for RCT studies, one article, Di Fabio, got excluded. Results are shown in table 2a.

In the quality assessment of the five articles covering prognosis, only one article did not report clear information about the groups. Follow-up was not complete in three out of five articles. The outcomes as well as the prognostic factors were explicit and objective in all five articles. This was also the case for the outcome measurements regarding validity and reliability. Blinding of the assessors was not reported in three out of five articles. Loss to follow-up was not present in one article and was not reported in one other article. The measurement of prognostic factors was similar for every patient, was valid and reliable and enough patients were included in all five articles. All the prognostic articles were included in the writing of this review. An overview of the scorings can be found in table 2b.

In the quality assessment of the pilot studies, results shown in table 2c, two articles were assessed. Every item was in order for both articles except that there was no statistical hypothesis tested in one article.

In the quality assessment of the three observational studies, all articles were clear about the setting and study design of their research. The title, abstract and the introduction passed all items of the STROBE checklist. Under methods, item matching criteria and the number of controls per case was unclear in all three articles. Under results, no article has used a flow diagram of their patients. Two out of three articles did not indicate a number of participants with missing data for each variable of interest. Also, two out of three articles did not report other analyses performed like for example sensitivity analysis. In the discussion of two articles, the generalizability of the study results was not discussed. The quality of these studies is sufficient. All the observational studies were included in this study. An overview of the scorings can be found in table 2d.

4.3 Patient characteristics

The patient characteristics and study objectives are summarized in table 3. The sample sizes ranged from 10 to 375 subjects. The EDSS score ranged from zero to ten but weren't reported in 17% of the articles. Relapsing-Remitting MS, Secondary-Progressive MS, Primary-Progressive MS as well as benigne MS were discussed in the articles, but only 78% of the

articles reported the MS clinical type of the included patients. The age of the included patients ranged from 17 to 78 years old. All studies had a sample size with more women than men, with the exception of one study.

The study objectives were all about multidisciplinary rehabilitation (MDR) and the impact of MDR on different outcome parameters. Forty-eight percent of the studies used only inpatient rehabilitation, 31% of the studies used only outpatient rehabilitation, 17% of the studies used inpatient as well as outpatient rehabilitation and 4% of the studies did not report the type of rehabilitation.

4.4 Therapy parameters

An overview of the different therapy parameters is provided in table 5.

Most of the studies used a multidisciplinary and individualized concept of rehabilitation. The individualized concept means that the amount of therapy and the combination of disciplines participating in the multidisciplinary team (MD team) is adjusted to the personal needs of the patient and depends on the patient's main focus area. Because of this, every patient received a different combination of interventions and a different amount of therapy. This made it difficult for the studies to describe the treatment precisely. There were not only differences within a study between participants, but there were also differences between studies. Which disciplines were used to compile the MD team differed from one study to another. Also, some studies included a general MDR program, some studies used a specially designed training program.

Because of these differences between participants and between studies, the interventions of the experiment group were often poorly described and they strongly differed from each other. This made it difficult to make a good overview.

In 21 of the 23 articles, the treatment was individualized. Nine articles mentioned group-based therapy and eight articles mentioned goal-oriented training. Education was given in 14 articles.

In the 23 articles, the following disciplines were mentioned when describing the MD team: occupational therapist (n=21), physical therapist (n=22), social worker (n=10), dietician (n=6), psychologist (n=11), neuropsychologist (n=4), nutritional therapist (n=1), neurologist

(n=12), nurses (n=8), urologist or bladder management (n=9), orthopedist (n=3), speech therapist (n=5) and medication (n=3).

The most common rehabilitation modality was an individualized, general MDR program (n=14). These programs are holistic and they focused on improving the patients' condition in general. These interventions differed from one study to another and from one participant to another. Nine of these studies employed an inpatient program, three an outpatient program and two an inpatient and outpatient program combined. The duration of the MDR programs differed from three days to twelve months.

Objectives of the includes studies were to decrease the impact of MS on ADL tasks (n=3), quality of life (n=4), general health state (n=4), amount of disability (n=4), functional independency (n=7), mobility skills (n=2), anxiety (n=2), depression (n=2), anger (n=1), fatigue (n=2), upper extremity function (n=1), muscle strength (n=1), lung function (n=1), mental state (n=1) and resilience (n=1). An overview of the reported objectives related to the MDR programs can be found in table 6a.

Besides these MDR programs, as described above, specially designed training programs were employed in nine articles. Among which, intravenous methylprednisolone (IVMP) management in combination with MDR team assessment (n=1), The OPTIMISE education program (n=1), a MDR program with intensive computer-assisted cognitive rehabilitation (n=1), cognitive rehabilitation (n=1), an intensive wellness program (n=2), a secure asynchronous program with electronic messaging (n=1), high dose methylprednisolone (HDMP) treatment in combination with MDR team assessment (n=1) and a community-based aquatic exercise program (n=1).

IVMP treatment included three days of intravenous methylprednisolone and a MD treatment depending on goals set during initial assessments. Therapy including physiotherapy, occupational therapy and other interventions like education, bladder management, … . The duration and amount of therapy strongly differed according to the needs of the patients. Referrals to other disciplines within the study center also varied between groups. The most common intervention was physiotherapy. Bladder management and advice on coping mechanisms were the main interventions offered by the specialist nurses.

The OPTIMISE program is an educational program specific to the participants' individual needs. This program was delivered over eight weekly sessions of three hours. It includes educational sessions about the complex nature of living with MS when making decisions regarding health-promoting activities. Subjects like exercise and physical activity, stress management, nutritional awareness, … are discussed.

Another specially designed training program is the MDR program with intensive computer-assisted cognitive rehabilitation. This program offers an individualized, goal-oriented inpatient program, based on practical ADL skills with standard physiotherapy. In addition they provide an intensive computer-assisted cognitive rehabilitation. For three months the patients received cognitive rehabilitation three times a week on top of the standard rehabilitation treatment three times a day for five days a week. When needed an additional individualized rehabilitation treatment is available.

In study of *Grasso (2017),* they used a cognitive rehabilitation with the main focus on formulating Goal Attainment Scaling (GAS) goals for coping with cognitive challenges. The patients were offered cognitive group sessions as well as individual sessions for three weeks. The first week of the program, it included cognitive group sessions aiming to increase their awareness of their cognitive strengths, problems, and coping strategies, conducted by the study neuropsychologist and occupational therapist. The sessions included lectures, practical exercises and discussions. In the second and third week, the patients received individual sessions with the occupation therapist and the neuropsychologist. The first 3 months after discharge they received 6 biweekly telephone sessions focusing on attainment of the individual GAS goals.

Two included studies investigated the effect of a wellness program. One study provided an intense multidisciplinary three-day social cognitive wellness program with the participation of support partners. Components of the Social Cognitive Can Do Program (SCDP) were large group sessions, small group sessions, consultations, a theatre evening and every day starting with a joint activity. The other wellness program consisted of a four-day multidisciplinary educational wellness program. This program consisted of group-based individual assessments, workshops, lectures and optional activities in group, as well as individual consultations and optional consultations. Participants navigated the program in groups of four or five, but specific content was individualized. Each participant group was

staffed by a multidisciplinary team. An integral part of these programs was a complementary program for participants' support persons.

The secure asynchronous program with electronic messaging investigated the secure electronic messaging with new MCCO components. The patients received quarterly automated notifications for twelve months to complete a scheduled self-monitoring.

Patients who participated with a MDR program with high-dose methylprednisolone treatment received after a four-days during steroid therapy an individually tailored three-week during MDR program tailored by the treating therapy team. They were offered five times a week one hour of physiotherapy, and three times a week half an hour of occupational therapy for three weeks.

The last specially designed training program is a five-week community-based aquatic exercise program. The aquatic exercises included aerobic exercises, strength training, flexibility exercises, balance training and walking activities. The participants received 60 minutes during sessions two times a week.

Objectives of these specially designed training programs were to improve impact of MS on ADL (n=3), quality of life (n=2), general health state (n=4), amount of disability (n=6), functional independency (n=3), mobility skills (n=2), anxiety (n=1), depression (n=3), fatigue (n=2), self-efficacy (n=4), neuropsychological state (n=1), health-promoting lifestyle (n=1), executive function (n=1), motor function (n=1), physical activity (n=2), satisfaction with medical care (n=1), balance (n=1) and muscle strength (n=1). An overview of the reported objectives related to the specially designed training programs can be found in table 6b.

The information provided about the control treatments is often limited. Three articles used a waiting-list group as control group. Other control treatments were a limited MD treatment (n=4), education (n=1), an MS-nurse consultation (n=1), hospital care (n=1), medication treatment (n=2), no additional treatment related to the study (n=3).

4.5 Therapy dosage

The amounts of therapy in the included articles ranged from 3,45 days to programs of twelve months. Most frequently used was a program of three to five weeks. Furthermore, the fact that almost every study used an individualized rehabilitation program per patient including the number of disciplines involved made sure that every patient received a different amount of daily or weekly therapy during the period of 3,45 days to twelve months. Another unknown

factor is the therapy intensity which is unknown for almost every article because of the individualized programs and the individualized progressions.

4.6 Outcome parameters

An overview of the outcome measures used were described in table 7. Because MS has a heterogeneous and an unpredictable clinical course and causes impairments and disabilities in the different levels of the International Classification of Functioning, Disability and Health (ICF), and because of the multidisciplinary aspect of the interventions included in this paper, a wide range of different outcome measures were found. Because it is relevant to describe the impact of MDR programs on every level of the ICF, a wide range of outcome measures were included in this paper. The outcome parameters have been categorized in five large groups, namely impact of MS on daily life, general health state, quality of life, coping with MS and physical measurements.

Earlier in this paper, the therapy programs were divided in two groups. The general MDR programs and the specially designed therapy programs. The general MDR programs are also subdivided in outpatient programs, inpatient programs and a combination of in- and outpatient programs. In table 6a and 6b, an overview of the different programs related to the objectives is reported. Mainly, functional independency, disability and the general health state are the objectives that are most focused on. Forty-three percent of the studies included functional independency and disability as an objective, while 35% of the studies included the general health state. More specific objectives like lung function, upper limb function, balance, motor function, resilience, muscle strength and satisfaction with medical care are all discussed in only one study of the 23 studies included. Most of these more specific objectives are focused on in the specially designed programs, rather than in the general MDR programs. When to elaborate more closely on MDR programs, it is noticeable that outpatient programs are focusing more on how participants cope with MS than inpatient programs. Objectives like anxiety, depression, anger, fatigue and mental state are discussed more in the outpatient programs than in inpatient programs. When to discuss the specially designed programs, it is noticeable that these programs are focusing on the general objectives (e.g. quality of life, general health state, disability, impact of MS on ADL) as well as the general MDR programs. In addition to that, they place greater emphasis on the more specific objectives like balance,

muscle strength, physical activity, satisfaction with medical care and self-efficacy, than the general MDR programs.

4.6.1 Impact of MS on daily life

The Multiple Sclerosis Impact Scale (MSIS-29) is used in five articles to discuss the impact of MS on daily life. Only one study, *Hanssen (2016),* showed a significant improvement on the psychological component after a cognitive rehabilitation program as intervention. One study, *Boesen (2018)*, including an individualized MDR program, showed a significant difference on the psychological component of the intervention group and the control group (waiting-list). All the results on the physical component were not significant. The Sickness Impact Profile (SIP) and the Impact on Participation and Autonomy (IPA) were both used in one study, there were no significant results for both outcome measures.

Four studies measured the extent to which MS fatigue affects your life. *Rietberg (2014)* described Modified Fatigue Impact Scale (MFIS) and Fatigue Severity Scale (FSS) as outcome parameters and found no significant results after an outpatient MDR program. Three other studies also described the MFIS and none of these studies found significant results.

4.6.2 General health state

Six articles reported The Short Form Health Survey (SF-36) as an outcome measure. Four articles found significant improvements on subscales of the SF-36. *Ennis (2006), Grasso (2017), Ng (2013) and Pozzilli (2002)* found significant improvements on different subscales, as can be seen in table 7. These results had small to medium effect sizes. The General Health Questionnaire (GHQ) was described in two studies. Both studies found no significant results.

Cognitive functions were also described separately. Executive functioning was measured by one study, *Hanssen (2016)* with the subscales Global Executive Composite (GEC) and Metacognition Index (MI) of the Behavior Rating Inventory of Executive Function (BRIEF). Both scales increased significantly after the cognitive rehabilitation and significantly decreased in the control group which underwent a standard inpatient MDR program. The Mini Mental State Examination (MMSE) and the Neuropsychological Test Battery (NPTB) were reported in one study without significant results.

4.6.3 Quality of Life

Six articles described quality of life with different outcome parameters. The functional Assessment of MS (FAMS) was used by two articles and the Life Appreciation and Satisfaction Questionnaire (LASQ) was used by one article. Both outcome measures were no significant results measured. *Boesen (2018)* used the 15-dimensional index (15D index) to measure quality of life after an individualized MDR program. They found a significant difference between the results of the intervention and the control group (waiting-list) on the 15D index. There were two studies who described Multiple Sclerosis Quality of Life-54 (MSQoL-54) as an outcome parameter for quality of life. *Jongen (2014)* found significant improvement with a medium effect size of the MSQoL after an intensive three-day social cognitive wellness program by participants with relapsing remitting MS. There were no significant results for the participants with secondary progressive and primary progressive MS after the same intervention. *Nedeljkovic (2016),* included HDMP treatment in combination with a MDR program as intervention, found a significant improvement with a medium effect size on physical quality of life for both the intervention and the control group (only HDMP treatment). The Nottingham Health Profile (NHP) is used by the study *Sitzia (1998)* to measure the quality of life and showed significant improvement after an individually adapted MDR program.

Health-related quality of life was measured with the EQ-5D instrument in two studies. The self-rated health on a vertical visual analogue scale improved significant with a small effect size after the intervention relative to the control group in one study, *Miller (2011)*. Other results in both studies were not significant.

QUALIVEEN, a questionnaire on urinary-specific quality of life in neuro-urological patients, was reported in one article but they found no significant results.

The satisfaction with medical care was described with the Seniors' General Satisfaction and Physician Quality of Care (SGSPQ) by the article *Miller (2011).* They found no differences between the satisfaction with medical care of the intervention group and the control group.

4.6.4 Coping with MS

Depression and anxiety were measured by two studies with the Hospital Anxiety and Depression Scale (HADS). The State-Trait Anxiety Inventory (STAI) and State-Trait Anger Expression Inventory (STAXI) were reported by one article to measure anxiety and anger. The results for HADS, STAI and STAXI were not significant. *Jonsson (1996)* found a significant

decrease in depression after a MDR treatment with the Beck Depression Inventory (BDI) as outcome measure. *Nedeljkovic (2016)* also used the BDI to measure depression. The study found no significant results in the intervention group and the control group. One article described the Montgomery Asberg Depression Rating Scale (MADRS) as an outcome measure for depression. *Grasso (2017),* including an individualized MD inpatient program with intensive computer-assisted cognitive rehabilitation, found a significant improvement of depression after the intervention, as well as after the control treatment, an individualized MD inpatient program. Resilience was measured with the Resilience Scale (RS) by one study. *Falk-Kessler (2012),* found a significant improvement with a high effect size after the intervention, a MDR program.

Three articles reported Multiple Sclerosis Self-Efficacy Scale (MSSES) as an outcome measure for self-efficacy. Only one article, *Ng (2013),* described significant improvement after the intervention, a four-day educational MD wellness program, IPbut these results were trivial because of the very small effect sizes.

Health-promoting lifestyle behavior was described in one article with the following outcome measures, Health Promoting Lifestyle Profile II (HPLP) and Self Rated Abilities for Health Practices Scale (SRAHP). *Ennis (2006),* as found an significant increase with a high effect size for both outcome measures (HLPL and SRAHP) after the educational OPTIMISE program intervention.

Physical activity was measured in one article with the Human Activity Profile (HAP) questionnaire. *Craig (2003)*, found a significant improvement with a small effect size of physical activity after a IVMP management with a planned, team MD assessment intervention. No improvements were found in the control group receiving only IVMP management.

4.6.5 Physical measurements

Six articles described the Expanded Disability Status Scale (EDSS). These studies found no significant results for the EDSS score after a MDR intervention. The London Handicap Scale was reported by two articles. Only one article, *Freeman (1997),* found a significant difference between the intervention group and the control group (wait-list group) after the intervention, an inpatient MDR program. One article measured disability with the Multiple Sclerosis Functional Composite (MSFC). The results were not significant. The Guy's Neurological Disability Scale (GNDS) was reported by two articles. *Storr (2006)* found no significant results.

Craig (2003) found a significant decrease of disability with a high effect size, after the intervention, IVMP management with planned MD assessment. The control group did not improve. *Hanssen (2016)* found a significant decrease of disability measured with the Hopkins Symptom Checklist (HSCL) after cognitive rehabilitation.

Salem (2011) found a significant improvement with a small effect size on balance measured with the Berg Balance Scale (BBS) after an aquatic exercise program.

One study measured muscle strength with the Checklist Individual Strength (CIS-20R) as outcome measure. They found no significant results. *Salem (2011)* measured grip strength. The grip strength of both the left and the right hand significantly improved with a small effect size after an aquatic exercise therapy.

Four articles examined mobility. *Salem (2011)* described the Timed Up and Go test (TUG). After the intervention, aquatic exercise therapy, the results for the TUG improved significantly and the gait speed significantly increased, but the effect sizes of these increasements were rather small. The Rivermead Mobility Index (RMI) was reported by three articles. *Grasso (2005), Grasso (2009) and Grasso (2017)* found significant improvement, with a small effect size, of mobility after the MDR intervention. Only Grasso (2017) had a control group. The control group had a significant improvement of mobility as well.

Functional independency was measured by ten studies. Six articles evaluated the functional independency with the Functional Independence Measure (FIM). Five studies found improvement on the FIM after the intervention but only one study, *Freeman (1997)*, reported a significant difference between intervention and control group after an inpatient MDR program as intervention. Khan (2008) found a decrease of independency after the intervention (comprehensive MD rehabilitation) and an increase of independency for the control group (wait-list group). This is a negative result. Four articles evaluated the functional independency with the Barthel Index (BI). *Craig (2003), Grasso (2005) and Grasso (2009)* found a significant increase of independency after the intervention, but these increasements were trivial because of the very small effect sizes. The fourth study found no significant results.

Motor function was measured in one article with the Amended Motor Club Assessment (AMCA). *Craig (2003)* found a significant improvement, with a very small effect size, of motor function after the IVMP management with MD team assessment. *Storr (2006),* including comprehensive inpatient MDR program, measured upper extremity function with the Nine Hole Peg Test (9-HPT) and found that the left arm improved after intervention. The difference

between intervention and control group was significant. There were no significant results reported for the right arm.

One study reported the COPD Diagnostic Questionnaire (CDQ) as outcome measure to evaluate lung function. They found no significant results.

4.6.6 Comparison between different kinds of programs

When the different programs are compared with each other, there are some notable differences. The specially designed MDR programs measured 77,8% significant improvements of the different outcome parameters after the intervention. In the individualized, general MDR programs, only 46,4% significant improvements of the outcome parameters after the intervention were observed

After dividing the general MDR programs in inpatient, outpatient and inpatient with outpatient combined programs, it is noteworthy that the inpatient MDR programs achieve more significant results than the outpatient MDR programs and the inpatient with outpatient combined MDR programs. The inpatient programs measured 61,1% significant results on the different outcome parameters after the intervention. When considering the three outpatient programs, only *Pozzilli (2002)*, found a significant improvement of some subscales of the SF-36 after the general, individualized MDR program. The other results of the outpatient programs were not significant. For the inpatient combined with outpatient programs, reported in two studies, only resilience improved significantly after the intervention in the study, Falk-Kessler (2012).

When dividing the specially designed MDR programs, following specific programs reported significant results: IVMP management with a MD team assessment *(Craig, 2003),* the OPTIMISE program *(Ennis, 2006)*, MD inpatient program with intensive computer-assisted cognitive rehabilitation *(Grasso, 2017)*, cognitive rehabilitation *(Hanssen, 2016),* a social cognitive wellness program *(Jongen, 1996)*, HDMP with a MDR program *(Nedeljkovic, 2016)*, an educational wellness program *(Ng, 2013)* and a community-based aquatic exercise program *(Salem, 2011)*.

4.6.7 Comparison between different kinds of MS

Most of the studies included all types of MS. However, six articles made a selection of which types of MS they included. Jongen (2014) divided the experimental groups in a relapse-

remitting (RR) MS group and a group with secondary-progressive (SP) and primary-progressive (PP) MS patients. After the intervention, a social cognitive wellness program, the RR MS group significantly improved while the SP and PP MS group had no significant results. Nevertheless, four studies, *Freeman (1999), Freeman (1997), Grasso (2005) and Grasso (2009),* included only SP and PP MS patients. These four studies reported all significant results for these patients after a general MDR program. *Nedeljkovic (2016)* only included RR MS patients and reported significant improvement after a HDMP treatment in combination with a MDR program.

5 Discussion

5.1 Quality of included articles

On average the scores of quality assessments for the included articles was found to be sufficient. Only one article got excluded because of low quality *(Di Fabio, 1998*). The risk for a selection bias was present in almost every RCT that was assessed (table 2a). The risk for selection bias was present because there was lack of, or total absence of concealment of allocation. Inadequate blinding is a weakness in a lot of research concerning rehabilitation. Not blinding the assessors could also bias the outcomes of more subjective outcome measures. It should be noted that blinding in the included studies was very difficult because of the interventions that were applied.

Intention to treat was present in every RCT that was assessed. Intention to treat is often used to describe the effectiveness of a new treatment because it mirrors the daily practice. The use of intention to treat in every article could provide a clearer sight on the possible effects of a treatment in real life practice.

For the articles that got assessed with a checklist for prognostic articles, follow-up was incomplete in three out of five articles (table 2b). When follow-up is incomplete, the information about long term effects of the intervention applied is lost or inaccurate. Blinding of the assessors in the articles was not reported in three out of five articles, the hazards of not blinding in a study have been described earlier in this section.

The pilot-studies that were assessed were sufficient in all categories of their checklist except the testing of a statistical hypothesis (table 2c). Conducting a study without testing a statistical hypothesis facilitates that no conclusions can be made or that conclusions are formed in function of the wanted outcomes instead of the hypothesis. The absence of statistical hypothesis also offers a chance to keep negative outcomes in the background.

5.2 Results

5.2.1 Patient characteristics

The articles included reported relapsing-remitting MS, secondary-progressive MS, primary progressive MS as well as benign MS which made sure that there was a variation of types of MS represented in the analysis of this review. The age of the patients included in the articles

ranged from 17 to 78 years old. This is a heterogenous range in patients. All studies but one had included more women then man which could make the generalizability questionable in terms of gender. Forty-six percent of the studies used inpatient rehabilitation only, 28% used outpatient only, 17% used a combination of both and 8% did not report the type of rehabilitation. The heterogeneity of these studies is good for generalizability but makes it difficult to offer a clear conclusion on the effects of inpatient versus outpatient versus a combination of both.

5.2.2 Therapy dosage

Because of the variations and a limited amount of studies with the same treatment dosage, conclusions made about treatment dosage are not very reliable. Furthermore, the fact that almost every study used an individualized rehabilitation program per patient including the number of disciplines involved made sure that every patient received a different amount of therapy. Another unknown factor is the therapy intensity which is probably caused by the individualized programs and the individualized progressions used in the included articles.

5.2.3 Therapy contents and effects

In general, functional independency, disability and the general health state are the objectives that are most focused on. The focus in the outpatient MDR programs lies on the same items as the inpatient MDR programs but in addition, they look at how the participants cope with MS (e.g. anxiety, depression, anger, fatigue and mental state).

The main emphasis in all the included studies was on the items concerned about the general health of the participants, namely QoL, general health state, disability, the impact of MS on ADL. The specific programs often add extra objectives with a more specific focus, like balance, muscle strength, physical activities and self-efficacy. Because these specific programs focused their therapy on improving specific outcome parameters, it could be hypothesized that this is the reason that they had more effect on the outcome measures used in the studies (table 7).

Concerning the general MDR programs, participants were feeling better physically and psychologically according to the subjective parameters, but the objective improvements of the physical components could not be confirmed. This as opposed to specially designed MDR programs, which reported significant improvements on objective outcome parameters.

Because of this it could be hypothesized that designing a multidisciplinary rehabilitation program in function of a couple of specific factors is more favorable over general multidisciplinary rehabilitation programs.

The specially designed MDR programs which reported significant improvements were the following programs: IVMP management with a MD team assessment, the OPTIMISE program, MD inpatient program with intensive computer-assisted cognitive rehabilitation, cognitive rehabilitation, a social cognitive wellness program, HDMP with a MDR, an educational wellness program and a community-based aquatic exercise program. These forms of specially designed MDR programs and the development of any other specially designed MDR programs may be opportunities for future further research.

From the results of these included articles, no unequivocal conclusion can be drawn regarding which type of MS is most likely to benefit from a MDR program. Further research is necessary.

5.2.4 Limitations and strengths of review

One of the limitations of this study is that only two databases were searched for relevant articles. The use of only two databases could have caused that not all relevant articles were found in the literature search that was applied. Articles of which the full text could not be obtained were excluded for analysis. This could imply that not all relevant outcomes have been documented in this review. Another limitation is that different checklists were used with the result that not all articles were screened on the same characteristics. One final limitation is that the research question was wide ranging, because of this it was hard to form any clear conclusions.

Even though forming conclusions was difficult because the wide-ranging research question, a strength of this study is that a general picture has been described concerning the effects of different MDR programs on the general health in pwMS. This paper elaborates on the difference between a general MDR program and a specially designed MDR program. This review could be a good starting point for future research.

5.2.5 Future recommendations

Future research should focus on the most efficient therapy dosage and intensity of therapy suited to every type of patient in function of the severity of the condition of the patient, which type of MS the patient has and the patient's personal needs.

Another recommendation is that specific designed MDR programs like, for example, the aquatic program, should be more compared to general multidisciplinary rehabilitation programs. In this paper, it seems that the specific MDR programs produce more significant improvements than the general MDR programs, but based on this paper, no certainty can be expressed about this comparison because the programs made use of different outcome parameters. It is an added value for estimating the value of MDR programs to investigate the differences between specific MDR programs and general MDR programs on the same outcome parameters.

The use of specific MDR programs to target specific disabilities could also be a subject of future research. Because every patient with MS has a different disease pattern and every patient has a diverse combination of disabilities. It can be useful to combine the MDR concept with a more specific approach to certain disabilities. If, after further investigation, specific MDR programs seems to be more effective than general MDR programs, the specific MDR programs give the opportunity to have significant improvements of certain disabilities without losing sight of the other disabilities caused by MS because of the MD team included in the program.

6 Conclusion

Multidisciplinary rehabilitation programs in MS ensures improvements in the categories of general health state, quality of life, coping with MS, physical measurements and the psychological aspects of the impact of ms on daily life. Because almost every intervention was individualized, forming conclusions about therapy dosage and intensity was difficult. The results of this review suggest that specially designed MDR programs are potentially more effective than general individualized MDR programs. The heterogeneity of the populations included, ensures a generalizable conclusion.

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8 Appendix part one – overview of literature

Figure 1: flowchart – Literature search strategy and results

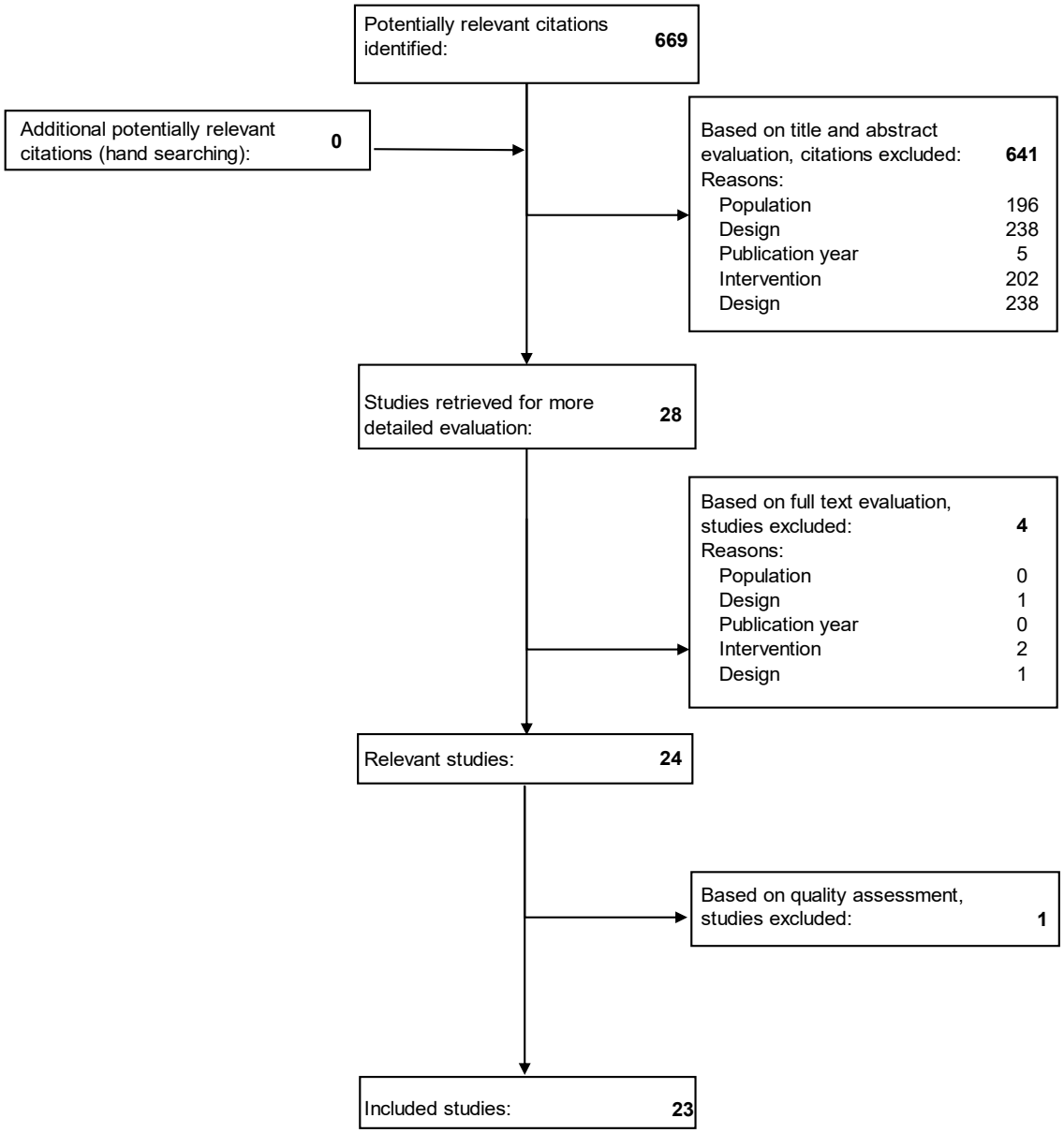


Table 1:
Literature search strategy

	Key words in Pubmed	Hits December '18	Hits March '19
#1	Multiple sclerosis [Title/abstract]	68328	69493
#2	Multidisciplinary [Title/abstract]	71937	73800
#3	Multi-disciplinary [Title/abstract]	5629	5702
#4	Interdisciplinary [Title/abstract]	31783	32519
#5	#1 AND (#2 OR #3 OR #4)	382	397
	Key words in Web of Science	**Hits December '18**	**Hits March '19**
#1	Multiple sclerosis [Topic]	120112	121117
#2	Multidisciplinary [Topic]	84648	86850
#3	Interdisciplinary [Topic]	67442	68151
#4	#1 AND (#2 OR #3)	535	549

Table 2a:
Quality assessment - RCT checklist

Author	1. Randomization?	2. Blinding randomization?	3. Blinding patients?	4. Blinding practicer?	5. Blinding effect rater?	6. Similarity sample size?	7. Loss to follow-up?	8. Intention to treat?	9. Same treatment?	10. Results valid?
Boesen, F., et al. (2018)	+	+	-	-	+	+	+	+	+	+
Craig, J., et al. (2003)	+	-	-	-	?	+	+	+	+	+
Di Fabio, R. P., et al. (1998)	-	-	-	-	-	?	+	+	-	-
Ennis, M., et al. (2006)	+	+	-	-	+	- / +	+	+	+	+
Freeman, J. A., et al. (1997)	+	+	-	-	-	+	+	+	?	?
Grasso, M. G., et al. (2017)	+	+	+	+	+	+	+	+	+	+
Hanssen, K. T., et al. (2016)	+	+	-	-	?	+	+	+	-	+
Khan, F., et al. (2008)	+	+	+	+	+	+	+	+	+	+
Miller, D. M., et al. (2011)	+	+	-	-	-	+	+	+	+	+
Nedeljkovic, U., et al. (2016)	+	+	-	-	-	+	+	+	+	+
Papeix, C., et al. (2015)	+	+	-	-	+	+	+	+	+	?
Pozzilli, C., et al. (2002)	+	+	-	-	+	-/+	+	+	-	+
Rietberg, M. B., et al. (2014)	+	+	-	-	+	+	+	+	+	+
Storr, L. K., et al. (2006)	+	+	?	+	-	-	+	+	+	?

Note: +: rated as present; -: rated as absent; -/+: First absent and afterwards corrected; ?: nog enough information available

Table 2b:

Quality assessment - Prognose checklist

	Item		Outcomes				Prognostic factors			
Author	1. Clear information about groups, similar disease course?	2. Follow-up complete?	3. Outcomes explicit and objective?	4. Measurement of outcomes valide and reliable?	5. Measurement of outcomes independent (blind)?	6. Prognostic factors explicit and objective?	7. Loss to follow-up?	8. Measurement of prognostic factors similar for every patient?	9. Measurement of prognostic factors valide and reliable?	10. Measuring of prognostic factors with enough patients?
Grasso, M. G., et al. (2005)	+	-	+	+	?	+	?	+	+	+
Grasso, M. G., et al. (2009)	+	-	+	+	?	+	+	+	+	+
Jonsson, A., et al. (1996)	+	-	+	+	?	+	-	+	+	+
Ng, A., et al. (2013)	+	+	+	+	+	+	+	+	+	+
Sitzia, J., et al. (1998)	-	+	+	+	+	+	+	+	+	+
Note: +: rated as present; -: rated as absent; ?: unknown information										

Table 2c:

Quality assessment - Pilot study checklist

Author	1. Reasons to conduct the study?	2. Aims and objectives are clearly stated?	3. Collected data are consistent with goals?	4. No statistical hypothesis is tested?	5. Sample size is justified?	6. The way of datacollection will be used in the larger study?	7. Answer question about full scale trial is worth pursuing?	8. Criteria for the larger study are specified?
Falk-Kessler, J., et al. (2012)	+	+	+	-	+	+	+	+
Salem, Y., et al. (2011)	+	+	+	+	+	+	+	+
Note: +: rated as present; -: rated as absent								

Table 2d:

Quality assessement - STROBE checklist

	Title and abstract		Introduction				Methods											
Author	1a.	1b.	2.	3.	4.	5.	6a.	6b.	7.	8.	9.	10.	11.	12a.	12b.	12c.	12d.	12e.
Freeman, J. A., et al. (1999)	+	+	+	+	+	+	+	?	+	+	+	+	+	+	+	+	+	?
Jongen, P. J., et al. (2014)	+	+	+	+	+	+	?	?	+	+	-	+/-	+	+/-	-	-	+	+
Onat, S. S., et al. (2015)	+	+	+	+	+	+/-	-	?	+	+	+/-	+	+	+	+	?	+	+

	Results											Discussion			Other information		
	13a.	13b.	13c.	14a.	14b.	14c.	15.	16a.	16b.	16c.	17.	18.	19.	20.	21.	22.	
Freeman, J. A., et al. (1999)	+	+	-	+	?	+	+	?	?	?	?	+	+	+	+	+	
Jongen, P. J., et al. (2014)	-	-	-	+	-	+	+	?	+	?	-	+	-	-	?	+	
Onat, S. S., et al. (2015)	+	?	-	+	-	?	?	?	?	?	-	+	+	+	?	+	
Note: +: rated as present; -: rated as absent; -/+: First absent and afterwards corrected; ?: nog enough information available																	

Table 3: *Strength-weakness analysis of included articles*

Study	LoE	Strength	Weakness
Boesen, F., et al. (2018)	1b	- Randomised sequence generation and concealment of allocation - Well trained, qualified MD team - Blinding of effect rater - No significant differences in baseline demographics - Same treatment for intervention group and control group	- Large variability in outcomes, likely due to the heterogeneity of the sample population - HRQoL scales are not ideal outcome measures, they could underestimate the benefit from MDR - Lack of power, this may represent a type II error - No blinding of patients or treating therapists - Using a wait-list as a control instead of a sham intervention
Craig, J., et al. (2003)	1b	- No significant differences in baseline demographics - The GNDS score is dictated only by the subject responses, therefore not influenced by the opinion of the person asking the question - Same treatment for intervention group and control group	- Difficult to ascertain whether the benefits obtained in the treatment group were accounted for by the acute intervention or the later community management - No blinding of patients or treating therapists - A type I error could potentially have occurred in the AMCA analysis - Short follow-up period - No description of randomised sequence generation and concealment of allocation
Ennis, M., et al. (2006)	1b	- Minimum influence of the researcher because of self-report questionnaire - No need for extra specific skills as therapist or need for special equipment - No significant differences in baseline demographics - Same treatment for intervention group and control group - Blinding of effect rater - Randomised sequence generation and concealment of allocation	- No blinding of patients or treating therapists - Self-selecting samples (potentially biased) - No follow-up measures to evaluate durability of intervention
Falk-Kessler, J., et al. (2012)	2b	- Aims and objectives are clearly stated - Justified sample size - Criteria for the larger study are specified	- Carried out in a center specifically designed to treat people with MS. Results cannot be generalized to other MS populations - No randomization - Not the same treatment for intervention and control group. Intervention group had more hours of therapy - Number of sessions received was based on the needs of each individual, the impact of these modalities on resilience is unknown

Table 3: *Strength-weakness analysis of included articles*

Study	LoE	Strength	Weakness
Freeman, J. A., et al. (1999)	2b	- High follow-up rate - Reported number, patient characteristics and reasons of drop-outs	- No control group - The generalizability of this study is limited due to selection biases - No blinding of patients or treating therapists
Freeman, J. A., et al. (1997)	1b	- Randomised sequence generation and concealment of allocation - No significant differences in baseline demographics - Limited likelihood of improvement due to spontaneous neurological recovery (inclusion and exclusion criteria) - Bias in terms of patient recruitment was negligible - Alternations in drugs did not have a notable effect on outcome - Absence of blinding was minimized in a number of ways: (1) nontreating assessors, (2) long time interval between two assessments, (3) assessors had no access to initial scores, (4) self-report method used to measure disability and handicap - In addition to researchers' disability scores, patients were independently rated	- Using a wait-list as a control instead of a sham intervention - No blinding of patients, assessors or treating therapists - Inability to control for the placebo effect - Deterioration in control group during study may reflect selection bias - Short time interval between two assessments in terms of evaluating carryover of change - Generalizability of the results is limited - No follow-up measures to evaluate durability of intervention
Grasso, M. G., et al. (2005)	2c	- No significant differences in baseline demographics	- No follow-up measures to evaluate durability of intervention - Uncontrolled study
Grasso, M. G., et al. (2009)	2c	- No significant differences in baseline demographics	- No follow-up measures to evaluate durability of intervention - Uncontrolled study
Grasso, M. G., et al. (2017)	1b	- Control group has sham therapy - Same treatment for intervention group and control group - No significant differences in baseline demographics - Same treatment for intervention group and control group - Blinding of effect rater - Randomised sequence generation and concealment of allocation	- Small sample size
Hanssen, K. T., et al. (2016)	1b	- No significant differences in baseline demographics - Randomised sequence generation and concealment of allocation	- Not the same treatment for intervention group and control group - No blinding of patients or treating therapists
Jongen, P. J., et al. (2014)	2b		- Uncontrolled study
Jonsson, A., et al. (1996)	2c	- No significant differences in baseline demographics	- Uncontrolled study - Number of drop-outs and reasons reported - No follow-up measures to evaluate durability of intervention

Table 3: *Strength-weakness analysis of included articles*

Study	LoE	Strength	Weakness
Khan, F., et al. (2008)	1b	- No significant differences in baseline demographics - Same treatment for intervention group and control group - Blinding of effect rater - Randomized sequence generation and concealment of allocation	
Miller, D. M., et al. (2011)	1b	- Study sample and findings are considered generalizable - No significant differences in baseline demographics - Same treatment for intervention group and control group - Randomized sequence generation and concealment of allocation	- Patient-driven intervention: it is possible the features of the enhanced system were not utilized often enough to make a difference in outcomes - No direct patient-clinician interaction - Amount of intervention between the 2 groups can be insufficient to produce between-group differences - More targeted, goal-directed interventions may have greater benefit - The duration of the intervention may limited its impact - The disease-specific system components and content make it difficult to compare our system utilization to that reported for other Web-based self-management programs - The number of participants with RR or PP MS were not determined - No follow-up measures to evaluate durability of intervention - No blinding of patients or treating therapists - Uncontrolled study
Nedeljkovic, U., et al. (2016)	1b	- No significant differences in baseline demographics - Same treatment for intervention group and control group - Randomized sequence generation and concealment of allocation	- The existence of psychological factors and education degree of our patients which could have influenced MSQoL-54 domains need to be mentioned - Small sample size - No blinding of patients or treating therapists - Short follow-up period - They did not analyze the effect of depression as a potential confounding factor in assessment of QoL
Ng, A., et al. (2013)	2c	- Selection within the participants are probably not influencing the overall results - No significant differences in baseline demographics	- Examination of longitudinal stability is missing - The improvement was independent of initial levels of EDSS --> generalization - No concurrent randomized control group - The PASIPD survey for physical activity may have lacked sensitivity to detect change in physical activity - Uncontrolled study - No information about type of MS and EDSS score

Table 3: *Strength-weakness analysis of included articles*

Study	LoE	Strength	Weakness
Onat, S. S., et al. (2015)	2b	- The personal rehabilitation programs planned in the hospital are in accordance with the literature	- The patients' distribution of MS clinical type was different from that of the general population - Retrospective study - Single-centered study (small sample size)
Papeix, C., et al. (2015)	1b	- Blinding of effect rater - Randomized sequence generation and concealment of allocation - INTERMED score used at inclusion to better characterize the population studied - No significant differences in baseline demographics - Same treatment for intervention group and control group	- No blinding of patients or treating therapists - Missing data could have influenced the results, small possibility - Small sample size - Included population is not representative of the whole MS population - Motivational factors/barriers influence individual long-term management of MS care - Follow-up calls by a dedicated MS nurse was not organized in a systematic way
Pozzilli, C., et al. (2002)	1b	- No significant differences in baseline demographics - Well trained, qualified MD team - Adequate recruitment and compliance of the patients - Blinding of effect rater - The sample group is representative of the entire MS population - Randomized sequence generation and concealment of allocation	- The results of the trial depend on local service provision, which can influence recruitment to the study - Professionals were aware of the assignment of patients to either group - Patients and physicians were not blinded - The quality of standard care in the control group must be considered in the interpretation of the results - No follow-up measures to evaluate durability of intervention - Not the same treatment for intervention group and control group - No blinding of patients or treating therapists
Rietberg, M. B., et al. (2014)	1b	- Well trained, qualified MD team - No significant differences in baseline demographics - Same treatment for intervention group and control group - Blinding of effect rater - Randomized sequence generation and concealment of allocation	- Small sample size - Selected population limits generalization - Unable to confirm that this procedure led to an optimal deployment of disciplines - No blinding of patients or treating therapists

Table 3: *Strength-weakness analysis of included articles*

Study	LoE	Strength	Weakness
Salem, Y., et al. (2011)	2b	- Adequate recruitment and compliance of the patients - Safe program and well tolerated intervention with no negative effects reported - Well trained, qualified therapists - Aims and objectives are clearly stated - Criteria for the larger study are specified	- Duration of the program was too short in combination with a low training intensity - Small sample size + a sample of convenience - The MFIS may be not sensitive enough to detect changes in fatigue over time - Use of a one-group, pretest/posttest design, lacked a control group - one-on-one water coaching would be difficult to provide in a typical community-based program - No follow-up measures to evaluate durability of intervention - Uncontrolled study
Sitzia, J., et al. (1998)	2c	- Participants' demographic characteristics are broadly representative - Good response rate - NHP-1 was selected for this study as it is well-tested, is suited for use with chronic conditions, and is not disease-specific	- Small sample size - Power associated with the tests of significance is relatively low - Follow-up period was short - It is impossible to seperate the benefits of this inpatient treatment from the hospital discharge scheme which continued for one month post discharge - Possible associations between HRQL results and changes in disability were not examined. - No follow-up measures to evaluate durability of intervention - Uncontrolled study
Storr, L. K., et al. (2006)	1b	- Same treatment for intervention group and control group - Randomized sequence generation and concealment of allocation	- Limited study time period - Unexpectedly low recruitment rate - Intervention time is very short in comparison with comparator studies - Unequal distribution of patients in the two groups. Bias toward greater tendency in the control group to give consent to participate - EDSS stratification reveals a skewed distribution with more patients severely disabled in the control group - No follow-up measures to evaluate durability of intervention

Note: LoE, Level of Evidence according to Oxford CEBM level of evidence guidelines.

Table 4: *Data-extraction - Patient characteristics and aim of the study*

Study	Aim		n	n Dropouts	EDSS score	Type of MS	Age (years) mean (range, SD)	Gender (%F)	Inpatient/ outpatient
Boesen, F., et al. (2018)	To evaluate the longer term effectiveness of inpatient multidisciplinary rehabilitation on the health-related quality of life of MS patients.	Exp	214	35	5 (3,5 - 6,5)	RR: 41,6% SP: 42,1% PP: 16,4%	51 (44-58)	67,8%	Inpatient
		Con	213	17	4,5 (3,5-6,5)	RR: 39,9% SP: 43,2% PP: 16,9%	51 (44-56)	68,5%	
Craig, J., et al. (2003)	To evaluate the benefits of IVMP with planned, comprehensive multidsciplinary team care compared to IVMP management with standard care.	Exp	20	1	0-3,5: 30% 4-6,5: 50% 7-10: 20%	?	38 (26-59, SD = 8,72)	55,0%	11/9
		Con	20	0	0-3,5: 25% 4-6,5: 55% 7-10: 20%		42 (22-67, SD = 11,09)	80,0%	12/8
Ennis, M., et al. (2006)	To evaluate the effectiveness of a health promotion education programme for people with multiple sclerosis (the OPTIMISE programma) in terms of increasing the level of health-promoting activity undertaken, improving self-efficacy and enhancing quality of life.	Exp	32	2	0-3: 22% 3,5-6: 69% 6,5-7: 9%	Benigne: 6% RR: 50% SP: 28% PP: 16%	45 (SD = 9)	63%	Outpatient
		Con	30	0	0-3: 23% 3,5-6: 74% 6,5-7: 3%	Benigne: 3% RR: 40% SP: 37% PP: 20%	46 (SD = 8)	63%	
Falk-Kessler, J., et al. (2012)	To examine the impact of multidisciplinary care, with a particular focus on occupational therapy, on resilience in individuals with MS.	Exp	26	1	?	?	46,2 (26-69, SD = 12,0)	76,90%	Inpatient and outpatient
		Con	9	0			45,1 (25-70, SD = 13,7)	77,80%	
Freeman, J. A., et al. (1999)	To determine the duration and pattern of carry-over of benefits gained after a short period of multidisciplinary inpatient rehabilitation.	Exp	50	6	6,8	SP: 86% PP: 14%	44,8 (25-66, SD = 9,7)	58%	Inpatient
Freeman, J. A., et al. (1997)	To evaluate the effectiveness of a short period of multidisciplinary inpatient rehabilitation in people with MS.	Exp	32	2	0-4,5: 0% 5-6,5: 53% 7-9,5: 47%	SP: 94% PP: 6%	43,2 (25-73, SD = 10,77)	66%	Inpatient
		Con	34	2	0-4,5: 0% 5-6,5: 56% 7-9,5: 44%	SP: 88% PP: 12%	44,6 (25-61, SD = 9,73)	62%	

Table 4: *Data-extraction - Patient characteristics and aim of the study*

Study	Aim		n	n Dropouts	EDSS score	Type of MS	Age (years) mean (range, SD)	Gender (%F)	Inpatient/ outpatient
Grasso, M. G., et al. (2005)	To evaluate the effectiveness and prognostic factors of inpatient multidisciplinary rehabilitation treatment in patients with MS.	Exp	230	0	< 6: 29 6-6,5: 69 > 6,5: 132	PP and SP	49,42, SD = 11,5	1:1:7 (female/male ratio)	Inpatient
Grasso, M. G., et al. (2009)	To evaluate the effectiveness of inpatient multidisciplinary rehabilitation treatment in MS and identify reliable prognostic factors.	Exp	200	0	2,5-6: 12,5% 6-6,5: 34% > 6,5: 53,5%	PP and SP	49,77, SD = 11,32	65%	Inpatient
Grasso, M. G., et al. (2017)	To evaluate the effectiveness of cognitive rehabilitation in a group of MS patients.	Exp	17	0	+/-7,54, SD= 0,8	RR: 47,1% SP: 41,1% PP: 11,8%	59,55, SD = 7,2	64,70%	Inpatient
		Con	17	0	+/-7,5, SD= 0,8	RR: 47,1% SP: 47,1% PP: 5,8%	58,67, SD = 10,3	64,70%	
Hanssen, K. T., et al. (2016)	To investigate the effects of cognitive rehabilitation on cognitive and executive coping, psychological well-being and psychological aspects of health-related quality of life in patients with MS.	Exp	60	2	+/-4,4, SD= 1,7	RR: 27% SP: 15% PP: 18%	53,9 (33-70)	40%	Outpatient
		Con	60	1	+/-4,2, SD= 1,7	RR: 32% SP: 18% PP: 10%	52,5 (32-71)	48%	
Jongen, P. J., et al. (2014)	To assess in persons with MS the effect of an intense multidisciplinary, 3-day, social cognitive wellness program with the participation of support partners, after 1, 3 and 6 months.	Exp1	20	7	3,1 (1,2) (1,5-6.0)	RR: 100%	42,7 (25-65, SD = 10,1)	80%	Inpatient
		Exp2	24		5,5 (1,4) (3,0-7,5)	SP: 91,7% PP: 8,3%	44,6 (25-61, SD = 9,73)	79,20%	
Jonsson, A., et al. (1996)	To evaluate the LLQ as a measure of quality of life and as an outcome measure.	Exp	43	22	6,59 (3,5-8,0)	RR: 23,8% SP: 61,9% PP: 14,3%	48 (37-63)	52,40%	Inpatient
Khan, F., et al. (2008)	To assess the effectiveness of rehabilitation in persons with MS in an Australian community cohort.	Exp	49	1	0-3: 14,3% 3,5-6: 55,1% 6,5+: 30,6%	RR: 26,5% SP: 59,2% PP: 14,3%	49,5 (30-63, SD = 8,64)	63,30%	Inpatient and outpatient
		Con	52	2	?	RR: 34,6% SP: 51,9% PP: 13,5%	51,1 (29-65, SD = 9,66)	78,80%	

Table 4: *Data-extraction - Patient characteristics and aim of the study*

Study	Aim		n	n Dropouts	EDSS score	Type of MS	Age (years) mean (range, SD)	Gender (%F)	Inpatient/ outpatient
Miller, D. M., et al. (2011)	To assess an Internet-based self-management system that utilized the e-PHR and determined its impact on self-assessed well-being, clinician-assessed well-eing, and healthcare utilization in patients with MS.	Exp	102	18	Unknown	RR and PP, more RR (specific numbers unknown)	48,1 (SD = 9,1)	72%	Outpatient
		Con	104	21			48,1 (SD = 9,7)	85%	
Nedeljkovic, U., et al. (2016)	To evaluate the potential benefits of short-term HDMP combined with multidisciplinary rehabilitation in persons with MS in relapse in order to assess whether combination of steroid therapy with MDR is more beneficial than steroid therapy alone.	Exp	17	5	+/- 4,5 (SD = 1,4)	RR: 100%	41,3 (22-61, SD = 9,9)	64,70%	Inpatient and afterwards outpatient
		Con	20	7	+/- 4,0 (SD = 0,9)		39,4 (18-62, SD = 10,7)	75%	
Ng, A., et al. (2013)	To determine if an intensive wellness program for persons with MS results in improved self-efficacy, qualtiy of life, or physical activity outcomes.	Exp	129	47	3,5 (0-9,5)	?	?	76,70%	?
Onat, S. S., et al. (2015)	To investigate the sociodemographic and clinical characteristics as well as rehabilitation methods of patients with MS undergoing an inpatient rehabilitation program.	Exp	104	0	< 4: 0% 4-5,5: 40,4% > 6: 59,6%	RR: 44,2% SP: 34,6% PP: 21,2%	40,53 (17-59, SD = 9,4)	65,40%	Inpatient
Papeix, C., et al. (2015)	To address the effectiveness of an integrated multidisciplinary approach versus usual care in MS patients.	Exp	25	4	6 (3-8)	RR: 20% SP: 56% PP: 24%	50 (34-69)	72%	Outpatient
		Con	25	4	6 (2,5-8,5)	RR: 12% SP: 76% PP: 12%	52 (26-78)	80%	

Table 4: *Data-extraction - Patient characteristics and aim of the study*

Pozzilli, C., et al. (2002)	To compare the effectiveness and the costs of multidisciplinary home based care in MS with hospital care in a prospective randomised controlled trial with a one year follow up.	Exp	133	10	6,0 (SD = 2,0)	RR: 19,6% SP: 59,9% PP: 20,5%	47 (SD = 10,3)	65%	Outpatient
		Con	68	3	5,8 (SD = 2,2)	RR: 20,6% SP: 58,8% PP: 20,6%	46,7 (SD = 13,3)	69%	
Rietberg, M. B., et al. (2014)	To assess the effects of individually tallored, multidisciplinary outpatient rehabilitation on chronic fatigue.	Exp	23	2	3	RR: 69,6% SP: 21,7% PP: 8,7%	45 (SD = 9,9)	60,9%	Outpatient
		Con	25	2	4	RR: 48% SP: 28% PP: 24%	47 (SD = 8,6)	68%	
Salem, Y., et al. (2011)	To determine the feasibility of providing a community-based aquatic exercise programma and to examine the effects of a group aquatic exercise programma in individuals with MS.	Exp	11	1	?	?	55,9 (44-69)	80%	Outpatient
Sitzia, J., et al. (1998)	To ascertain whether or not an inpatient multidisciplinary treatment programme for patients with Parkinson's disease or MS resulted in a measurable change in patients' health-related quality of life.	Exp(MS)	42	9	?	?	49,0 (17-70, SD = 12,9)	74%	Inpatient
Storr, L. K., et al. (2006)	To evaluate the short-term efficacy of multidisciplinary, inpatient rehabilitation of MS patients.	Exp	38	3	0-4,5: 5% 5-6,5: 82% 7-9,5: 13%	RR: 13% SP: 63% PP: 24%	45 (SD = 9,9)	57,9%	Inpatient
		Con	52	13	0-4,5: 13% 5-6,5: 56% 7-9,5: 31%	RR: 23% SP: 56% PP: 21%	47 (SD = 8,6)	69,2%	

Note: exp: experimental group; con: control group; RR: relapse-remitting; PP: primary progressive; SP: secondary progressive; SD: standard deviation; n: number; ?: not reported; SD: standard deviation; %F: Female percentage of the sample size

Table 5: *Data-extraction - therapy parameters*

Study		Type of training				MD team													What?	Organisation program	Amount of therapy
		Group-based training	Individualized training	Goal-oriented training	Education	OT	PT	SW	D	P	NP	NT	N	Nss	U	O	ST	M			
Boesen, F., et al. (2018)	Exp	X	X	X	X	X	X	X	X	X	X	X	X	X					- An individualized, holistic and balanced MDR program. - Disciplines depending on patient's main focus area. - Educational lessons on different topics.	4 weeks continuous hospitalization with 20 days of scheduled rehabilitation.	Total: 3,5 h of therapy/day. Pt and Ot + supervised self-directed exercise: 2 h of interrupted sessions/day.
	Con																		- Wait-list control group. - Regularly seen by their neurologists at the MS Clinics.	Not precluded from participating in local community-based training or services, including Pt and Ot.	/
Craig, J., et al. (2003)	Exp		X	X	X	X	X							X	X	X		X	- IVMP management + MD assessment. - Treatment depended on goals. - Education: about continuing self- management referral to other agencies on discharge. - Comprehensive Pt, Ot. - Other MD interventions available.	Duration of therapy and specialist nursing given to the groups differed according to the group protocols. Pt was most common intervention and had the longest duration of treatment among those given. Bladder management and advice on coping mechanisms were the main interventions given by MS nurses.	Mean Pt: 2.62 h Mean Ot: 1.49 h Mean length of stay: 3.45 days No. of subjects seen by: ST: 3, MS Nss: 20, O: 3, further Pt: 13, further Ot: 10
	Con		X	X	X	X	X								X			X	- IVMP: 3 days. - Standard ward care. - Referral to other disciplines and subsequent outpatient therapy.	Same as intervention group	Mean Pt: 0.26 h Mean Ot 0.075 h Mean length of stay: 4.8 days No. of subjects seen by: MS Nss: 9, further Pt: 3, further Ot: 2

Table 5: *Data-extraction - therapy parameters*

Study		Type of training				MD team												What?	Organisation program	Amount of therapy
		Group-based training	Individualized training	Goal-oriented training	Education	OT	PT	SW	D	P	NP	NT	N	Nss	U	O	ST	M			
Ennis, M., et al. (2006)	Exp	X	X		X	X	X		X				X						- The OPTIMISE program. - To provide with knowledge, skills and confidence to undertake health-promoting activities. - Education: specific to the participants' individual needs. It was split into 5 component subjects: exercise & physical activity, lifestyle, exercise & physical activity, lifestyle, adjustment/fatigue and stress management, nutritional awareness and responsible health practices	Delivered in sessions in group format, held within the hospital environment. Following sessions: Introduction session, session for each of the component subjects, session about exercise and physical activity, final session: summary for family/friends and planning longer term goals - Relevant health care sessions (OT, PT, D, MS nurse specialist).	The program was delivered over 8 weekly sessions of 3 hours.
	Con																		- No additional interventions. - The control subjects continued with their present level of care	/	/
Falk-Kessler, J., et al. (2012)	Exp		X		X	X	X	X		X			X	X					- MD intervention program with extra Ot. - The usual and customary MD intervention provided at the MS center tailored to meet the individual's specific needs. - Other MD interventions based on individually needs.	8 weeks of MD treatment with extra Ot sessions.	?
	Con		X																- MD intervention program. - The usual and customary MD intervention provided at the MS center tailored to meet the individual's specific needs. - No Ot.	8 weeks of MD treatment without extra Ot sessions.	?

Table 5: *Data-extraction - therapy parameters*

Study		Type of training				MD team												What?	Organisation program	Amount of therapy
		Group-based training	Individualized training	Goal-oriented training	Education	OT	PT	SW	D	P	NP	NT	N	Nss	U	O	ST	M			
Freeman, J. A., et al. (1999)	Exp		X	X	X	X	X	X	X	X			X	X	X	X			- An individualized, goal-oriented, MD inpatient program. - Based on a model of comprehensive care, the essential features of which have been recently described. - Services recommended at discharge: wheelchair services clinic, community Ot, district nurse, regular outpatient Pt, other, outpatient Pt review, community Pt, psychology, social worker, home help, care manager, day care, re-housing, respite care, house adaptations.	Mean duration of inpatient stay = 23 days.	?
Freeman, J. A., et al. (1997)	Exp		X	X		X	X		X	X			X		X		X		- An individualized, goal-oriented, MD inpatient program. - All patients had medical, nursing, and OT and PT input. - Consultation was possible from psychiatric, urological, and dietetic services.	An individualized, goal-oriented program, addressing a wide range of areas, for an average of 20 days.	On average, 2 45-min Pt sessions and 1 Ot session per day were undertaken. 85% were assessed by the NP, 64% by the ST, and 48% by the SW.
	Con																		- Wait-list control group. - No rehabilitation intervention was provided and no other interventions were arranged.	Waiting period of 6 weeks	/

Table 5: *Data-extraction - therapy parameters*

Study	Type of training				MD team												What?	Organisation program	Amount of therapy
	Group-based training	Individualized training	Goal-oriented training	Education	OT	PT	SW	D	P	NP	NT	N	Nss	U	O	ST	M			
Grasso, M. G., et al. (2005)																				
	Exp	X	X	X	X	X			X					X		X		- Individualized, inpatient, goal-oriented, MD program. - Program based on practical ADL skills. Physical rehabilitation program (PRP) with Pt and Ot. – Evaluation for possible specific treatment by U, ophthalmologist, otolaryngologist, and pneumologist - Treatment was possible by a therapist specialized in cognitive, speech, bladder management, swallowing, ocular movement and respiratory rehabilitation treatment.	The length of rehabilitation varied according to the clinical conditions of the patients, patients who needed multiple treatments being hospitalized for a longer period.	The Pt program consisted in twice-daily 45-min sessions for 6 days/week, and lasted for about 10 weeks. The frequency of the other sessions was 3x/week for 8 weeks.
Grasso, M. G., et al. (2009)																				
	Exp	X		X	X	X												- An individualized, goal-oriented, MD inpatient program. - Program based essentially on practical ADL skills. - PRP with Pt and Ot - Evaluation by a U, otolaryngologist, ophtalmologist and pneumologist, who assessed the need for specific treatment.	10-week during program.	The PRP consisted in twice-daily 45-min sessions, 6x/week.
Grasso, M. G., et al. (2017)																				
	Exp	X		X	X	X												- An individualized, goal-oriented, MD inpatient program - Based on practical ADL skills with standard Pt. - Intensive computer-assisted cognitive rehabilitation.	All the patients were inserted in a MD rehabilitation approach program according to their clinical needs and to a published protocol.	Cognitive rehabilitation: - 3x/week for 3 months Standard rehabilitation: - 3h/day for 5days/week - Incl. 2 daily Pt sessions Additional individualized rehabilitation as needed.
	Con				X													- An individualized, goal-oriented, MD inpatient program. - Program is based above all on practical ADL with standard Pt.	To have the same amount of therapy, they received additional Ot sessions.	Ot sessions: 3x/week for 3 months.

Table 5: *Data-extraction - therapy parameters*

Study		Type of training				MD team												What?	Organisation program	Amount of therapy
		Group-based training	Individualized training	Goal-oriented training	Education	OT	PT	SW	D	P	NP	NT	N	Nss	U	O	ST	M			
Hanssen, K. T., et al. (2016)	Exp	X	X	X	X	X	X				X								- Cognitive rehabilitation. - Neuropsychological assessment with subsequent feedback and took part in general MS MDR. - Cognitive group sessions as well as individual sessions. - Main focus: formulate Goal Attainment Scaling goals for coping with cognitive challenges. - For 3 months past rehabilitation: biweekly telephone follow-up, focusing on goal attainment.	Week 1: Cognitive group sessions (3-6 patients) aiming to increase their awareness of their cognitive strengths, problems, and coping strategies, conducted by the study NP and the study OT. The sessions included lectures, practical exercises and discussions. Week 2 and 3: Individual sessions, 1 with OT, 1 with NP. First 3 months after discharge: 6 biweekly telephone sessions focusing on attainment of the individual GAS goals.	NP assessment with feedback: 4 h Individual sessions: 5 h Cognitive group sessions: 6 h One lecture about MS 6 telephone calls of 10 min each.
	Con																		- Standard inpatient rehabiliation program. - Neuropsychological assessment with subsequent feedback and took part in general MS MDR.	Treatment was given for 4 weeks.	?
Jongen, P. J., et al. (2014)	Exp	X	X		X	X	X												- An intense MD social cognitive wellness program. - With the participation of support partners, after 1, 3 and 6 months.	Components of the Social Cognitive Can Do Program (SCDP) are 1) large group sessions, 2) small group sessions, 3) consultations (carrousel), 4) a theatre evening, and 5) start of the day with a joint activity (optionally).	The SCDP was given during a 3-day intensive program.

Table 5: *Data-extraction - therapy parameters*

Study	Type of training				MD team												What?	Organisation program	Amount of therapy
	Group-based training	Individualized training	Goal-oriented training	Education	OT	PT	SW	D	P	NP	NT	N	Nss	U	O	ST	M			
Jonsson, A., et al. (1996)																				
Exp		X			X	X			X	X		X						- Standard MDR treatment. - Medical care, Pt, Ot, neuropsychological/psychological treatment, etc.	Treatment was given at the hospital for 5-8 weeks. Half of the patients were referred to psychological treatment, either to neuropsychological treatment or to psychotherapy only.	?
Khan, F., et al. (2008)																				
Exp	X	X	X	X	X	X	X							X		X		- A MDR program including individual, achievable, functional goal oriented MDR with active involvement of the family. - The treating therapy team assessed each patient to benefit from either an inpatient (IP) or outpatient (OP) program. - Intensive treatment beyond symptomatic management of MS, aimed to educate patients, and improve activity and participation. - Wide range of interventions offered (education, health promotion, bladder retraining and mobilisation). - Subsequently they were involved in maintenance programs (stretching, home exercises) similar to those undertaken by the control group.	MD rehabilitation over a 12 month period. - IP rehabilitation program: Pt and Ot daily. Additionally other sessions with ST, NP and SW - OP program: lower intensity of therapy. Therapy sessions with PT, OT, SW and ST	IP program: - 5-day program, 3 h of therapy/day - Pt and Ot: 2 blocks of 45-min sessions - Other sessions: half hour sessions 3x/week or more (as required) for between 3-6 weeks OP program: - 30-min blocks of therapy sessions with PT, OT, SW and ST, 2-3x/week as needed for up to 6 weeks
Con																		- Wait-list control group. - Received an 8 weekly monitoring phone call for information about medical and hospital visits in previous month.	Maintenance programs (stretching, home exercises).	/

Table 5: *Data-extraction - therapy parameters*

Study		Type of training				MD team												What?	Organisation program	Amount of therapy
		Group-based training	Individualized training	Goal-oriented training	Education	OT	PT	SW	D	P	NP	NT	N	Nss	U	O	ST	M		
Miller, D. M., et al. (2011)	Exp																		- Standard care + new MCCO components. - Access to the secure asynchronous electronic messaging component of the system and can generate messages (= standard care). - Secure electronic messaging plus new MCCO components.	They received quarterly automated notifications to complete a scheduled self-monitoring.	In 12 months total of 395 unique notifications were sent to the 102 patients.
	Con																		- Standard care: Access to the secure asynchronous electronic messaging component of the system and can generate messages (= standard care).	/	/
Nedeljkovic, U., et al. (2016)	Exp		X		X	X	X	X		X			X		X			X	- High-dose methylprednisolone (HDMP) - MDR program is individually tailored by the treating therapy team.	5 days during steroid therapy, 3-week period MDR program.	3 weeks of Pt and Ot. Pt: 1 h, 5x/week Ot: 30 min, 3x/week
	Con																	X	- Only HDMP	5 days during steroid therapy.	/
Ng, A., et al. (2013)	Exp	X	X	X	X	X	X		X	X			X	X	X		X		- A 4-day MD educational wellness program - Components: - Group-based individual assessments - Group workshops - Group lectures - Group optional activities - Individual consultations - Individual optional consultations	Participants navigated the program in groups of 4-5, but specific content was indivudalized. Each participant group was staffed by 2-3 physical therapists, exercise physiologists, or OT with at least one physical therapist. An integral part of these programs was a complementary program for participants' support persons.	4 days intensive inpatient program.

Table 5: *Data-extraction - therapy parameters*

Study	Type of training				MD team												What?	Organisation program	Amount of therapy
	Group-based training	Individualized training	Goal-oriented training	Education	OT	PT	SW	D	P	NP	NT	N	Nss	U	O	ST	M			
Onat, S. S., et al. (2015)																				
	Exp		X			X	X								X	X		X	-The basic approach in MS rehabilitation, including functional training, development of compensatory behaviors, healing of current neurological impairments symptomatically, selection of assistive devices, environmental arrangements, and counseling of the patient and his/her family.	Methods used in rehabilitation of MS patients: orthosis, assistive devices, spasticity treatment, pain treatment, urination, medical treatment arranged for bladder, additional rehabilitation applications	?
Papeix, C., et al. (2015)																				
	Exp		X	X	X	X	X	X		X	X		X	X	X				-An integrated MD group (IMD). - Individually tailored assessment. - The schedule allowed each required medical specialist or allied health professional to assess the patient's status and needs.	Evaluation during the inclusion visit and re-evaluation during the MD visit. At the end of the visit, a summary of the MD evaluation, along with the resulting therapeutic propositions, was discussed with the patient and caregivers.	Max. 3-month period after inclusion. 4-6 h individually tailored assessment by the MD group.
	Con																		- Successive, non-integrated interventions with different specialists and allied health professionals, at different times and sites.	/	/

Table 5: *Data-extraction - therapy parameters*

Study	Type of training				MD team												What?	Organisation program	Amount of therapy
	Group-based training	Individualized training	Goal-oriented training	Education	OT	PT	SW	D	P	NP	NT	N	Nss	U	O	ST	M			
Pozzilli, C., et al. (2002)																			
	Exp	X		X	X	X	X		X			X	X	X			X	- MD home based care in MS . - The MD team could be easily reached for a telephone intervention or direct face to face intervention when required. - The type of care was more than is normally available in the community. It consisted of observation, administration of intravenous drugs, nursing care, rehabilitation of the patients in their home, patient and caregiver education, psychological support, and the services of the social secretariat.	Patients were followed through home visits and telephone follow up. A dedicated phone number was available five days a week from 9 am to 5 pm. - Inpatient care includes ordinary, rehabilitation, and day hospital - Outpatient medical care includes outpatients, home care, and telephone service provided by N, U, and rehabilitation physician. - Outpatient non-medical care includes outpatients, home care, and telephone service provided by P, SW, PT, and nurses.	- Inpatient care: 0.34 events/patient - Outpatient and home care: - Medical: 4.49 events/patient - Non-medical: 6.00 events/patient - Home care programme
	Con	X		X	X	X	X		X			X	X	X			X	- Hospital care in MS. - A brief monitoring phone call once a month was used to obtain information about the patient's medical visits and hospital admissions in the previous month.	Patients were followed as usual in their MS referral centres.	- Inpatient care: 1.01 events/patient - Outpatient and home care: - Medical: 2.59 events/patient - Non-medical: 0.50 events/patient

Table 5: *Data-extraction - therapy parameters*

Study	Type of training				MD team												What?	Organisation program	Amount of therapy
		Group-based training	Individualized training	Goal-oriented training	Education	OT	PT	SW	D	P	NP	NT	N	Nss	U	O	ST	M			
Rietberg, M. B., et al. (2014)	Exp	X	X			X	X	X											- Individually tailored, MDR. - Program that focused on optimising self management behaviour in daily life activities on the domains of physical fitness, behaviours or cognitions that perpetuate fatigue, and energy conservation. - Participants received Pt, Ot, Sw, or any combination of these treatments. - Homework assignments.	Pt number of treatment sessions was predefined, for other intervention types the number of sessions was on an as-needed basis, with a min. of 2 sessions.	Pt: 12-week training program, 2 45-minute sessions a week.
	Con		X											X					- MS-nurse consultation. - Consultation according to the Nursing Intervention Classification. - Homework assignments.	Goals were set in the first sessions. Patients were subsequently evaluated in follow-up consultations every 3 weeks.	One-hour sessions every three weeks.
Salem, Y., et al. (2011)	Exp	X				X	X												- community-based aquatic exercise program. - Aquatic exercises included aerobic exercises, strength training, flexibility exercises, balance training and walking activities.	5-week during program.	Aquatic exercises 2x/week, 60-min. sessions.
Sitzia, J., et al. (1998)	Exp(MS)		X			X	X	X	X				X				X		- An individually adapted, MDR program	- Patients returned home so that patients and carers could evaluate the benefits of any changes.	5-10 days intervention.

Table 5: *Data-extraction - therapy parameters*

Study	Type of training				MD team												What?	Organisation program	Amount of therapy
	Group-based training	Individualized training	Goal-oriented training	Education	OT	PT	SW	D	P	NP	NT	N	Nss	U	O	ST	M			
Storr, L. K., et al. (2006)																			
	Exp	X			X	X	X		X			X	X					- A MD inpatient rehabilitation	- Composition of the treatment caried in accordance with the patient's needs. - Individual Pt sessions	An average of 35,5 days (3-5 weeks inpatient). Pt: 45-min sessions, 4-5x/week Ot: 30-min sessions, 3x/week Training in the gym: 30-60min/day Time spent with other team members: unknown
	Con																	- No treatment related to the study	/	/

Note: MD: multidisciplinary; MDR: multidisciplinary rehabilitation; OT: occupational therapist; PT: physical therapist; SW: social worker; D: dietician; P: psychologist; NP: neuropsychologist; NT: nutritional therapist; N: neurologist; Nss: nurses; Ns A: nursing assistants; U: urologist; O: orthopedist; ST: speech therapist; M: medication; Ot: occupation therapy; Pt: physical therapy; Sw: social work; /: item not applicable; ?: information unknown; X: note is applicable

Table 6a: *Overview of included general MDR studies related to objectives*

		Impact of MS on ADL	QoL	General health state	Disability	Functional independency	Mobility skills	Anxiety	Depression	Anger	Fatigue	Upper limb function	Lung function	Mental state	Resilience
All general MDR programs	**Boesen (2018)**	X	X	X											
	Freeman (1997)				X	X									
	Freeman (1999)			X	X	X									
	Grasso (2005)				X	X	X								
	Grasso (2009)					X	X								
	Jonsson (1996)								X						
	Sitzia (1998)		X												
	Storr (2006)	X	X		X		X					X			
	Inpatient MDR	2	3	2	4	4	3	0	1	0	0	1	0	0	0
	Falk-Kessler (2012)														X
	Khan (2008)	X		X		X									
	In- + outpatient MDR	1	0	1	0	1	0	0	0	0	0	0	0	0	1
	Papeix (2015)		X					X	X		X				
	Rietberg (2014)	X				X					X				
	Pozilli (2002)			X	X	X		X		X			X	X	
	Outpatient MDR	1	1	1	1	2	0	2	1	1	2	0	1	1	0
	All MDR programs	4	4	4	5	7	3	2	2	1	2	1	1	1	1

Note: X: item is applicable; ADL: activities of daily life; QoL: quality of life

Table 6b: *Overview of different specially designed MDR studies related to objectives*

		Impact of MS on ADL	QoL	General health state	Disability	Functional independency	Mobility skills	Anxiety	Depression	Fatigue	Self-efficacy	Neuro-psychological state	Motor function	Physical activity	Satisfaction with medical care	Balance	Muscle strength
Specially designed training programs	**Craig (2003)**			X	X	X							X	X			
	Ennis (2006)			X													
	Grasso (2017)			X					X			X					
	Hanssen (2016)	X			X							X					
	Jongen (2014)	X	X					X	X	X	X						
	Miller (2011)	X		X	X						X				X		
	Nedeljkovic (2016)		X		X	X			X								
	Ng (2013)				X	X	X				X			X			
	Salem (2011)						X			X						X	X
		3	2	4	5	3	2	1	3	2	3	2	1	2	1	1	1

Note: X: item is applicable; ADL: activities of daily life; QoL: quality of life

Table 7: *Data-extraction - outcome parameters*

Study	Clinical measures	Experimental treatment 1											Control group										p be-tween groups
		Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	
Boesen, F., et al. (2018)	**FAMS** (0-176) mean (95% CI)	115.9 (111.0, 120.8)	126 (10.0, 15.2)	/	/	/	/	+ 0.6 (-2.1, 3.5)	/	/	/	/	115.1 (110.0, 120.4)	/	/	/	/	/	- 1.0 (-3.5, 1.6)	/	/	/	/	0.232
	MSIS-29																						
	- Physical (0-100) mean (95% CI)	40.8 (37.0, 44.6)	/	- 12.0 (-14.1, -10.2)	/	/	/	- 0.2 (-3.0, 2.3)	/	/	/	/	41.0 (37.1, 45.1)	/	/	/	/	/	+ 0.2 (-2.1, 2.8)	/	/	/	/	0.640
	- Psychological (0-100) mean (95% CI)	31.8 (27.9, 35.2)	/	- 9.7 (-11.6, -7.9)	/	/	/	- 1.2 (-3.8, 1.2)	/	/	/	/	29.8 (25.7, 33.3)	/	/	/	/	/	+ 1.5 (-0.7, 3.6)	/	/	/	/	0.046
	15D Index (0.106-1.00) mean (95% CI)	0.77 (0.75, 0.79)	/	/	/	/	/	+ 0.01 (-0.01, 0.03)	/	/	/	/	0.78 (0.76, 0.79)	/	/	/	/	/	- 0.01 (-0.02, 0.01)	/	/	/	/	0.008
	EQ-5D-5L Index (-0.624-1.000) mean (95% CI)	0.64 (0.61, 0.67)	/	/	/	/	/	- 0.03 (-0.07, 0.001)	/	/	/	/	0.64 (0.60, 0.67)	/	/	/	/	/	- 0.04 (-0.08, 0.002)	/	/	/	/	0.596
	EQ-VAS (0-100) mean (95% CI)	60.4 (56.7, 64.1)	/	+ 9.7 (7.1, 12.4)	/	/	/	+ 3.8 (-0.1, 7.1)	/	/	/	/	62.9 (58.9, 66.6)	/	/	/	/	/	+ 1.2 (-2.5, 4.8)	/	/	/	/	0.112

Table 7: *Data-extraction - outcome parameters*

Study	Clinical measures	Experimental treatment 1										Control group										p be-tween groups
		Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	
Craig, J., et al. (2003)	**GNDS** (0-60) mean (SD)	21.1 (7.1)	/	/	/	/	14.1 (6.9)	/	0.998	0.030	13.1 (8.9)	/	21.5 (7.2)	/	/	/	/	18.5 (8.2)	/	0.39	/	19.7 (10.6)	/	/
	AMCA (0-76) mean (SD)	56.1 (15.4)	/	/	/	/	67.5 (10.3)	/	0.18	0.035	69.1 (6.9)	/	48.0 (13.8)	/	/	/	/	57.6 (12.7)	/	0.72	/	54.3 (18.0)	/	/
	HAPM (0-94) mean (SD)	54.4 (20.2)	/	/	/	/	67.9 (13.4)	/	0.14	0.004	69.9 (14.2)	/	58.3 (16.2)	/	/	/	/	61.6 (17.8)	/	0.19	/	54.5 (25.1)	/	/
	HAPA (0-94) mean (SD)	35.1 (19.0)	/	/	/	/	48.1 (20.2)	/	0.25	0.019	53.2 (20.7)	/	33.2 (15.4)	/	/	/	/	40.6 (20.6)	/	0.41	/	36.7 (23.7)	/	/
	BI (0-20) mean (SD)	14.8 (2.7)	/	/	/	/	17.2 (2.3)	/	0.09	0.018	17.4 (2.3)	/	14.7 (2.2)	/	/	/	/	15.8 (2.6)	/	0.46	/	15.1 (4.1)	/	/
	SF-36 (0-100) mean (SD)																							
	- PF	23.5 (19.2)	/	/	/	/	38.7 (24.4)	/	0.25	0.122	45.5 (29.1)	/	23.7 (17.2)	/	/	/	/	36.7 (29.9)	/	0.53	/	33.0 (29.2)	/	/
	- SF	34.3 (26.0)	/	/	/	/	63.8 (21.8)	/	0.19	0.051	68.4 (25.6)	/	34.8 (21.2)	/	/	/	/	62.2 (27.0)	/	1.13	/	50.1 (33.5)	/	/
	- RP	5.0 (13.1)	/	/	/	/	38.7 (45.6)	/	0.25	0.243	35.0 (38.4)	/	11.2 (28.6)	/	/	/	/	20.0 (33.1)	/	0.28	/	27.5 (42.1)	/	/
	- RE	33.3 (45.9)	/	/	/	/	66.6 (44.6)	/	0.00	0.250	66.6 (44.6)	/	45.0 (47.5)	/	/	/	/	65.0 (41.2)	/	0.45	/	55.0 (48.7)	/	/
	- MH	56.2 (16.3)	/	/	/	/	70.8 (21.2)	/	0.25	0.155	75.6 (17.6)	/	58.6 (20.6)	/	/	/	/	69.2 (18.4)	/	0.54	/	64.3 (25.0)	/	/
	- E	29.2 (17.0)	/	/	/	/	51.4 (20.9)	/	0.15	0.217	48.2 (22.4)	/	25.0 (19.9)	/	/	/	/	41.7 (20.5)	/	0.83	/	34.0 (24.7)	/	/
	- P	67.1 (25.6)	/	/	/	/	85.1 (15.4)	/	0.32	0.494	78.4 (24.9)	/	43.3 (25.4)	/	/	/	/	64.3 (25.1)	/	0.83	/	50.5 (27.5)	/	/
	- GH	43.8 (21.9)	/	/	/	/	55.6 (25.3)	/	0.11	0.159	52.8 (24.3)	/	45.6 (23.5)	/	/	/	/	51.2 (23.9)	/	0.24	/	44.2 (29.8)	/	/

Table 7: *Data-extraction - outcome parameters*

Study	Clinical measures	Experimental treatment 1											Control group										p be-tween groups
		Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	
Ennis, M., et al. (2006)	**HPLP** mean (SD)	117.8 (13.2)	139.8 (18.4)	/	1.36	/	/	/	/	/	/	/	116.6 (21.3)	121.8 (23.7)	/	0.23	/	/	/	/	/	/	/	< 0.01
	SRAHP mean (SD)	71.1 (16.5)	86.2 (18.5)	/	0.85	/	/	/	/	/	/	/	66.8 (22.9)	70 (21.3)	/	0.14	/	/	/	/	/	/	/	< 0.01
	SF-36 mean (SD)																							
	- PF	28.6 (23.8)	36.6 (25.2)	/	0.32	/	/	/	/	/	/	/	31.2 (25.5)	34 (26.4)	/	0.11	/	/	/	/	/	/	/	0.03
	- SF	57.8 (22.7)	67.8 (22)	/	0.44	/	/	/	/	/	/	/	53.3 (25)	54.1 (19.8)	/	0.04	/	/	/	/	/	/	/	0.16
	- RP	26.6 (38.1)	50 (56.3)	/	0.48	/	/	/	/	/	/	/	20.8 (36.6)	17.5 (25.5)	/	0.10	/	/	/	/	/	/	/	0.06
	- RE	63.5 (64.6)	78.5 (56.1)	/	0.24	/	/	/	/	/	/	/	60 (45)	68.9 (40.1)	/	0.21	/	/	/	/	/	/	/	0.47
	- MH	66.1 (17.8)	71.7 (17)	/	0.32	/	/	/	/	/	/	/	65.7 (19.5)	57.1 (16.3)	/	0.47	/	/	/	/	/	/	/	< 0.01
	- E	35.7 (19.4)	42.9 (21.6)	/	0.35	/	/	/	/	/	/	/	34.1 (19.7)	36.4 (19.2)	/	0.12	/	/	/	/	/	/	/	0.22
	- P	63 (28.6)	67.4 (26.1)	/	0.16	/	/	/	/	/	/	/	55.9 (28.5)	54.7 (30.1)	/	0.04	/	/	/	/	/	/	/	0.56
	- GH	44 (20.7)	54.1 (23.6)	/	0.45	/	/	/	/	/	/	/	46.9 (20.9)	45.8 (20.5)	/	0.05	/	/	/	/	/	/	/	< 0.01
Falk-Kessler, J., et al. (2012)	**RS** mean (SD)	123 (32.4)	146.9 (24.9)	/	0.81	< 0.001	/	/	/	/	/	/	126.2 (15.0)	118.6 (23.7)	/	0.37	< 0.05	/	/	/	/	/	/	< 0.01

Table 7: *Data-extraction - outcome parameters*

Study	Clinical measures	Experimental treatment 1											Control group										p be-tween groups
		Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	
Freeman, J. A., et al. (1999)	**EDSS** (0-10) median (range)	6.8 (6.0-9.0)	6.8 (5-9)	/	/	/	7.0 (6-9.5)	/	/	/	8.0 (5-9.5)	/	/	/	/	/	/	/	/	/	/	/	/
	FIM motor domain (13-91) median (range)	61.5 (13-87)	74 (13-90)	/	/	/	67.5 (13-88)	/	/	/	63.5 (13-90)	/	/	/	/	/	/	/	/	/	/	/	/
	LHS total score (0-100) mean (SD)	60.3 (13.1)	64.4 (11.8)	/	0.13	/	63.4 (13.1)	/	/	/	61.6 (13.7)	/	/	/	/	/	/	/	/	/	/	/	/
	SF-36 (0-100) mean (SD)																						
	- PCS	27.8 (6.9)	46.1 (7.9)	/	2.27	/	46.6 (7.9)	/	/	/	28.4 (8.0)	/	/	/	/	/	/	/	/	/	/	/	/
	- MCS	39.2 (9.6)	43.4 (14.6)	/	0.80	/	55.7 (13.5)	/	/	/	45.0 (12.9)	/	/	/	/	/	/	/	/	/	/	/	/
	GHQ (0-28) median (range)	9.5 (0-28)	1.5 (0-24)	/	/	/	5 (0-25)	/	/	/	4 (0-28)	/	/	/	/	/	/	/	/	/	/	/	/
Freeman, J. A., et al. (1997)	**FIM** motor domain (13-91) median (range)	67 (13-87)	/	+ 4.0 (-10-19)	/	/	/	/	/	/	/	/	69.5 (18-84)	/	- 2.5 (-16-5)	/	/	/	/	/	/	/	0.001
	LHS total score (0-100) mean (SD)	61.5 (13.0)	/	+ 2.9 (8.9)	/	/	/	/	/	/	/	/	66.2 (8.74)	/	- 2.7 (8.6)	/	/	/	/	/	/	/	0.01
Grasso, M. G., et al. (2005)	**EDSS** (0-10) mean (SD)	6.93 (1.44)	6.83 (1.45)	/	0.07	n.s.	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	BI (0-20) mean (SD)	54.06 (30.6)	58.91 (31.1)	/	0.16	< 0.002	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	RMI mean (SD)	4.83 (4.41)	5.49 (4.49)	/	0.15	< 0.002	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Grasso, M. G., et al. (2009)	**BI** mean (SD)	58.40 (27.30)	/	- 8.31 *	/	< 0.001	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	RMI mean (SD)	5.20 (4.24)	/	- 7.43 *	/	< 0.001	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/

Table 7: *Data-extraction - outcome parameters*

Study	Clinical measures	Experimental treatment 1											Control group									p be-tween groups
		Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	
Grasso, M. G., et al. (2017)	**EDSS** (0-10) mean (SD)	7.54 (0.8)	7.36 (0.8)	/	0.22	/	/	/	/	/	/	/	7.5 (0.8)	7.38 (0.8)	/	0.15	/	/	/	/	/	/	/	/
	BI (0-20) mean (SD)	39 (20.8)	39 (20.8)	/	0.00	/	/	/	/	/	/	/	41.33 (16.6)	44.22 (19.6)	/	0.16	/	/	/	/	/	/	/	/
	RMI mean (SD)	2.36 (1.3)	2.73 (1.5)	/	0.26	0.026	/	/	/	/	/	/	2.78 (2.5)	3.22 (2.4)	/	0.18	0.026	/	/	/	/	/	/	/
	MADRS mean (SD)	20 (9.1)	16.73 (6.8)	/	0.40	0.000	/	/	/	/	/	/	21.33 (10.1)	20.44 (10)	/	0.07	0.005	/	/	/	/	/	/	/
	SF-36 mean (SD)																							
	- P	/	/	/	/	0.005	/	/	/	/	/	/	/	/	/	/	n.s.	/	/	/	/	/	/	/	/
	- GH	/	/	/	/	0.012	/	/	/	/	/	/	/	/	/	/	n.s.	/	/	/	/	/	/	/	/
	- E	/	/	/	/	0.006	/	/	/	/	/	/	/	/	/	/	n.s.	/	/	/	/	/	/	/	/
	- SF	/	/	/	/	0.010	/	/	/	/	/	/	/	/	/	/	n.s.	/	/	/	/	/	/	/	/
	- PCS	/	/	/	/	0.002	/	/	/	/	/	/	/	/	/	/	<0.05	/	/	/	/	/	/	/	/
	- MCS	/	/	/	/	0.013	/	/	/	/	/	/	/	/	/	/	n.s.	/	/	/	/	/	/	/	/
	Neuropsychological test battery mean (SD)																							
	- SRT-LTS	29 (8.1)	31.9 (6.3)	/	0.40	/	34.1 (6.7)	/	/	/	/	/	30.5 (7.3)	28.9 (7.1)	/	0.22	/	33.7 (7.4)	/	/	/	/	/	/	/
	- SRT-D	3 (5.4)	4.2 (3.7)	/	0.25	/	4.1 (4.1)	/	/	/	/	/	3.3 (4.3)	1.8 (2.7)	/	0.42	/	3.1 (1.7)	/	/	/	/	/	/	/
	- SPART	12.9 (7.1)	13.8 (6.9)	/	0.13	/	13.7 (6.7)	/	/	/	/	/	14.1 (4.3)	14.6 (5.9)	/	0.10	/	14.7 (7.1)	/	/	/	/	/	/	/
	- SPART-D	6.2 (3.1)	6.1 (3.7)	/	0.03	/	6.1 (5.1)	/	/	/	/	/	5.9 (4.1)	5.8 (3.3)	/	0.03	/	6 (4.8)	/	/	/	/	/	/	/
	- SDMT	18.2 (7.1)	18.1 (4.9)	/	0.02	/	18.3 (6.7)	/	/	/	/	/	17.9 (4.8)	18.5 (4.5)	/	0.13	/	19.1 (7.3)	/	/	/	/	/	/	/
	- PASAT 3	17.4 (6.1)	17.9 (7.9)	/	0.03	/	18.5 (9.7)	/	/	/	/	/	16.9 (6.4)	17.1 (9.1)	/	0.03	/	17.9 (8.1)	/	/	/	/	/	/	/
	- PASAT 2	15.9 (6.3)	16.1 (9.1)	/	0.02	/	16.9 (5.6)	/	/	/	/	/	16.2 (5.7)	17.1 (9.1)	/	0.12	/	17.7 (7.3)	/	/	/	/	/	/	/
	- WLG	10 (7.1)	11.4 (6.1)	/	0.21	/	12.5 (8.9)	/	/	/	/	/	13.1 (7.7)	12.4 (6.8)	/	0.10	/	14.1 (9.1)	/	/	/	/	/	/	/
	- ST	27.1 (8.4)	30.4 (6.3)	/	0.43	/	31.5 (7.1)	/	/	/	/	/	28.3 (7.1)	27.1 (9.3)	/	0.14	/	30.5 (13.4)	/	/	/	/	/	/	/

Table 7: *Data-extraction - outcome parameters*

Study	Clinical measures	Experimental treatment 1											Control group										p be-tween groups
		Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	
Hanssen, K. T., et al. (2016)	**GEC (BRIEF-A)** T-score (SD)	61.1 (11.0)	/	/	/	/	56.4 (11.7)	/	/	< 0.01	56.3 (11.8)	/	60.0 (10.6)	/	/	/	/	56.7 (11.7)	/	/	< 0.01	55.2 (11.5)	/	/
	MI (BRIEF-A) T-score (SD)	62.7 (11.3)	/	/	/	/	58.2 (11.8)	/	/	< 0.01	57.7 (11.9)	/	61.0 (10.5)	/	/	/	/	57.8 (10.7)	/	/	< 0.01	56.7 (10.9)	/	/
	MSIS-29 Psychological scale (SD)	21.3 (7.0)	/	/	/	/	18.3 (6.9)	/	/	< 0.01	18.3 (7.2)	/	20.9 (6.6)	/	/	/	/	19.9 (7.7)	/	/	n.s.	20.6 (8.0)	/	/
	HSCL-25 total score (SD)	1.76 (0.53)	/	/	/	/	1.60 (0.49)	/	/	< 0.01	1.62 (0.47)	/	1.75 (0.42)	/	/	/	/	1.74 (0.50)	/	/	n.s.	1.65 (0.53)	/	/
Jongen, P. J., et al. (2014)	**MSSES**-Function mean (SD)	81.80 (12.15)	81.70 (12.52)	/	0.06	> 0.05	74.75 (19.33)	/	/	/	81.30 (12.00)	/	53.59 (19.62)	54.09 (19.31)	/	0.03	> 0.05	54.23 (20.28)	/	/	/	50.94 (18.07)	/	/
	MSSES-Control mean (SD)	57.01 (19.67)	58.04 (15.01)	/	0.06	< 0.01	53.52 (18.28)	/	/	/	64.26 (13.66)	/	41.63 (15.29)	43.84 (16.24)	/	0.14	> 0.05	45.50 (20.77)	/	/	/	46.18 (19.44)	/	/
	IPA-Limitations mean (SD)	2.43 (0.57)	2.34 (0.53)	/	0.16	> 0.05	2.26 (0.51)	/	/	/	2.30 (0.55)	/	2.89 (0.50)	2.76 (0.65)	/	0.22	> 0.05	2.85 (0.56)	/	/	/	2.88 (0.64)	/	/
	IPA-Problems mean (SD)	1.95 (0.36)	1.73 (0.39)	/	0.57	> 0.05	1.74 (0.48)	/	/	/	1.86 (0.52)	/	2.17 (0.32)	2.11 (0.43)	/	0.16	> 0.05	2.07 (0.54)	/	/	/	2.14 (0.48)	/	/
	MSQoL-54 physical mean (SD)	46.3 (13.1)	53.7 (14.6)	/	0.52	< 0.05	52.2 (16.7)	/	/	/	57.1 (15.2)	/	42.6 (11.6)	41.9 (14.2)	/	0.05	> 0.05	41.6 (16.9)	/	/	/	40.9 (11.6)	/	/
	MSQoL-54 mental mean (SD)	52.8 (13.4)	60.5 (15.2)	/	0.53	< 0.05	59.8 (14.3)	/	/	/	60.6 (13.3)	/	54.1 (13.8)	58.8 (13.7)	/	0.34	> 0.05	57.5 (14.3)	/	/	/	53.6 (16.1)	/	/
	HAD-A mean (SD)	7.67 (3.65)	5.39 (3.31)	/	0.64	> 0.05	5.67 (3.69)	/	/	/	5.11 (2.19)	/	8.35 (3.45)	7.41 (3.62)	/	0.26	> 0.05	7.45 (3.63)	/	/	/	7.81 (4.39)	/	/
	HAD-D depression mean (SD)	6.38 (4.25)	4.67 (3.55)	/	0.43	> 0.05	5.11 (3.55)	/	/	/	4.72 (3.49)	/	6.61 (4.20)	6.55 (3.97)	/	0.02	> 0.05	6.18 (3.47)	/	/	/	7.14 (4.68)	/	/
	MFIS-5 mean (SD)	12.43 (3.65)	11.00 (3.31)	/	0.40	> 0.05	10.94 (3.59)	/	/	/	11.89 (3.55)	/	12.09 (4.08)	12.19 (3.53)	/	0.03	> 0.05	11.77 (3.95)	/	/	/	12.05 (3.50)	/	/
													(these values are the values for a second experimental group)										
Jonsson, A., et al. (1996)	**BDI** mean	11.0	7.14	/	/	0.001	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/

Table 7: *Data-extraction - outcome parameters*

Study	Clinical measures	Experimental treatment 1											Control group										p be-tween groups
		Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	
Khan, F., et al. (2008)	**FIM** motor domain mean (SD)	75.2 (12.66)	/	- 3.0 (4.2)	/	/	/	/	/	/	/	/	78.87 (13.04)	/	+ 1.8 (4.3)	/	/	/	/	/	/	/	/	< 0.001
	FIM cognitive domain mean (SD)	32.56 (2.68)	/	- 0.15 (1.5)	/	/	/	/	/	/	/	/	33.55 (2.21)	/	+ 0.4 (1.1)	/	/	/	/	/	/	/	/	0.04
	MSIS-29 physical scale mean (SD)	51.45 (17.21)	/	+ 0.1 (7.7)	/	/	/	/	/	/	/	/	46.46 (20.76)	/	- 1.1 (6.5)	/	/	/	/	/	/	/	/	0.43
	MSIS-29 psychological scale mean (SD)	19.92 (8.26)	/	- 1.1 (16.9)	/	/	/	/	/	/	/	/	17.54 (7.0)	/	+ 2.3 (12.7)	/	/	/	/	/	/	/	/	0.27
	GHQ-28 anxiety mean (SD)	6.46 (4.18)	/	+ 0.3 (4.8)	/	/	/	/	/	/	/	/	4.53 (3.24)	/	+ 0.2 (4.0)	/	/	/	/	/	/	/	/	0.95
	GHQ-28 depression mean (SD)	4.03 (4.57)	/	+ 0.1 (4.4)	/	/	/	/	/	/	/	/	2.6 (3.9)	/	+ 0.3 (3.1)	/	/	/	/	/	/	/	/	0.78
	GHQ-28 somatic mean (SD)	7.07 (3.57)	/	+ 1.2 (4.5)	/	/	/	/	/	/	/	/	6.38 (4.15)	/	- 0.1 (5.3)	/	/	/	/	/	/	/	/	0.23
	GHQ-28 social mean (SD)	8.69 (2.8)	/	+ 1.0 (3.8)	/	/	/	/	/	/	/	/	7.88 (2.41)	/	+ 0.3 (3.7)	/	/	/	/	/	/	/	/	0.37
Miller, D. M., et al. (2011)	**SIP** mean (SD)	20.4 (15.3)	21.7 (2.0)	/	0.12	/	/	/	/	/	/	/	21.7 (11.9)	22.4 (1.8)	/	0.08	/	/	/	/	/	/	/	0.77
	MSFC mean (SD)	-0.67 (2.0)	-0.80 (0.24)	/	0.09	/	/	/	/	/	/	/	-0.56 (1.7)	-0.63 (0.22)	/	0.06	/	/	/	/	/	/	/	0.51
	MSSE mean (SD)	64.5 (17.2)	64.5 (2.8)	/	0.00	/	/	/	/	/	/	/	59.7 (17.3)	62.5 (2.6)	/	0.23	/	/	/	/	/	/	/	0.50
	SGSPQ-GSMC mean (SD)	23.3 (4.5)	23.3 (0.72)	/	0.00	/	/	/	/	/	/	/	23.4 (4.1)	23.2 (0.67)	/	0.07	/	/	/	/	/	/	/	0.96
	SGSPQ-PPQ mean (SD)	32.8 (3.1)	33.2 (0.47)	/	0.18	/	/	/	/	/	/	/	32.9 (3.5)	33.7 (0.43)	/	0.32	/	/	/	/	/	/	/	0.30
	EQ-5D index score mean (SD)	0.75 (0.18)	0.757 (0.025)	/	0.05	/	/	/	/	/	/	/	0.75 (0.17)	0.756 (0.023)	/	0.05	/	/	/	/	/	/	/	0.96
	EQ-5D VAS mean (SD)	73.4 (15.7)	76.3 (2.6)	/	0.26	/	/	/	/	/	/	/	75.5 (18.7)	70.2 (2.4)	/	0.40	/	/	/	/	/	/	/	0.04

Table 7: *Data-extraction - outcome parameters*

Study	Clinical measures	Experimental treatment 1											Control group										p be-tween groups
		Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	
Nedeljkovic, U., et al. (2016)	**EDSS** mean (SD)	4.5 (1.4)	/	/	/	/	/	- 0.9 (1.3)	/	/	/	- 1.4 (1.4)	4.0 (0.9)	/	/	/	/	/	- 0.5 (0.6)	/	/	/	- 0.9 (0.8)	0.184
	BDI mean (SD)	12.2 (8.9)	/	/	/	/	/	- 3.8 (3.4)	/	/	/	- 3.5 (6.2)	14.0 (8.3)	/	/	/	/	/	- 2.0 (11.0)	/	/	/	- 2.7 (7.0)	0.725
	FIM motor score mean (SD)	73.1 (16.1)	/	/	/	/	/	+ 15.6 (16.0)	/	/	/	+ 15.4 (16.3)	77.5 (8.2)	/	/	/	/	/	+ 9.1 (6.4)	/	/	/	+ 10.3 (6.9)	0.217
	FIM cognitive score mean (SD)	34.6 (0.8)	/	/	/	/	/	0.0 (0.0)	/	/	/	0.0 (0.0)	33.7 (2.9)	/	/	/	/	/	+ 0.7 (2.4)	/	/	/	+ 0.8 (7.8)	0.657
	MSQoL-54 mean (SD)																						
	- overall QoL	51.8 (17.3)	/	/	/	/	59.6 (17.8)	/	0.43	< 0.01	63.3 (17.4)	/	50.0 (13.9)	/	/	/	/	54.0 (18.1)	/	0.24	> 0.05	52.7 (20.4)	/	/
	- physical health composite	47.7 (19.8)	/	/	/	/	58.4 (21.2)	/	0.56	< 0.01	63.7 (22.4)	/	46.9 (17.2)	/	/	/	/	54.9 (17.6)	/	0.45	< 0.05	55.0 (20.8)	/	/
	- mental health composite	52.9 (23.8)	/	/	/	/	65.4 (20.6)	/	0.54	< 0.01	69.1 (21.7)	/	54.8 (19.7)	/	/	/	/	61.3 (19.5)	/	0.32	> 0.05	58.7 (20.3)	/	/
Ng, A., et al. (2013) **	**SF-36**																						
	- PF	/	↑	/	/	<0.01	↑	/	/	0.04	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	- SF	/	=	/	/	n.s.	=	/	/	n.s.	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	- RP	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	- RE	/	=	/	/	n.s.	=	/	/	n.s.	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	- MH	/	↑	/	/	0.004	=	/	/	0.07	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	- E	/	↑	/	/	0.004	↑	/	/	0.08	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	- P	/	=	/	/	n.s.	=	/	/	n.s.	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	- GH	/	↑	/	/	0.03	↑	/	/	0.02	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	MSSE	/	↑	/	/	<0.01	↑	/	/	< 0.01	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	PASIPD	/	=	/	/	n.s.	=	/	/	n.s.	/	/	/	/	/	/	/	/	/	/	/	/	/	/

Table 7: *Data-extraction - outcome parameters*

Study	Clinical measures	Experimental treatment 1										Control group										p be-tween groups
		Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	
Papeix, C., et al. (2015)	**HAD-A** median (range)	8 (2, 19)	/	/	/	/	/	+ 1 (-9, 7)	/	/	/	- 1 (-11, 6)	10 (3, 8)	/	/	/	/	/	0 (-6, 4)	/	/	/	0 (-8, 6)	0.7
	HAD-D median (range)	8 (1, 17)	/	/	/	/	/	+ 1 (-10, 7)	/	/	/	0 (-6, 8)	9 (0, 14)	/	/	/	/	/	+ 1 (-5, 4)	/	/	/	- 0.5 (-4, 6)	0.5
	MFIS median (range)	54 (26, 82)	/	/	/	/	/	- 2 (-35, 29)	/	/	/	- 1 (-20, 20)	61 (33, 81)	/	/	/	/	/	- 7.5 (-32, 17)	/	/	/	- 2 (-36, 11)	0.4
	QUALIVEEN median (range)	1.04 (0.03, 3.04)	/	/	/	/	/	- 0.1 (-1.3, 1.3)	/	/	/	+ 0.03 (-1.8, 1.2)	0.9 (0.03, 2.95)	/	/	/	/	/	- 0.3 (-1.3, 0.6)	/	/	/	- 0.2 (-0.9, 0.7)	0.6
Pozzilli, C., et al. (2002)	**EDSS** mean (SD)	6.0 (2.0)	/	/	/	/	/	/	/	/	/	/	5.8 (2.2)	/	/	/	/	/	/	/	/	/	/	n.s.
	FIM mean (SD)	87.3 (27.7)	/	/	/	/	/	/	/	/	/	/	87.4 (28.6)	/	/	/	/	/	/	/	/	/	/	n.s.
	MMSE mean (SD)	27.8 (3.1)	/	/	/	/	/	/	/	/	/	/	27 (4.5)	/	/	/	/	/	/	/	/	/	/	n.s.
	STAXI	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	n.s.
	STAI	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	n.s.
	CDQ %	/	/	- 7.8	/	/	/	/	/	/	/	/	/	/	/	/	/	/	+ 0.7	/	/	/	/	n.s.
	SF-36 %																							
	- PF	/	/	/	/	/	/	> -5	/	/	/	/	/	/	/	/	/	/	< +5	/	/	/	/	0.55
	- SF	/	/	/	/	/	/	> +10	/	/	/	/	/	/	/	/	/	/	> +5	/	/	/	/	0.09
	- RP	/	/	/	/	/	/	> +30	/	/	/	/	/	/	/	/	/	/	< -5	/	/	/	/	0.0001
	- RE	/	/	/	/	/	/	> +30	/	/	/	/	/	/	/	/	/	/	0	/	/	/	/	0.0001
	- MH	/	/	/	/	/	/	> +10	/	/	/	/	/	/	/	/	/	/	> +5	/	/	/	/	0.41
	- E	/	/	/	/	/	/	> +5	/	/	/	/	/	/	/	/	/	/	< +5	/	/	/	/	0.001
	- P	/	/	/	/	/	/	> +5	/	/	/	/	/	/	/	/	/	/	> -5	/	/	/	/	0.0001
	- GH	/	/	/	/	/	/	> +5	/	/	/	/	/	/	/	/	/	/	> -5	/	/	/	/	0.19
	- PCS	/	/	/	/	/	/	< -5	/	/	/	/	/	/	/	/	/	/	< -5	/	/	/	/	0.0001
	- MCS	/	/	/	/	/	/	> +5	/	/	/	/	/	/	/	/	/	/	> +5	/	/	/	/	0.0001

Table 7: *Data-extraction - outcome parameters*

Study	Clinical measures	Experimental treatment 1											Control group										p be-tween groups
		Pre	Post	Δ pre - post	g'	p-value	Follow-up 1	Δ pre - follow-up 1	g'	p-value	Follow-up 2	Δ pre - follow-up 2	Pre	Post	Δ pre - post	g'	p-value	Follow-up 1	Δ pre - follow-up 1	g'	p-value	Follow-up 2	Δ pre - follow-up 2	
Rietberg, M. B., et al. (2014)	**CIS-2OR** (20-140) median (IQR)	78 (13.5)	/	/	/	/	76 (1.4)	/	/	/	81 (9.5)	/	79 (13)	/	/	/	/	79 (12)	/	/	/	80 (11)	/	0.14
	FSS (9-63) median (IQR)	52 (11.5)	/	/	/	/	49 (7.5)	/	/	/	51 (9.5)	/	48 (12)	/	/	/	/	50 (13)	/	/	/	47 (11)	/	0.27
	MFIS (0-84) median (IQR)	43 (18.75)	/	/	/	/	42 (24)	/	/	/	42 (11)	/	36 (14.5)	/	/	/	/	37 (20)	/	/	/	42 (21)	/	0.78
	FIM (18-126) median (IQR)	118.5 (6.75)	/	/	/	/	120 (7)	/	/	/	121 (6)	/	122 (11)	/	/	/	/	119 (9)	/	/	/	120 (11)	/	0.34
	MSIS-29 physical (0-100) median (IQR)	53 (20)	/	/	/	/	50 (22.5)	/	/	/	45 (19.5)	/	43 (19)	/	/	/	/	39 (28)	/	/	/	41 (21)	/	0.50
	MSIS-29 psychological (0-100) median (IQR)	18 (6.5)	/	/	/	/	16 (8.75)	/	/	/	18 (5)	/	17 (6)	/	/	/	/	18 (11)	/	/	/	18 (12)	/	0.99
Salem, Y., et al. (2011)	**Gait speed** (cm/sec) mean (SD)	33.06 (21)	40.27 (8)	/	0.43	0.049	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	TUG (sec) mean (SD)	44.21 (20.6)	36.71 (17)	/	0.38	0.001	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	BBS mean (SD)	24 (15)	27 (14)	/	0.20	0.008	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	Grip strength right (kg) mean (SD)	14.55 (11)	18.77 (9)	/	0.40	0.03	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	Grip strength left (kg) mean (SD)	16.34 (10)	19.96 (11)	/	0.33	0.02	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	MFIS mean (SD)	27.7 (4.1)	28.5 (5.5)	/	0.16	0.85	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/

Table 7: *Data-extraction - outcome parameters*

Study	Clinical measures	Experimental treatment 1										Control group										p be-tween groups
		Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	
Sitzia, J., et al. (1998)	**NHP-1** median																						
	- Energy	100.0	100.0	/	/	n.s.	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	- Pain	16.3	19.8	/	/	< 0.01	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	- Emotional reactions	34.2	23.7	/	/	< 0.01	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	- Sleep	28.7	12.6	/	/	n.s.	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	- Social isolation	22.5	22.5	/	/	n.s.	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	- Physical mobility	66.1	55.5	/	/	< 0.05	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	- Total score	268.7	219.5	/	/	< 0.01	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/

Table 7: *Data-extraction - outcome parameters*

Study	Clinical measures	Experimental treatment 1										Control group										p be-tween groups
		Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	Pre	Post	Δ pre - post	g'	p-value (pre-post)	Follow-up 1	Δ pre - follow-up 1	g'	p-value (pre - follow-up)	Follow-up 2	Δ pre - follow-up 2	
Storr, L. K., et al. (2006)	**MSIS** median (range)	56.0 (18-110)	/	+ 2.03 (11.9) ***	/	/	/	/	/	/	/	/	57.0 (5-151)	/	- 0.13 (10.6) ***	/	/	/	/	/	/	/	/	0.44
	EDSS median (range)	6.5 (3.5-8.0)	/	+ 0.04 (0.50) ***	/	/	/	/	/	/	/	/	6.5 (1.5-8.0)	/	- 0.13 (0.51) ***	/	/	/	/	/	/	/	/	0.13
	GNDS mean (SD)	19.4 (6.45)	/	+ 0.53 (4.46)	/	/	/	/	/	/	/	/	19.9 (8.04)	/	+ 0.94 (3.84)	/	/	/	/	/	/	/	/	0.64
	TW10 mean (SD)	18.3 (8.29)	/	- 0.86 (8.77)	/	/	/	/	/	/	/	/	16.8 (12.3)	/	+ 0.03 (6.86)	/	/	/	/	/	/	/	/	0.67
	9HPT mean (range)																							
	- right hand	32 (19-115)	/	+ 0.83 (5.85) ***	/	/	/	/	/	/	/	/	26 (14-98)	/	- 1.54 (6.46) ***	/	/	/	/	/	/	/	/	0.38
	- left hand	27 (16-187)	/	+ 1.48 (15.2) ***	/	/	/	/	/	/	/	/	28.5 (12-133)	/	+ 1.10 (6.32) ***	/	/	/	/	/	/	/	/	0.03
	LASQ mean (SD)	2.38 (2.02)	/	- 0.15 (1.02)	/	/	/	/	/	/	/	/	1.99 (2.13)	/	+ 0.04 (1.23)	/	/	/	/	/	/	/	/	0.43
	FAMS mean (SD)	110 (24.5)	/	+ 2.57 (16.0)	/	/	/	/	/	/	/	/	109 (27.1)	/	- 1.88 (12.9)	/	/	/	/	/	/	/	/	0.40

*Note: *: z-score, **: no values available, ***: mean (SD);*

=: no change; ↑: increased value; /: item not applicable; g': hedges' g effect size; Δ: change score; sec = seconds; cm = centimeters; IQR: interquartile range; FAMS: Functional Assessment in Multiple Sclerosis; MSIS-29: Multiple Sclerosis Impact Scale-29; 15D Index: 15-dimensional index; EQ-VAS: EuroQol-visual analogue scales; EQ-5D-5L: EuroQol 5 Dimensions 5 Levels; GNDS: Guy's Neurological Disability Scale; AMCA: Amended Motor Club Assessment; HAP: Human Activity Profile; SF-36: Short Form 36 Health Survey; PF: Physical Function; SF: Social Function; RP: Role Physical; RE: Role Emotional; MH: Mental Health; E: Energy; P: Pain; GH: General Health; PCS: physical composite summary; MCS: mental composite summary; BI: Revised Barthel Index; MS-RS: MS-Related Symptom Checklist; RIC-FAS: Rehabilitation Institute of Chicago functional assessment scale; HPLP: Health Promoting Lifestyle Profile; SRAHP: Self-Rated Abilities for Health Practices Scale; RS: Resilience Scale; EDSS: Expanded Disability Status Scale; FIM: Functional Independence Measure; LHS: London Handicap Scale; GHQ-28: General Health Questionnaire; RMI: Rivermead Mobility Index; MADRS: Montgomery Asberg Depression Rating Scale; SRT-LS: Selective Reminding Test-Long-Term Storage; SRT-D: Selective Reminding Test-Delayed; SPART: Spatial Recall Test; SPART-D: Spatial Recall Test-Delayed; SDMT: Symbol Digit Modalities Test; Pasat-3: Paced auditory serial addition-3 seconds; Pasat-2: Paced auditory serial addition-2 seconds; WLG: word list generation; ST: stroop test; BRIEF-A: Behabior Rating Inventory of Executive Function for adults; GEC: General Executive Composite; MI: Metacognition Index; HSCL-25: Hopkins Symptoms Checklist-25; MSSES: Multiple Sclerosis Self-Efficacy Scale; IPA: The Impact on Participation and Autonomy; MSQoL-54: Multiple Sclerosis Quality of Life 54-Item questionnaire; HADS: Hospital Anxiety and Depression Scale; MFIS-5: Modified Fatigue Impact Scale 5-Item Version; BDI: Beck Depression Inventory; MSFC: MS-Functional Composite; MS-FSE: The Multiple Sclerosis-Fatigue Self-Efficacy scale; SIP: Sickness Impact Profile; SGSPQ-GSMC: Seniors' General Satisfaction and Physician Quality of Care-General Satisfaction with Medical Care; SGSPQ-PPQ: Seniors' General Satisfaction and Physician Quality of Care-Perception of Physician Quality; PASIPD: Physical Activity Scale for Individuals with Physical Disabilities; MMSE: Mini mental state examination; CIS-20R: Checklist Individual Strength; FSS: Fatigue Severity Scale; DIP: Disability and Impact Profile; TUG: Timed 'Up and Go' test; BBS: Berg Balance Scale; NHP-1: Nottingham Health Profile; TW10: Timed 10-metre walk; 9HPT: Nine-Hole Peg test; LASQ: Life Appreciation and Satisfaction Questionnaire.

Appendix 1: Randomized Control Checklist

VALIDITEIT

1. Was de toewijzing van de interventie aan de patiënten gerandomiseerd?
   [ ] Ja
   [ ] Nee
   [ ] Te weinig informatie in het artikel om dit te beantwoorden

2. Degene die patiënten in het onderzoek insluit hoort niet op de hoogte te zijn van de randomisatievolgorde. Was dat hier het geval?
   [ ] Ja
   [ ] Nee
   [ ] Te weinig informatie in het artikel om dit te beantwoorden

3. Waren de patiënten geblindeerd voor de behandeling?
   [ ] Ja
   [ ] Nee
   [ ] Te weinig informatie in het artikel om dit te beantwoorden

4. Waren de behandelaars geblindeerd voor de behandeling?
   [ ] Ja
   [ ] Nee
   [ ] Te weinig informatie in het artikel om dit te beantwoorden

5. Waren de effectbeoordelaars geblindeerd voor de behandeling?
   [ ] Ja
   [ ] Nee
   [ ] Te weinig informatie in het artikel om dit te beantwoorden

6. Waren de groepen aan het begin van de trial vergelijkbaar?
   [ ] Ja
   [ ] Nee, maar in de analyses is hiervoor wel gecorrigeerd
   [ ] Nee, en in de analyses is hiervoor niet gecorrigeerd
   [ ] Te weinig informatie in het artikel om dit te beantwoorden

7. Is van een voldoende proportie van alle ingesloten patiënten een volledige follow-up beschikbaar?
   [ ] Ja
   [ ] Nee ⇐ Is selectieve loss-to-follow-up voldoende uitgesloten?
   [ ] Ja
   [ ] Nee
   [ ] Te weinig informatie in het artikel om dit te beantwoorden / loss-to-follow-up niet beschreven

8. Zijn alle ingesloten patiënten geanalyseerd in de groep waarin ze waren gerandomiseerd?
   [ ] Ja
   [ ] Nee
   [ ] Te weinig informatie in het artikel om dit te beantwoorden

9. Zijn de groepen, afgezien van de interventie, gelijk behandeld?
   [ ] Ja
   [ ] Nee
   [ ] Te weinig informatie in het artikel om dit te beantwoorden

TUSSENOORDEEL

10. Zijn de resultaten van het onderzoek valide en toepasbaar?
    [ ] Voldoende valide en toepasbaar ⇐ ga verder bij 11
    [ ] Twijfelachtig ⇐ ga verder bij 11
    [ ] Onvoldoende valide en toepasbaar U kunt stoppen met het invullen van de checklist, tenzij er geen betere artikelen op dit gebied zijn (terugkoppelen naar de werkgroep)

Appendix 2 : Prognose checklist

VALIDITEIT

Item	+	–	?
1. Wordt uitgegaan van een duidelijk omschreven groep patiënten die is samengesteld op een gelijk moment in het ziektebeloop?			
2. Is de follow-up voldoende compleet?			
Uitkomst(en)			
3. Zijn de uitkomsten van het onderzoek expliciet en in objectieve termen beschreven?			
4. Was de meting van de uitkomst(en) valide en betrouwbaar?			
5. Werd(en) de uitkomst(en) onafhankelijk ('blind') vastgesteld?			
Prognostische factoren			
6. Zijn de prognostische factoren expliciet en in objectieve termen beschreven?			
7. Is van een voldoende proportie van alle ingesloten patiënten een volledige follow-up beschikbaar?			
8 Is de meting van de prognostische factoren voor alle patiënten op dezelfde manier uitgevoerd?			
9. Was de meting van de prognostische factoren valide en betrouwbaar?			
10. Is de meting van prognostische factoren bij een voldoende proportie van de populatie uitgevoerd?			

Appendix 3: Pilot study checklist

☐At least one of the following reasons to conduct the study applies
- Study administration
- Data management
- Scientific

☐Aims and objectives are clearly stated

☐Collected data are consistent with goals

☐No statistical hypothesis is tested

☐Sample size is justified (not necessarily in a statistical sense)

☐The way in which the data collected will be used in the design of a larger study has been addressed

☐This study will answer the question of whether a full scale trial/experiment is worth pursuing

☐Criteria that will determine continuation to a larger study are specified

Appendix 4: STROBE checklist

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Table of Contents

PART 2: RESEARCH PROTOCOL

1 Introduction

Multiple Sclerosis (MS) is a progressive disease of the central nervous system, which affect the axons and myelin sheats, with inflammatory and neurodegenerative components. MS has a heterogeneous and an unpredictable clinical course and causes impairment and disability in the different levels of the International Classification of Functioning, Disability and Health (ICF) (Nedeljkovic et al., 2016) (Storr, Sorensen, & Ravnborg, 2006). This leads to muscle weakness, neuritis optica and fatigue. The first clinical manifestation of MS is mostly a clinical isolated syndrome (CIS). Most patients (85-90%) develop relapsing-remitting (RR) MS where clinical relapses and remissions alternate. Approximately 40% of the RR-MS patients develops secondary progressive (SP) MS with chronic neurological progression. In 10-20% of the patients, primary progressive (PP) MS with a progressive course occurs from the beginning (Onat, Delialioglu, Ozisler, & Ozel, 2015). The mechanisms that cause MS are not known but different scientific studies have shown that it is a caused by a mix of genetic and environmental factors.

MS is a complex disease in which different factors play a role. Given the complexity of the disease, it is important to attain an overview of the different medical and paramedical parameters in patients with MS (Khan, Turner-Stokes, Ng, & Kilpatrick, 2008) (Onat et al., 2015). The different parameters used in this project are already being used for diagnostic and follow-up purposes for the medical and paramedical treatment in persons with MS. All these parameters are compiled in the medical and paramedical files of the patient. Together, all these parameters could give more insights in the course of the disease and the effects of medical and paramedical treatment in persons with MS. Furthermore, MS is characterized with a heterogenous course, treatment and age. Clear conclusions concerning the effects of multidisciplinary rehabilitations have yet to be made. A lot of studies have been written about the effects of multidisciplinary rehabilitation in people with MS, but the interventions used were poorly described. This study will provide clear insights about the contents of the interventions used and, as a consequence it will be able to make a clearer conclusion about the effects of multidisciplinary rehabilitation in people with MS.

2 Study objective

2.1 Research question related to master thesis

The main objective of this retrospective study is to investigate the effects of multidisciplinary rehabilitation in persons with MS. In addition, the study aims to provide insights which patients with MS are enrolled in multidisciplinary rehabilitation programs, what are their rehabilitation needs and are the effects different in different MS subpopulations.

2.2 Hypothesis

The outcome expected is that the patients show improvement regarding how they leave the program versus when they sign up for the program. In addition, the kind of patients with MS that participate in such program are expected to be the patients with a higher grade of disability or with a higher perceived lower quality of everyday functioning. Expectations are that the needs of the patients are mostly focused on specific activities that are individually determined. The effects are expected to be different between the different MS subpopulations.

3 Method

3.1 Research design

A retrospective observational study design will be used.

3.2 Participants

3.2.1 Inclusion criteria

In order to participate in this study, participants have to be at least 18 years old, needed to have the definitive diagnosis of clinical isolated syndrome (CIS) or multiple sclerosis (MS), and followed a multidisciplinary rehabilitation program in the Rehabilitation and MS center in Pelt.

3.2.2 Exclusion criteria

Participants will be excluded when they are under-age, when they have severe cognitive dysfunction and/or when they suffered a relapse during the data collection of the study.

3.2.3 Patient recruitment

All medical and paramedic data collected since 2010 will be used in this retrospective study. This data was collected in the rehabilitation and MS centrum Pelt under supervision of Prof. dr. Bart Van Wijmeersch.

3.3 Medical ethics

Approval from the UHasselt and Local Committee of Mariaziekenhuis was obtained 06/11/2018.

3.4 Study procedure

The data is collected from 2010 onwards. The project will take place from January 2019 until December 2029. Patients with MS following the MDR program will be evaluated on different outcome measures by different disciplines before and after the intervention (week zero and week twelve). Results of these assessments can be found in the medical and paramedical data that has been collected.

3.5 Outcome measure

3.5.1 Descriptive measures

The medical data will contain the date of diagnosis, type of MS, the number of relapses, medical background, clinical score for the EDSS and information about the medical treatment. Other medical data in function of diagnostics and patient follow up are neurophysiological measurements (latency, amplitude and dispersion of motor, somatosensory, visual and brainstem auditory evoked potentials), lab results (blood and cerebrospinal fluid analysis) and MRI measurements (number of and volume of T2 lesions and black holes, brain volume, …)

3.5.2 Experimental measures

The paramedical data will provide an overview of the different disciplines (physiotherapist, psychologist, speech therapist and occupational therapist). Every therapist within the multidisciplinary team evaluates the patient regularly to adjust the paramedical treatment.

All clinically relevant data will be coded by the Revalidatie en MS centrum. The personal data will not be seen by the researchers. The researchers will only see the coded information and are going to process the data in collaboration with the CENSTAT-UHasselt under the supervision of Prof. dr. Bart Van Wijmeersch. The results of this study will be announced at congresses and published in scientific magazines. All these things will happen without any patient being specifically mentioned.

3.5.2.1 Assessment physiotherapist

3.5.2.1.1 Pain assessment

The tests battery used by the physiotherapists contains the Visual Analogue Scale (VAS). The VAS is a scale to subjectively express the pain someone is experiencing. The higher the score, the higher the discomfort experienced by the patient.

3.5.2.1.2 Spasticity

The Tardieu Scale (TS) was used to assess spasticity. This test was executed in both lower limbs for hip extension, adduction, external rotation, internal rotation. Knee extension, flexion and plantar flexion. All subtests are scored from zero to five and will be added up to a total score on 35.

3.5.2.1.3 Balance-proprioception

3.5.2.1.3.1 Trunk control test (TCT)

The TCT is a scale used to assess the trunk stability in neurological patients. The test is divided in four subtests all scored on 25. The subtests are rolling over the left flank, rolling over the right flank, keeping your balance while sitting on a bedside for 30 seconds and rise from sit to stand. All these subtest scores are added up to a total score of 100 in which a higher score equals a higher self-dependence

3.5.2.1.3.2 Mini BESTest

The MiniBESTest is a test consisting of 14 different tasks which require trunk stability and maintaining one's balance. All subitems are scored between zero and two which are added up to sub scores on six. Subsequently, these sub scores are added up to a total score on 28. A score under 19/28 indicates a higher risk of falling.

3.5.2.1.3.3 Timed up and go test (TUG)

The TUG is a test where the patient has to sit on a chair, walk three meters, turn around, walk back to the chair and sit back on the chair. The patient is not allowed to run but can use a walking aid if necessary. In this research project, the test was done with single-task and double-task settings. The score was measured in seconds. A score faster than 20 seconds means the patient walks independently and safe. A score slower than 30 seconds indicates a need for help during gait.

3.5.2.1.4 Gait

3.5.2.1.4.1 Two Minutes Walking Test (2MWT)

The 2MWT is used to assess the gait speed, the stamina and the gait pattern of the patient. The patients are asked to walk on a speed so that when the two minutes have passed, they feel like they have performed on their maximum. The distance walked is measured. Use of a walking aid is allowed. The formula to find the estimated distance is: '252,583 – (1,165 x age) + (19,987 x gender)' where male equals one and female equals zero.

3.5.2.2 Occupational therapist

3.5.2.2.1 Strength

3.5.2.2.1.1 Isometric hand grip strength

This test is executed bilateral using the Jamar Handgrip Dynamometer and the scoring is measured in kilograms force and is the average of three trials with a few minutes rest in between trials.

3.5.2.2.1.2 Isometric grip strength

The different isometric grip strengths tests used, were the palmar grip pinch (thumb, index and middle finger), tip grip (tip of the thumb and index finger) and the key pinch grip (thumb pad and lateral aspect of index finger). This test is executed bilateral using the Pinch Gauche. Scoring is measured in kilograms force ans is the average of three trials with a few minutes rest in between trials.

3.5.2.2.2 Sensory

3.5.2.2.2.1 Semmes-Weinstein Monofilaments

With the use of a monofilament the pressure perception is evaluated. Every filament is placed perpendicular on the skin and pressure gets build up to the point where a filament makes a C-turn. The patient must indicate when they feel something. The test is executed bilateral on the thumbs and index fingers. The scoring is between 2.83 and 6.65 seconds.

3.5.2.2.2.2 Vibration

The perception of vibration is evaluated bilateral on the dorsal side of the distal interphalangeal joint of the index finger and the processus styloideus ulnae. This item can get scored up to an eight.

3.5.2.2.3 Hand dexterity

3.5.2.2.3.1 Nine Hole Peg Test (NHPT)

The NHPT is a test to measure the dexterity of the fine motor functioning of the hand. The patient has to put 9 pegs from a box and put them into small openings. After all the pegs are put in place, the patient has to put them back in the box as fast as possible. Important is that the same hand is used during the same trial and the pegs have to be transferred one by one. The left and right hand get two trials each where the score is measured in seconds.

3.5.2.2.3.2 Action Research Arm Test (ARAT)

The ARAT evaluates the arm-hand functioning and is executed bilateral. The test is divided in four subtests: five finger grip, cylinder grip, pincer grip, gross motor functioning. Every subtest contains between three and six items which are scored from zero to three. The five-finger grip is score goes up to 18 points, the cylinder grip goes up to 12 points, pincer grip goes up to 18 points and the gross motor functioning goes up to 9 points. The total test goes up to 57 points where a higher score equals a better hand dexterity.

3.5.2.2.3.3 Test Evaluant les Membres superieurs des Personnes Agees (TEMPA)

The TEMPA is a test used to evaluate the performance of certain tasks. The TEMPA measures three criteria: the speed in which the task is performed, the autonomy the person has while performing the task and the analysis of the task itself. The TEMPA has three sub scores: functional rating of bilateral tasks which scores from 0 to -15, functional rating of unilateral tasks left and right which both scores from 0 to -12. These three subscores are added up to a total score ranging from 0 to -39.

3.5.2.2.4 Perceived Upper Limb Performance

3.5.2.2.4.1 Manual Ability Measure – 36 (MAM-36)

The MAM-36 is a task-oriented, patient reported outcome measure to support objective evaluations of functional limitations. It is a four-point rating scale ranging from one to four, where one equals not being able to perform the item and four which equals that the test was easy. The MAM-36 contains 36 everyday items like e.g. cutting meat or taking something out a wallet. During the performance of these items, it doesn't matter which hand is used, as long as no assistive devices are used to perform the task. The total score of the MAM-36 goes up to 144 were the higher, the better the tasks went according to the patient. In this research, the Rasch transformed score will also be examined which goes up to 100. The Rasch transformed score gives a transformation of an ordinal score into a linear, interval-level variable.

3.5.2.2.5 Participation

3.5.2.2.5.1 Community Integration Questionnaire (CIQ)

The CIQ is an item used to gain insights on the integration of patients in the community. The item focusses on behavior instead of emotional experiences the patient has. The focus for the

scoring lies on the frequency a task is performed in which it is of secondary importance whether the task is performed individually or in a group. The CIQ can be answered by the patient or by a proxy. The test consists of 15 items divided in three subscales: home integration which scores up to 10, social integration which scores op to 12 and productivity which scores up to 17. These three subscales are all added on a score of 39. The higher the score, the higher the integration of the patient in the community.

3.5.2.2.6 Functional mobility

For this item, the researchers ask the patient whether they use a walking aid indoors to get around the house. This ranges from independently, crutches, rollator, manual wheelchair, electrical wheelchair to 'others'. Patients were also asked whether they use a walking aid outdoors to get around the community. This ranges from independently, crutches, rollator, manual wheelchair, electrical wheelchair to 'others'

3.5.2.3 Psychologist

3.5.2.3.1 Symbol Digit Modalities Test (SDMT)

The SDMT is a test that evaluates cognitive impairment. The test consists of symbols which ae linked with numbers. There are rows with symbols and the patients have to convert the symbols to numbers. This test is measured in seconds and the longer it takes, the higher the indication for cognitive impairment.

3.5.2.3.2 Hospital Anxiety and Depression Scale (HADS)

The HADS is used to measure complaints about anxiety and depression without taking physical complaints into account. Both the scale about anxiety and depression contain seven items. For both anxiety and depression, a score over eight is an indication for a psychiatric status image.

3.6 Intervention

The intervention in the Rehabilitation and MS Centre Pelt consists of three fases that the pwMS must go though. These interventions are all fitted in a care- and treatment plan to help the different involved disciplines to coordinate with each other in function of time

management. In order to work together efficiently, multidisciplinary consultation moments are organized, as well as the communication of patient information through the electronic patient files. The three fases in the intervention are the bilanfase, exercise- and evaluation fase and the discharge fase.

3.6.1 Bilanfase

The bilanfase is the first fase of the rehabilitation. During this fase, the different disciplines carry out there tests and observations. An objective picture is made about the possibilities and disabilities of the patient. Multidisciplinary dialogue is included in which the treating physician also takes part. The treatment goals and the treatment plan are determined for each discipline at the end of this fase.

3.6.2 Exercise- and evaluation fase

This fase is characterized by intensive training and follow-up by the physiotherapist, occupational therapist, speech therapist and the psychological services. The nurses have a specific role for the inpatient rehabilitating patients. The nurses guide, educate and exercise the items that the patients have learned during the different therapy sessions. During regular time intervals, a multidisciplinary team meeting about the patient's state is evaluated. At the same meetings, treatment goals are re-evaluated and adjusted.

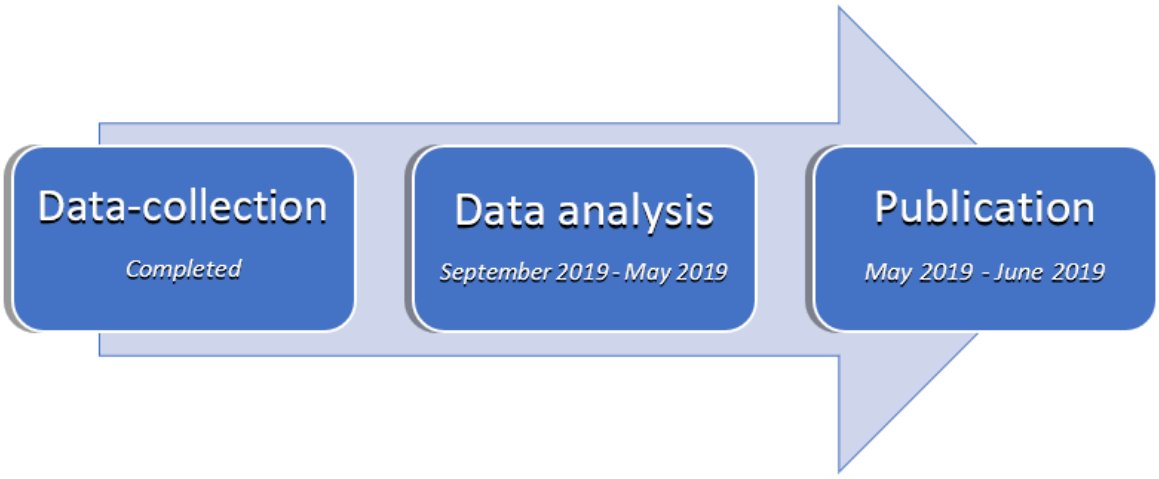
3.6.3 Discharge fase

3.7 When a team meeting concludes that a patient has made enough progression to return to their home environment or can be enrolled in a continuation institution, the discharge fase is put into motion. During this fase, intensive work is being done towards discharge. Needed preparations are made to make the switch to the new situation as smooth as possible. After discharge outpatient rehabilitation is still possible in the rehabilitation center.

3.8 Data-analysis

The computer program JMP will be used to perform data-analysis. Descriptive statistics will be applied to summarize participant characteristics. Differences between pre- and post-intervention will be investigated with paired t-test. When there is no normality the Wilcoxon test will be performed. Normality will be tested with Shapiro-Wilke test between groups.

4 Time planning



5 Critical appraisal

5.1 Inclusion criteria

Because only patients of the MS Centre Pelt were included in this retrospective study, the generalizability of this study could be limited. Contrary to this, the generalizability of this study could be strengthened by the wide characteristics of the population included. The age of the included patients was 18 years old and above and all the types of MS were represented in the study. The strengthen the generalizability more, the inclusion of more rehabilitation centers could have been considered.

5.2 Assessment physiotherapist

There are no assessments concerning continence, sexual dysfunction,… . This are frequent disabilities in pwMS which could be overlooked at during assessments if not specifically checked. This because the patients might be too embarrassed to spontaneously talk about these subjects. Possible assessment tools could be the Incontinence Impact Questionnaire and the Vragenlijst voor het signaleren van Seksuele Dysfuncties (questionnaire concerning sexual dysfunction in Dutch).

5.3 Intervention

For the intervention itself, a control group could have been used to compare intervention effect. The control group could have been given non-significant education. Also, the use of a specific intervention like the aquatic program by *Salem (2011)* could be integrated to compare to the intervention of the MS center as well as to the control group.

During the interventions the significant other or relatives could be involved during the bilanfase and the discharge fase. The involvement of the significant other or relatives could possibly have positive effects on the experience of the patients. Also, this could give the involved persons insights on how to assist pwMS in their home environment.

6 Appendix

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