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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Clinical guidelines for rehabilitation treatment in MS

Jason Fraiponts
Pieter Hayen

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

PROMOTOR :
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Prof. dr. Peter FEYS

COPROMOTOR :
Mevrouw Joke RAATS

Acknowledgement

I would first like to thank my thesis promotor Prof. dr. Peter FEYS, and daily supervisor Joke RAATS of the faculty Revalidatiewetenschappen en kinesitherapie at the UHasselt. They were helpful when we ran into a trouble spot or had a question about our research or writing. They consistently to guided our work in the right direction, while allowing this paper to be our own work.

Zonhoven (België), 3/6/2019 J.F

Hasselt (België), 3/6/2019 P.H

Highlights: Clinical guidelines for rehabilitation treatment in MS

"Which are the effective evidence-based clinical rehabilitation interventions for MS?"

"Which are the evidence-based service recommendations related to rehabilitation for MS?"

Jason Fraiponts (1436857)

Pieter Hayen (1437163)

"After assessing the quality of the seven guidelines, four recent clinical practise guidelines were found who scored over 22 on seven essential items. And passed on four of the essential items of the AGREE II and had a clear definition for the level of recommendation and strength of recommendation. These were; "Spanish clinical practise guideline on the management of people with Multiple Sclerosis (2012), Multiple Sclerosis: Management of MS in primary and secondary care (NICE 2014), Management of Multiple Sclerosis (2015 Malaysia), Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS (2014)"

"The Spanish guideline consisted of 70 recommendations of which 41 are related to rehabilitation of MS. The other 29 recommendations are related to disease modifying therapies. With recommendations categorized under 8 different ICF categories"

"The NICE guideline consisted of 66 recommendations of which 58 are related to rehabilitation of MS. The other 8 recommendations are related to disease modifying therapies. With recommendations categorized under 10 different ICF categories"

“The Malaysian guideline consisted of 53 recommendations of which 28 are related to rehabilitation of MS. The other 25 recommendations are related to disease modifying therapies. With recommendations categorized under 10 different ICF categories.”

“The fourth guideline, Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS, consisted of 7 recommendations. All 7 recommendations are related to rehabilitation of MS. All recommendations are categorized under 1 ICF category, namely Mental functions.”

Promotor: Prof Dr. Peter Feys and daily supervisor: Joke Raets

Context of the master thesis

This master thesis addresses a subject in the research domain of neurological rehabilitation, specifically patients suffering from multiple sclerosis and it runs parallel with a broader research project, namely the WHO's Rehabilitation Action Plan 2030.

Rehabilitation 2030 is a call for action to scale up rehabilitation so that countries can be prepared to address the evolving needs of populations up to 2030. Information on this research project can be found on 'Rehabilitation 2030: A Call for Action'. Retrieved from https://www.who.int/rehabilitation/rehab-2030/en/.

Rehabilitation is defined by the WHO as: "*a set of interventions designed to reduce disability and optimize functioning in individuals with health conditions in interaction with their environment, this is a highly-person-centered health strategy where treatment caters to the underlying health condition(s) as well as goals and preferences of the user. And it is also a multidisciplinary process that uses professionals that are from both health and other sectors (education and labour, for example).* "

One of the projects of Rehabilitation 2030 is the development of a package of priority rehabilitation interventions for several health conditions, which can assist countries in the selection of target areas in their rehabilitation policy at national level. The package of priority interventions will include those interventions that are considered as priority by expert clinicians and are supported by scientific evidence. Interventions include both rehabilitation services and clinical interventions, across the care continuum and in different delivery setting. The evidence on rehabilitation interventions/services will be searched in high quality and recent practice clinical guidelines or systematic reviews or meta-analyses if recommendations are not available, this data will be converted in the global conceptual framework of the ICF in order to categorize the interventions/services for the rehabilitation of MS.

However Multiple Sclerosis isn't included in the WHO action plan, because its high variation in prevalence, therefore MS is not a priority health condition for WHO in a worldwide perspective. The highest age-standardised multiple sclerosis prevalence estimates per 100 000 population were in high-income North America (164.6, 95% UI, 153.2–177.1), western Europe (127.0, 115.4–139.6), and Australasia (91.1, 81.5–101.7), and the lowest

were in eastern sub-Saharan Africa (3.3, 2.9–3.8), central sub-Saharan Africa (2.8, 2.4–3.1), and Oceania (2.0, 1.71–2.29). However because the prevalence is so high in high-income North America, western Europe and Australasia it is still important to search for the clinical effective interventions and services for the rehabilitation of MS.(Wallin, 2019)

The literature study of this master thesis is focused on the following research questions: "Which are the effective evidence-based clinical rehabilitation intervention for MS?" and "Which are the evidence-based service recommendations related to rehabilitation for MS?"

This part of the master thesis is performed under the supervision of Prof. Dr. Peter Feys, and Dr. Joke Raats at the rehabilitation research centre REVAL of UHasselt in Diepenbeek.

For this duo master thesis was the central format applied.

The final research questions, literature strategy and quality assessment were developed by the WHO and supervised by Prof. Dr. Peter Feys and Dr. Joke Raats. The further data-extraction and analysis of the selected guidelines were supervised by Prof. Dr. Peter Feys and Dr. Joke Raats.

The guideline selection, quality assessment, data-extraction, context, introduction and results were done by J.F., and guideline selection, quality assessment, data-extraction, methodology, results and discussion were done by P.H..

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1.Abstract

Purpose --- The aim of this master thesis is to identify the effective, evidence-based clinical/service rehabilitation intervention recommendations for Multiple Sclerosis.

Methods --- Several databases were used for the identification and selection of recent and high-quality clinical practise guidelines. All included guidelines were assessed by the AGREE II instrument to assess the methodological quality. Further coding and analysis of the recommendations were only done on the guidelines who scored >22 on the seven essential items, passed all four of the predetermined items of the AGREE II and had a clear definition for the level of evidence and strength of recommendation.

Results --- Four guidelines met the in- and exclusion criteria. The Spanish guideline consists of 41 recommendations which are related to rehabilitation of MS. These recommendations were categorized under 8 different ICF categories. The NICE guideline and the Malaysian guideline consists respectively of 58 and 28 recommendations related to rehabilitation. Both were categorized under 10 different ICF categories.

The fourth guideline; 'Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS' consists of 7 recommendations related to rehabilitation of MS. All are categorized under 1 ICF category, namely Mental functions.

Conclusion --- A total of 134 recommendations were coded into different ICF categories. These were all put into a list per ICF category to provide an overview of what actions are effective and evidence-based for the management of that specific ICF category. We consider that this overview could be a helpful tool in the rehabilitation of patients with Multiple Sclerosis.,

Keywords --- guideline, MS, rehabilitation

2.Introduction

Multiple sclerosis (MS), a chronic demyelinating disease, is characterised by a heterogeneous set of symptoms that can lead to severe disability and have an impact on functional capacity of the patient, and health-related quality of life (HRQOL).(Guijarro-Castro et al., 2017) and it's one of the world's most common neurologic disorders, and in many countries it is the leading cause of nontraumatic neurologic disability in young adults. (Browne, 2014) Affecting approximaly 2.2 million cases of multiple sclerosis globally, with 18 932 deaths and 1 151 478 DALYs due to multiple sclerosis in 2016. (Wallin, 2019)

The prevalence of MS has a high variation and has MS has a latitudinal discrepancy and occurs more frequently in temperate regions away from the equator. The likelihood of a person getting the disease is predicted by a person's residence for the first 15 years of their life (DETELS, 1978). With the highest age-standardised multiple sclerosis prevalence estimates per 100 000 population in high-income North America (164.6, 95% UI, 153.2–177.1), western Europe (127.0, 115.4–139.6), and Australasia (91.1, 81.5–101.7), and the lowest were in eastern sub-Saharan Africa (3.3, 2.9–3.8), central sub-Saharan Africa (2.8, 2.4–3.1), and Oceania (2.0, 1.71–2.29).(Wallin, 2019)

In Belgium specifically there are around 12 000 people living with MS in, which constitutes to a prevalence is 100 per 100,0001. Workforce participation decreases from 76% in the very early stages to 4% in the very late stages, leading to a rise in productivity losses in the late stages of disease. These productivity losses (short-term absence, long-term sick leave, and early retirement) represent 36% of the total MS cost to society.(Platform, 2015)

Although neurological disability progression is variable, DALYs peaked in the sixth decade of life. Because onset is most frequently in early adulthood and because survival has been improved, people with multiple sclerosis are affected throughout adult life, leading to the high number of YLDs. The disability weights for multiple sclerosis are generally high and YLDs begin to increase steeply early in the second decade of life.(Wallin, 2019)

The International Classification of Functioning, Disability and Health provides a global conceptual framework to categorize abilities and problems of pwMS within a standard system and offers common language for clinicians for describing function, disability, and health of an individual.((WHO), 2001)

Person with MS (pwMS) can present to rehabilitation with various combinations of deficits, such as physical, cognitive, psychosocial, behavioural and environmental problems. Classified according to the WHO ICF, these include impairments (strength, coordination, balance, spasticity, memory, urinary urgency), which result in activity limitation (mobility, self-care) and restriction in societal participation (impact on work, driving, family, finances).(Frankel, 2001)

According to Amatya, Khan, & Galea, 2019, regular specialist evaluation and follow-up to assess the needs of persons with all types of MS for appropriate rehabilitation interventions may be of benefit, although the certainty of evidence varies across the different types of interventions evaluated by the reviews. Structured, multidisciplinary rehabilitation programmes and physical therapy (exercise or physical activities) can improve functional outcomes (mobility, muscle strength, aerobic capacity), and quality of life (Amatya, 2019)

This study focuses on the rehabilitation of Multiple Sclerosis. Rehabilitation is defined by the WHO as "*a set of measures that assist individuals who experience, or are likely to experience, disability to achieve and maintain optimal functioning in interaction with their environments*" (WHO, 2017)

The aim of this study is to identify which are the effective evidence-based clinical/service rehabilitation intervention recommendations for Multiple Sclerosis. This will be done by searching for recent, high-quality clinical practise guidelines. According to the institute of medicine, Clinical practice guidelines are "*evidence based statements that include recommendations intended to optimise patient care and assist health care practitioners to make decisions about appropriate health care for specific clinical circumstances, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options*." (Greenfield, 2011)

3. Methods

3.1 Literature search

For this literature search different medical databases (TRIP, Pubmed), International Guideline Databases (Guidelines International Network), National Guideline databases (New Zealand Guidelines Group) and websites of MS organisations (MS society Canada) were used for the identification and selection of recent and high-quality clinical practise guidelines. According to the institute of medicine, *Clinical practice guidelines are "evidence based statements that include recommendations intended to optimise patient care and assist health care practitioners to make decisions about appropriate health care for specific clinical circumstances, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."(Greenfield, 2011)*

3.2 Selection criteria

The following inclusion criteria for the selection of clinical guidelines were used;

(1) Published within the last 10 years (2009-2019)
(2) Relevant to the multidisciplinary rehabilitation of Multiple Sclerosis
(3) Written in English
(4) Includes recommendation on rehabilitation

Clinical guidelines obtained via this scoping review were excluded if they;

(1) Addressed only care for children
(2) Included rehabilitation of other pathologies

Every retrieved clinical guidelines were checked for possible recent updates. If there were any, then the updated version of the clinical guideline was chosen for the evaluation.

3.3 Quality assessment

Each guideline was evaluated individually by two appraisers using the Appraisal of Guidelines for Research and Evaluation II (AGREE II): The AGREE II instrument evaluates the guideline development process and quality of the guideline. The AGREE II comprises 23 items organized into 6 quality domains including: (1) Scope and purpose
(2) Stakeholder involvement,
(3) Rigour of development,

(4) Clarity of presentation,

(5) Applicability, and

(6) Editorial independence.

Each item is given a score between 1 and 7, with 1 meaning strongly disagree, and 7 meaning strongly agree. An item is given a score between 1 and 6 if it doesn't meet the full criteria, each criteria for each item can be found in the instruction manual of the AGREE II instrument. This instruction manual can be found on the 'Welcome to the AGREE Enterprise website'. Retrieved from https://www.agreetrust.org/. Besides the item scores there will also be domain scores, these will be calculated by summing up all the scores of the individual items within each domain. Afterwards the average item and domain scores between the two appraisers will be calculated and be put in a percentage (100% representing a strong score), these scores will be used for comparing the quality of the selected guidelines.

According to the AGREE manual can the domain scores be useful for comparing guidelines and it will inform the appraisers whether a guideline should be recommended for use, however the Consortium has not set minimum domain scores or patterns of scores across domains to differentiate between high quality and poor quality guidelines.(Consortium, 2019) However in this master thesis a guideline is considered of poor methodological quality if; (a) it's rated on the AGREE with a score of <22 on seven essential items or (b) fail on any the four predetermined items (item score <4).

Item 7: Systematic methods were used to search for evidence	Pass/Fail
Item 10: The methods for formulating recommendations are clearly described	Pass/Fail
Item 12:There is an explicit link between recommendation and the supportive evidence	Pass/Fail
Item 13: The guideline has been externally reviewed by experts	
Item 15: The recommendations are specific and unambiguous	
Item 22: The views of the funding body have not influenced the content of the guidance	
Item 23: Competing interests of guideline development group members have been recorded and addressed.	Pass/Fail

3.4 Coding of the recommendations

The coding of the recommendations is only done on the guidelines who scored >22 on the seven essential items and passed on the four predetermined items.

All recommendations were coded on four categories;

(1) An ICF code, this is decided on what the goal/target is of the recommendation. All definitions and in/exclusion criteria for all the different ICF codes can be found online on the ICF browser. (https://apps.who.int/classifications/icfbrowser/)
(2) An International Classification of Health Intervention (ICHI) code (Action), this is decided on what action the recommendation gives information about. All definitions and in/exclusion criteria for the different ICHI codes can be found online on the ICHI browser (https://mitel.dimi.uniud.it/ichi/)
(3) Level of evidence, the definition can differ among guidelines. This gives information on how low/high the evidence is on which the recommendation is based. A list of all the different definitions of the level of evidence of the selected guidelines can be found in Appendix D.
(4) Strength of recommendation, the definition can differ among guidelines. This gives information on the trade-off between benefits and harms, and on the certainty that the recommendation can be made. A list of all the different definitions of the strength of recommendations of the selected guidelines can be found in Appendix E.

The aim of this analysis was to obtain a global view of the amount of recommendations focussed on rehabilitation in one guideline, and the amount of recommendations on the different topics (ICF codes). This was done by doing a descriptive analysis on the recommendations grouped per ICF code. This was put in a pie chart to visualize the potential differences between guidelines.

3.5: Analysis of the coded recommendations

The aim of this analysis is to identify possible overlap/ gaps in the recommendations and to form an overview of the different recommendation per ICF code and ICHI code. Recommendations were grouped together by ICF and ICHI codes, and each recommendation

was documented in terms of strength of recommendation, level of evidence and the corresponding guidelines where the recommendations can be found.

4. Results

4.1: Results study selection

A total of 309 potential guideline were identified up until February 2019, 12 of which met the in/exclusion criteria. After checking for updates and duplicates the number reduced to 7 guidelines. An overview of the study search can be found in table 1.

Table 1: Overview of the literature search

Database	**Search terms**	**Results**	**Met in/exclusion criteria**
Pubmed	Multiple Sclerosis + Filter: Practice guideline + 10 years	45	2
Trip	Multiple sclerosis rehabilitation + filter: guideline	141	3
Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS)	Esclerosi multiple guideline -> Publications -> Clinical Practise Guidelines	15	1
Agency for healthcare research and quality	Multiple sclerosis	0	0
MS society Canada	Multiple sclerosis guideline	6	1
Guidelines International Network	Multiple sclerosis	28	2
Canadian Medical Association infobase of clinical practice guidelines	Multiple sclerosis	0	0
eGuidelines	MS + filter: Multiple Sclerosis	2	0
National Institute for Clinical Excellence	Multiple sclerosis + filter: clinical guideline	28	1
New Zealand Guidelines Group	Multiple sclerosis	1	0
Scottish Intercollegiate Guidelines Network	Multiple sclerosis	0	0
American academy of neurology	Multiple sclerosis	43	2
Total		309	12

The excluded guidelines can be found in appendix A.

The flowchart can be found in appendix B.

4.2: Results quality assessment

After assessing with the AGREE II instrument all included guidelines scored >22 on the 7 essential items, however the guideline “Recommendations for the detection and therapeutic management of cognitive impairment in MS (2012)” was excluded because it failed on item 23. The average AGREE II item scores on the seven essential items can be found in table 2.

After checking for definitions for the level of evidence and strength of recommendation, only 4 guidelines were able to formulate a definition for the level of evidence and strength of recommendation, these were;

- Spanish clinical practise guideline on the management of people with Multiple Sclerosis (2012)
- Multiple Sclerosis: Management of MS in primary and secondary care (NICE 2014)*
- Management of Multiple Sclerosis (2015 Malaysia)*
- Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS (2014)*

The three other guidelines; ‘Canadian Physical Activity Guidelines for adults with Multiple Sclerosis (2011)’, ‘Recommendations for the detection and therapeutic management of cognitive impairment in multiple sclerosis (2012)’ and ‘Summary of comprehensive systematic review: Rehabilitation in multiple sclerosis (2015)’ were excluded for the reason that there was no definition formulated for the strength of recommendation.

Table 2: The average AGREE II item scores on the seven essential items of the seven included guidelines

	Item 7	**Item 10**	**Item 12**	**Item 13**	**Item 15**	**Item 22**	**Item 23**	**Total**
Spanish clinical practise guideline on the management of people with Multiple Sclerosis (2012)	6	7	7	4.5	7	7	5.5	44
Multiple Sclerosis: Management of MS in primary and secondary care (NICE 2014)	7	5.5	7	6	7	1.5	7	41
Management of Multiple Sclerosis (2015 Malaysia)	7	4.5	7	5.5	7	5.5	7	43.5
Canadian Physical Activity Guidelines for adults with MS (2011)	7	6.5	7	7	7	7	7	48.5
Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS (2014)	7	6.5	6	2	6.5	7	7	42
Recommendations for the detection and therapeutic management of cognitive impairment in MS (2012)	7	6.5	5.5	5.5	6.5	7	1	39
Summary of comprehensive systematic review: Rehabilitation in MS (2015)	7	6	6	5	6.5	6	6.5	43

A more detailed report of the item/ domain scores of the AGREE II can be found in appendix E.

4.3: Coding of the recommendations

First, all recommendations of the four included guidelines were listed. After screening the recommendations, eighteen ICF domains were determined to assign each recommendation to. Namely, fatigue, muscle tone functions, urinary functions, mental functions, pain, mobility, seeing functions, education, support and relationships, ingestion functions, defecation functions, sexual functions, muscle functions, procreation functions, structure of brain, health services systems and policies, functions of the cardiovascular system, health professionals, self-care.

After listing all recommendations, a total of 63 recommendations were excluded. The reason for exclusion was because the content of the recommendations was not discussing rehabilitation of MS. These recommendations are related to disease modifying therapies or the diagnostic process of MS itself.

The Spanish guideline consisted of 70 recommendations of which 40 are related to rehabilitation of MS. The other 30 recommendations are related to disease modifying therapies, and the diagnostic process for MS. Figure 1.A shows the number of recommendations who are related to rehabilitation of MS.

The NICE guideline consisted of 66 recommendations of which 58 are related to rehabilitation of MS. The other 8 recommendations are related to disease modifying therapies, and the diagnostic process for MS. Figure 1.B shows the number of recommendations who are related to rehabilitation of MS.

The Malaysian guideline consisted of 53 recommendations of which 28 are related to rehabilitation of MS. The other 25 recommendations are related to disease modifying therapies, and the diagnostic process for MS. Figure 1.C shows the number of recommendations who are related to rehabilitation of MS.

The fourth guideline, Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS, consisted of 7 recommendations. All 7 recommendations are related to rehabilitation of MS. Figure 1.D shows the number of recommendations who are related to rehabilitation of MS.

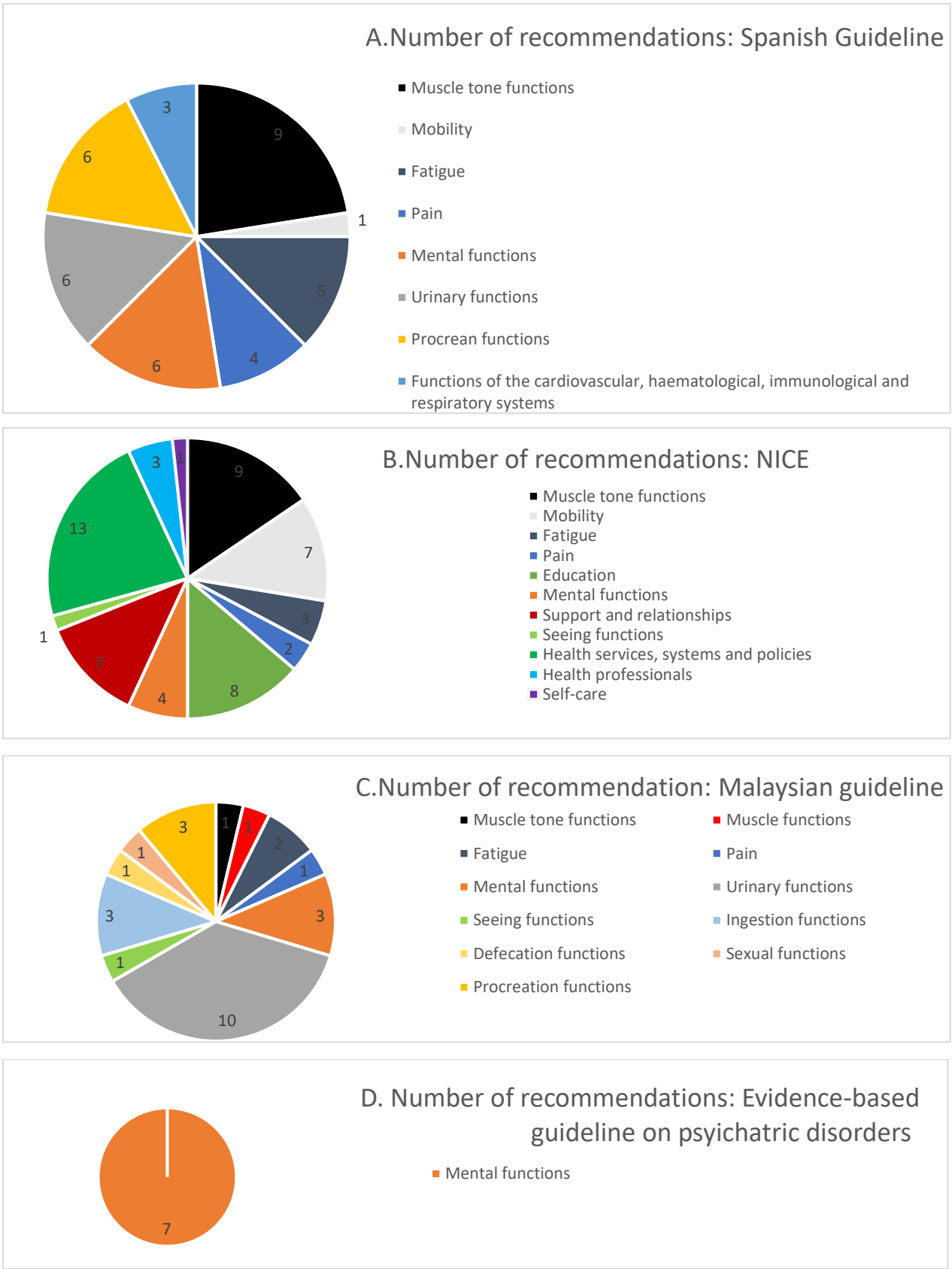

Figure 1: Number of recommendations in the included guidelines

Afterwards a comparison of all recommendations between the four guidelines was made. The 18 different ICF domains used are structured into three ICHI categories, namely therapeutic, diagnostic and managing. The subcategory 'Therapeutic' describes the therapeutic actions used to treat MS. 'Diagnostic' describes the diagnostic imaging, observation used to diagnose symptoms or functioning problems of MS. 'Managing' stands for the individualised planning, prescription and collaborating to treat MS.
An overview of the amount of recommendations on each ICHI category can be found on table 3.

Table 3: Overview of the amount of recommendations on each ICHI category

ICF category	**ICHI category**	**Guideline (1): Spanish guideline**	**Guideline (2): NICE guideline**	**Guideline (3): Malaysian guideline**	**Guideline (4): Evidence-based guideline:**	Total
Muscle tone functions	Diagnostic		1			1
	Therapeutic	9	7	1		17
	Managing		1			1
Muscle functions	Therapeutic			2		2
Mobility	Diagnostic		1			1
	Therapeutic	1	4			5
	Managing		2			2
Fatigue	Diagnostic		1			1
	Therapeutic	5		2		7
	Managing		2			2
Pain	Diagnostic		1			1
	Therapeutic	4		1		5
	Managing		1			1
Education	Therapeutic		7			7
	Managing		1			1
Mental functions	Diagnostic		2		3	5
	Therapeutic	6	1	3	4	14
	Managing		1			1
Support and relationships	Diagnostic		1			1
	Therapeutic		2			2
	Managing		4			4

Urinary functions	Diagnostic			1		1
	Therapeutic	6		9		15
Seeing functions	Managing		1	1		2
Ingestion functions	Therapeutic			3		3
Defecation functions	Managing			1		1
Sexual functions	Managing			1		1
Procreation functions	Therapeutic	2		3		5
	Managing	4				4
Health services, systems and policies	Diagnostic		7			7
	Managing		6			6
Functions of the cardiovascular, haematological, immunological and respiratory systems	Diagnostic	3				3
Health professionals	Diagnostic		1			1
	Managing		2			2
Self-care	Managing		1			1
Total		40	58	28	7	

4.4. Analysis of the coded recommendations

All recommendations were grouped together by ICF and ICHI codes and each recommendation was documented in terms of strength of recommendation, level of evidence and a number for the corresponding guidelines where the recommendations can be found.

(1): Spanish clinical practise guideline on the management of people with Multiple Sclerosis (2012)

(2): Multiple Sclerosis: Management of MS in primary and secondary care (NICE 2014)

(3): Management of Multiple Sclerosis (2015 Malaysia)

(4): Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS (2014)

When similar recommendations were in different guidelines these were written in red, and all recommendations were listed from strong -> weak-> weak against -> strong against.
A global overview of the amount and type of recommendation across the four guidelines can be found in table 40 in Appendix D

4.4.1 **ICHI: Therapeutic**

4.4.1.1 Fatigue (b4552): "Functions related to susceptibility to fatigue, at any level of exertion."

Across the 4 included guidelines there were a total of 25 recommendation on fatigue. These were on different therapeutic topics, namely 7 on Medication (mostly weak, strong against), 2 on Education (strong), 3 on Energy conservation management (strong, weak) and 6 on Exercise training (strong, weak). Recommendations on the use of amantadine and the use of energy-saving rehabilitation strategies for the treatment of fatigue in MS were found in 3 different guidelines. However the strength of recommendation and level of evidence differs across guidelines. The list for all the recommendations on fatigue, therapeutic can be found in table 4 in Appendix C.

4.4.1.2 Muscle tone functions (b735): "Functions related to the tension present in the resting muscles and the resistance offered when trying to move the muscles passively."

Across the 4 included guidelines there were a total of 17 recommendation on muscle tone functions. These were on different therapeutic topics, namely 1 on Observation (clinical experience), 14 on Medication (mostly weak) and 2 on Exercise training (weak). The recommendations on the use of baclofen, tizanide and gabapentin to treat spasticity in MS were found in 2 different guidelines. The strength of evidence is weak and level of evidence low to very low in both guidelines. The list for all the recommendations on muscle tone functions, therapeutic can be found in table 5 in Appendix C.

4.4.1.3 Urinary functions (b610 – b639)

Across the 4 included guidelines there were a total of 15 recommendation on urinary functions. These were on different therapeutic topics, namely 8 on Medication (mostly

weak), 2 on Exercise training (Clinical experience), 4 on Surgery (varying) and 1 on Education (weak). The recommendations on the use of intermittent bladder catheterisation and the use of desmopressin to treat urinary dysfunctions in MS were found in 2 different guidelines. However the strength of recommendation and level of evidence differs across the two guidelines. The list for all the recommendations on urinary functions, therapeutic can be found in table 6 in Appendix C.

4.4.1.4 Mental functions (b1), learning and applying knowledge (d1), general tasks and demands (d2)

Across the 4 included guidelines there were a total of 13 recommendation on mental functions, learning and applying knowledge and general tasks and demands.
These were on different therapeutic topics, namely 9 on Medication (weak and strong against) and 4 on Exercise training (weak). The recommendations on cognitive rehabilitation and the use of dextromethorphan/ quinide to treat cognitive impairments in MS were found in 2 different guidelines. However the strength of recommendation and level of evidence differs across the two guidelines. The list for all the recommendations on mental functions, learning and applying knowledge, general tasks and demands, therapeutic can be found in table 7 in Appendix C.

4.4.1.5 Pain (b280 – b289):

Across the 4 included guidelines there were a total of 5 recommendation on pain. These were all on the same therapeutic topic, namely Medication (weak). The recommendations on the use of antidepressants to treat pain in MS were found in 2 different guidelines. However the strength of recommendation was weak and the level of evidence differs across the two guidelines. The list for all the recommendations on pain, therapeutic can be found in table 8 in Appendix C.

4.4.1.6 Mobility (d4):

Across the 4 included guidelines there were a total of 5 recommendation on mobility. These were on different therapeutic topics, namely 2 on Medication (strong and strong against) and 3 on Exercise training (mostly weak). The recommendations on the use of dalfampridine to treat walking impairment in MS were found in 2 different guidelines. However, a different

outcome was calculated. Also the strength of recommendation and the level of evidence differs across the two guidelines. The list for all the recommendations on mobility, therapeutic can be found in table 9 in Appendix C.

4.4.1.7 Seeing functions (b210):

Across the 4 included guidelines there were a total of 2 recommendations on seeing functions. These were 2 different recommendations in the same guideline (NICE). The strength of recommendation of both recommendations was weak and the level of evidence was low to very low. The list for all the recommendations on seeing functions, therapeutic can be found in table 10 in Appendix C.

4.4.1.8 Education (d810 – d829):

Across the 4 included guidelines there were a total of 7 recommendations on education. These different recommendations come out off one guideline (NICE). The strength of recommendation was strong for each recommendation. The list for all the recommendations on education, therapeutic can be found in table 11 in Appendix C.

4.4.1.9 Support and relationships (e3):

Across the 4 included guidelines there were a total of 2 recommendations on support and relationships. These were 2 different recommendations in the same guideline (NICE). The strength of recommendation of both recommendations was strong. The list for all the recommendations on support and relationships, therapeutic can be found in table 12 in Appendix C.

4.4.1.10 Ingestion functions (b510):

Across the 4 included guidelines there were a total of 3 recommendations on ingestion functions. These were 3 different recommendations from the same guideline (Malaysia) and were on different therapeutic topics, namely 2 on Exercise therapy (weak) and 1 on Medication (weak). The level of evidence was level III. The list for all the recommendations on ingestion functions, therapeutic can be found in table 13 in Appendix C.

4.4.1.11 Muscle functions (b730 – b749):

Across the 4 included guidelines there were 2 recommendations on muscle functions. These were 2 different recommendations from the same guideline (Malaysia) and were on different therapeutic topics, namely on Exercise therapy (weak) and on Medication (weak). The list for all the recommendations on muscle functions, therapeutic can be found in table 14 in Appendix C.

4.4.1.12 Procreation function (b660):

Across the 4 included guidelines there were 3 recommendations on procreation functions. These were different recommendations from the same guideline (Malaysia) and these were on different therapeutic topics, namely 1 on Education (strong) and 2 on Medication (weak and strong against). The list for all the recommendations on procreation function, therapeutic can be found in table 15 in Appendix C.

4.4.2 **ICHI: Diagnostic**

4.4.2.1 Fatigue (b4552): "Functions related to susceptibility to fatigue, at any level of exertion."

Across the 4 included guidelines there was a total of 1 recommendation on fatigue and it was a strong recommendation. The list for all the recommendations on fatigue, diagnostic can be found in table 16 in Appendix C.

4.4.2.2 Muscle tone functions (b735): "Functions related to the tension present in the resting muscles and the resistance offered when trying to move the muscles passively."

Across the 4 included guidelines there was a total of 1 recommendation on muscle tone functions and it was a strong recommendation. The list for all the recommendations on muscle tone functions, diagnostic can be found in table 17 in Appendix C.

4.4.2.3 Urinary functions (b610 – b639):

Across the 4 included guidelines there was a total of 1 recommendation on urinary functions and it was a weak recommendation. The list for all the recommendations on urinary functions, diagnostic can be found in table 18 in Appendix C.

4.4.2.4 Mental functions (b1), learning and applying knowledge (d1), general tasks and demands (d2)

Across the 4 included guidelines there were a total of 5 recommendation on mental functions, learning and applying knowledge and general tasks and demands. These were from different guidelines and were on different diagnostic topics, namely 2 on Assessment (strong), and 3 on Testing (mostly level C). The list for all the recommendations on Mental functions, learning and applying knowledge, general tasks and demands, diagnostic can be found in table 19 in Appendix C.

4.4.2.5 Pain (b280 – b289):

Across the 4 included guidelines there was only 1 recommendation on pain and it was a strong recommendation. The list for all the recommendations on pain, diagnostic can be found in table 20 in Appendix C.

4.4.2.6 Mobility (d4):

Across the 4 included guidelines there was only 1 recommendation on mobility and it was a strong recommendation. The list for all the recommendations on mobility, diagnostic can be found in table 21 in Appendix C.

4.4.2.7 Support and relationships (e3):

Across the 4 included guidelines there was only 1 recommendation on support and relationships and it was a consensus recommendation. The list for all the recommendations on support and relationships, diagnostic can be found in table 22.

4.4.2.8 Health services, systems and policies (e580):

Across the 4 included guidelines there was a total of 8 recommendations on health services, systems and policies. These were on differ diagnostic topics, namely 1 on Diagnostic imaging (clinical experience), 2 on Inspection (clinical experience) and 6 on Assessment (consensus). The list for all the recommendations on health services, systems and policies, diagnostic can be found in table 23 in Appendix C.

4.4.2.9 Functions of the cardiovascular, haematological, immunological and respiratory systems (b4):

Across the 4 included guidelines there was a total of 3 recommendations on functions of the cardiovascular, haematological, immunological and respiratory systems. These were on different diagnostic topics, namely 2 on Observation (clinical experience) and 1 on Assessment (clinical experience). The list for all the recommendations on functions of the cardiovascular, haematological, immunological and respiratory systems, diagnostic can be found in table 24 in Appendix C.

4.4.2.10 Health professionals (e355):

Across the 4 included guidelines there was only 1 recommendation on health professionals and it was a strong recommendation. The list for all the recommendations on health professionals, diagnostic can be found in table 25 in Appendix C.

4.4.3 **ICHI: Managing**

4.4.3.1 Fatigue (b4552): "Functions related to susceptibility to fatigue, at any level of exertion."

Across the 4 included guidelines there was a total of 2 recommendations on fatigue. These were on the same managing topic, namely individualised planning (strong). The list for all the recommendations on fatigue, managing can be found in table 26 in Appendix C.

4.4.3.2 Muscle tone functions (b735): "Functions related to the tension present in the resting muscles and the resistance offered when trying to move the muscles passively."

Across the 4 included guidelines there was only 1 recommendation on muscle tone functions and it was a strong recommendation. The list for all the recommendations on muscle tone functions, managing can be found in table 27 in Appendix C.

4.4.3.3 Mental functions (b1), learning and applying knowledge (d1), general tasks and demands (d2)

Across the 4 included guidelines there was only 1 recommendation on mental functions, learning and applying knowledge, general tasks and demands and it was a weak recommendation. The list for all the recommendations on mental functions, learning and applying knowledge, general tasks and demands, managing can be found in table 28 in Appendix C.

4.4.3.4 Pain (b280 – b289):

Across the 4 included guidelines there was only 1 recommendation on pain and it was a strong recommendation. The list for all the recommendations on pain, managing can be found in table 29 in Appendix C.

4.4.3.5 Mobility (d4):

Across the 4 included guidelines there were 2 recommendations on mobility. These were 2 recommendations in the same guideline (NICE) and all on the topic of Individualised planning

(strong). The list for all the recommendations on mobility, managing can be found in table 30 in Appendix C.

4.4.3.6 Support and relationships (e3):

Across the 4 included guidelines there were 4 recommendations on support and relationships. These were 4 recommendations from the same guideline (NICE) and there were 2 managing topics, namely 2 on Collaborating (mostly strong) and 1 on Individualised planning (consensus). The list for all the recommendations on support and relationships, managing can be found in table 31 in Appendix C.

4.4.3.7 Seeing functions (b210):

Across the 4 included guidelines there were 2 recommendations on seeing functions. These were recommendations from different guidelines and were on the topic of Collaborating (strong and consensus). The list for all the recommendations on seeing functions, managing can be found in table 32 in Appendix C.

4.4.3.8 Education (d810 – d829):

Across the 4 included guidelines there was only 1 recommendation on education and it was on the topic of Collaborating (strong). The list for all the recommendations on education, managing can be found in table 33 in Appendix C.

4.4.3.9 Health services, systems and policies (e580):

Across the 4 included guidelines there was a total of 6 recommendations on health services, systems and policies. These were different recommendations from the same guideline (NICE) and there were 1 on the topic of Individualised planning (consensus), 1 on Navigating (strong) and 4 on Collaborating (mostly consensus). The list for all the recommendations on health services, systems and policies, managing can be found in table 34 in Appendix C.

4.4.3.10 Health professionals (e355):

Across the 4 included guidelines there were 2 recommendations on health professionals. These were different recommendations from the same guideline (NICE) and on the same managing topic, namely Collaborating (strong). The list for all the recommendations on health professionals, managing can be found in table 35 in Appendix C.

4.4.3.11 Procreation functions (b660):

Across the 4 included guidelines there were 4 recommendations on procreation functions. These were different recommendations from the same guideline (Spanish) and there were 1 on Individualised planning (clinical experience) and 3 on Prescription (weak and strong). The list for all the recommendations on procreation function, managing can be found in table 36 in Appendix C.

4.4.3.12 Self-care (d5):

Across the 4 included guidelines there was only 1 recommendation on self-care and it was on the topic of Prescription (strong against). The list for all the recommendations on self-care, managing can be found in table 37 in Appendix C.

4.4.3.13 Defecation functions (b525):

Across the 4 included guidelines there was only 1 recommendation on defecation functions and it was on the topic of Individualised planning (weak). The list for all the recommendations on defecation functions, managing can be found in table 38 in Appendix C.

4.4.3.14 Sexual functions (b640):

Across the 4 included guidelines there was only 1 recommendation on sexual functions and it was on the topic of Individualised planning (strong). The list for all the recommendations on sexual functions, managing can be found in table 39 in Appendix C.

5. Discussion

In this study a total of 196 recommendations of 4 different guidelines were coded into one of 18 ICF domains, however a total of 63 recommendations were excluded because the content of the recommendations was not addressing the rehabilitation of MS. Instead these recommendations were related to disease-modifying therapies or the diagnostic process of MS itself. The 18 ICF domains included fatigue, muscle tone functions, urinary functions, mental functions, pain, mobility, seeing functions, education, support and relationships, ingestion functions, defecation functions, sexual functions, muscle functions, procreation functions, structure of brain, health services systems and policies, functions of the cardiovascular system, health professionals and self-care. Of these ICF domains the vast majority where on the functioning level of the ICF framework. Only 2 ICF domains (mobility, self-care) were on the level of activity and participation and 3 ICF domains (support and relationships, health services systems and policies and health professionals) were on the level of support and relationships. An overview of the ICF framework can be found online on the ICF browser (https://apps.who.int/classifications/icfbrowser/).

However there is recent evidence on the effectiveness of rehabilitation in MS on activity and participation levels. According to (Khan & Amatya, 2017) There is "strong" evidence for physical therapy for improved activity and participation, and for exercise-based educational programs for the reduction of patient-reported fatigue and "moderate" evidence for multi-disciplinary rehabilitation for longer-term gains at the levels of activity (disability) and participation, for cognitive-behavior therapy for the treatment of depression, and for information-provision interventions for improved patient knowledge.

Also there is recent evidence on different ICF domains, then there was used in the included guidelines like ‘Hand and Arm use (d445)’, according to Lamers et al., 2016 They concluded that different types of upper limb rehabilitation strategies can improve upper limb function in PwMS.

After analysing the recommendations of the included guidelines we found that (1) the recommendations were only reflecting on the use of certain therapies, without giving any information on dosage, training parameters or progression, and (2) There were no

recommendations on the use and psychometric characteristics of instruments/ questionnaires that help with the inventarisation, analysis and evaluation of problem areas. These factors reduced the usability of these recommendations in the clinical field.

However in our literature search we found the Canadian Physical Activity Guideline (Canadian Society for Exercise Physiology (CSEP) , 2013), in this guideline there was only 1 recommendation, but it had clear parameters and a way of progression to prepare the person with MS. Ultimately this guideline was excluded in this study because the guideline had no definition on the level of evidence, or strength of recommendation. And in the 'Ergotherapierichtlijn Multiple Sclerose', they gave recommendations on the use and psychometric characteristics of different instruments/ questionnaires, however this guideline was excluded because it was written in Dutch.

During the quality assessment of the included guidelines there are some methodological consideration. During the literature search we only included articles written in English, this may have been a limiting factor for the number of guidelines that would be included in this article. In this article the guidelines were assessed on the AGREE II by two appraisers, however according to the instruction manual of the AGREE II instrument, they recommend that each guideline is assessed by at least 2 appraisers and preferably 4 as this will increase the reliability of the assessment. This instruction manual can be found on the 'Welcome to the AGREE Enterprise website'. Retrieved from https://www.agreetrust.org/. And although there are specific criteria on how to rate each item, the AGREE II instrument requires some subjective judgement to score each item, this can bias the results in an over/underscoring of certain items, however when comparing the individual results of the two appraisers no great conflicts (difference >2 were observed).

In the included guidelines there were also different definitions used for the level of evidence, this can explain the potential difference between guidelines. The Malaysian guideline definition for a level I level of evidence was that the Evidence comes from at least one properly randomised controlled trial, where the Spanish and NICE guidelines had an extensive quality assessment to determine the probability that further research is likely to change the confidence in the estimate of effect before grading them. A list of all definitions

of level of evidence can be found in appendix E. And in the definition of the strength of recommendation of the Malaysian guideline they used the 'overall quality of evidence' as one of the aspects for considering the strength of recommendation. This could lead to a potential overestimation (number of strong recommendations) in the Malaysian guideline. In our opinion the Spanish and NICE guidelines had the best definition for their level of evidence, and strength of recommendation, and thus had the lowest risk of an overestimation.

The lists of recommendations on the different ICF domains can be a guide for therapists, managers in hospitals and politicians to make an educated choice on which interventions/ services can be used in the rehabilitation of patients with MS, however adherence to these recommendations may not necessarily lead to the best possible outcome in every case, therefore it is important to understand that it's every healthcare providers responsibility that they manage his/her patient based on the clinical picture presented by the patient and the management options available locally.

We suggest that there should be updates of already existing clinical practise guideline on the rehabilitation of MS, or the formation of new clinical practise guidelines that include recommendations on more ICF domains in total, and more recommendation on an activity/ participation level to improve the applicability of the recommendations in the work field.

This could be further improved by including dosages, training parameters and a way of progression in the formulation of the recommendation and including recommendations on which instruments/questionnaires could be used for the diagnosis/treatment of symptoms of MS.

We would also suggest that all clinical practise guidelines should have an English version, in order to improve the usability for clinicians of other countries as English is the de facto universal language of science. (Drubin & Kellogg, 2012)

6. Conclusion

The design of this article aims to answer the questions of which are the effective evidence-based clinical/service rehabilitation intervention recommendations for Multiple Sclerosis. This was done by searching for recent, high quality clinical practise guidelines, coding the recommendation into the ICF and ICHI framework and formulating a list of all recommendations per ICF category.

In this article a total of 134 recommendations were coded into one of eighteen ICF categories. These were all put into a list per ICF category to give a clear view of what actions are effective and evidence-based for the management of that specific ICF category.

We consider that this article could be a helpful tool for therapists and managers of hospitals to make an educated choice on which interventions/ services can be used in the rehabilitation of patients with MS, however further research and updates/development of new clinical practise guidelines on the rehabilitation of MS is recommended and should be improved with the inclusion of dosages training parameters and a way of progression in the formulation of the recommendations to improve the applicability of the recommendations.

7. Reference list

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Browne, P., Chandraratna, D., Angood, C., Tremlett, H., Baker, C., Taylor, B. V., & Thompson, A. J. . (2014). Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. *Neurology, 83*, 1022–1024.

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Guijarro-Castro, C., Aladro-Benito, Y., Sanchez-Musulim, A., Belen-Caminero, A., Perez Molina, I., Gomez-Moreno, I., . . . Cerezo-Garcia, M. (2017). Face-to-Face or Telematic Cognitive Stimulation in Patients with Multiple Sclerosis and Cognitive Impairment: Why Not Both? *Behav Neurol, 2017*, 5713934. doi:10.1155/2017/5713934

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Wallin, M. T., Culpepper, W. J., Nichols, E., Bhutta, Z. A., Gebrehiwot, T. T., Hay, S. I., … Murray, C. J. L. . (2019). Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. . *The Lancet Neurology, 18(3)*, 269-285.

WHO. (2017). Rehabilitation: key for health in the 21st century. *Rehabilitation 2030: A Call for Action*.

8. Appendix

Appendix A: List of excluded guidelines

Appendix B: Flowchart

Appendix C: Lists of recommendations per ICF domain

Appendix D: A global overview of the amount and type of recommendation across the four guidelines

Appendix E: A detailed view on the individual/ average item/domain scores of the AGREE II

Appendix F: List of definitions level of evidence

Appendix G: List of definitions strength of recommendation

Appendix A: List of excluded guidelines

Excluded Guideline	Source + reason for exclusion
Zephir, Puyade, M., Gueguen, A., Michel, L., Terriou, L., Dive, D., . . . Farge, D. (2019). Indications de l'autogreffe dans la sclérose en plaques : recommandations de la Société francophone de greffe de moelle et de thérapie cellulaire (SFGM-TC) en lien avec la Société francophone de la sclérose en plaques. Bulletin du Cancer, 106(1), 92–101.	Source: Pubmed Excluded: -Article not written in English -Does not address rehabilitation
Marques, V. D., Dos Passos, G. R., Mendes, M. F., Callegaro, D., Lana-Peixoto, M. A., Comini-Frota, E. R., . . . Becker, J. (2018). Brazilian Consensus for the Treatment of Multiple Sclerosis: Brazilian Academy of Neurology and Brazilian Committee on Treatment and Research in Multiple Sclerosis. Arquivos de Neuro-Psiquiatria, 76(8), 539–554.	Source: Pubmed Excluded: -Does not address rehabilitation
Arevalo, O., Riascos, R., Rabiei, P., Kamali, A., & Nelson, F. (2019). Standardizing Magnetic Resonance Imaging Protocols, Requisitions, and Reports in Multiple Sclerosis. Journal of Computer Assisted Tomography, 43(1), 1–12.	Source: Pubmed Excluded: -Does not address rehabilitation
Abreu, P., Pedrosa, R., Sá, M. J., Cerqueira, J., Sousa, L., Da Silva, A. M., . . . Vale, J. (2018). Recomendações e Consensos do Grupo de Estudos de Esclerose Múltipla e da Sociedade Portuguesa de Neurorradiologia sobre Ressonância Magnética na Esclerose Múltipla na Prática Clínica: Parte 1. Acta Médica Portuguesa, 31(5), 281.	Source: Pubmed Excluded: -Does not address rehabilitation
Cianferotti, L., Bertoldo, F., Bischoff-Ferrari, H. A., Bruyere, O., Cooper, C., Cutolo, M., . . . Brandi, M. L. (2017). Vitamin D supplementation in the prevention and management of major chronic diseases not related to mineral homeostasis in adults: research for evidence and a scientific statement from the European society for clinical and economic aspects of osteoporosis and osteoarthritis (ESCEO). Endocrine, 56(2), 245–261.	Source: Pubmed Excluded: -Not related to MS -Does not address rehabilitation
Alifirova, V. M., Boiko, A. N., Vlasov, Y. V., Davydovskaya, M. V., Zakharova, M. N., Malkova, N. A., . . . Shmidt, (2017). Clinical guidelines for the use of dimethyl fumarate in relapsing-remitting multiple sclerosis. Zhurnal nevrologii i psikhiatrii im. S.S. Korsakova, 117(1), 97. h	Source: Pubmed Excluded: -Article not written in English -Does not address rehabilitation
Comini-Frota, E. R., Vasconcelos, C. C. F., & Mendes, M. F. (2017). Guideline for multiple sclerosis treatment in Brazil: Consensus from the Neuroimmunology Scientific Department of the Brazilian Academy of Neurology. Arquivos de Neuro-Psiquiatria, 75(1), 57–65.	Source: Pubmed Excluded: -Does not address rehabilitation
Traboulsee, A., Simon, J., Stone, L., Fisher, E., Jones, D., Malhotra, A., . . . Li, D. (2015). Revised Recommendations of the Consortium of MS Centers Task Force for a Standardized MRI Protocol and Clinical Guidelines for the Diagnosis and Follow-Up of Multiple Sclerosis. American Journal of Neuroradiology, 37(3), 394–401.	Source: Pubmed Excluded: -Does not address rehabilitation
Wattjes MP. (2015). MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis—establishing disease prognosis and monitoring patients. Nature Reviews Neurology, 11(10), 597–606.	Source: Pubmed Excluded: -Does not address rehabilitation
Remes A et al. (2015). Update on Current Care Guideline: Multiple sclerosis. Duodecim, 131(5):500-1	Source: Pubmed Excluded: -Article not written in English
Rovira, À., Wattjes, M. P., Tintoré, M., Tur, C., Yousry, T. A., Sormani, M. P., . . . Montalban, X. (2015). MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis—clinical implementation in the diagnostic process. Nature Reviews Neurology, 11(8), 471–482.	Source: Pubmed Excluded: -Does not address rehabilitation
Cotton, F., Kremer, S., Hannoun, S., Vukusic, S., & Dousset, V. (2015). OFSEP, a nationwide cohort of people with multiple sclerosis: Consensus minimal MRI protocol. Journal of Neuroradiology, 42(3), 133–140.	Source: Pubmed Excluded: -Does not address rehabilitation
Perry, M., Swain, S., Kemmis-Betty, S., & Cooper, P. (2014). Multiple sclerosis: summary of NICE guidance. BMJ, 349(oct08 10), 5701.	Source: Pubmed Included
Broadley, S. A., Barnett, M. H., Boggild, M., Brew, B. J., Butzkueven, H., Heard, R., . . . Willoughby, E. (2014). Therapeutic approaches to disease modifying therapy for multiple sclerosis in adults: An Australian and New Zealand perspective Part 3 Treatment practicalities and recommendations. Journal of Clinical Neuroscience, 21(11), 1857–1865.	Source: Pubmed Excluded: -Does not address rehabilitation
Broadley, S. A., Barnett, M. H., Boggild, M., Brew, B. J., Butzkueven, H., Heard, R., . . . Willoughby, E. (2014b). Therapeutic approaches to disease modifying therapy for multiple sclerosis in adults: An Australian and New Zealand perspective Part 1 Historical and established therapies. Journal of Clinical Neuroscience, 21(11), 1835–1846.	Source: Pubmed Excluded: -Does not address rehabilitation
Broadley, S. A., Barnett, M. H., Boggild, M., Brew, B. J., Butzkueven, H., Heard, R., . . . Willoughby, E. (2014b). Therapeutic approaches to disease modifying therapy for multiple sclerosis in adults: An Australian and New Zealand perspective Part 1 Historical and established therapies. Journal of Clinical Neuroscience, 21(11), 1835–1846.	Source: Pubmed Excluded: -Does not address rehabilitation
Bertolotto, A., Capobianco, M., Amato, M. P., Capello, E., Capra, R., Centonze, D., . . . Malucchi, S. (2013). Guidelines on the clinical use for the detection of neutralizing antibodies	Source: Pubmed Excluded:

(NAbs) to IFN beta in multiple sclerosis therapy: report from the Italian Multiple Sclerosis Study group. Neurological Sciences, 35(2), 307–316.	-Does not address rehabilitation
Giampaolo, D., Bhigjee, A., Retief, C., Isaacs, M., Britz, M., Opperman, D., . . . Van Rensburg, M. (2013). Guideline for the diagnosis and management of multiple sclerosis: A Southern African perspective. South African Medical Journal, 103(9), 670.	Source: Pubmed Excluded: -Does not address rehabilitation
Oreja-Guevara, et al. (2013). Consensus document on spasticity in patients with multiple sclerosis. Grupo de Enfermedades Desmielinizantes de la Sociedad Española de Neurología. Rev Neurol. 16;57(8):359-73	Source: Pubmed Excluded: -Article not written in English -Does not address rehabilitation
Filippi, M., Rocca, M. A., Bastianello, S., Comi, G., Gallo, P., Gallucci, M., . . . De Stefano, N. (2013). Guidelines from The Italian Neurological and Neuroradiological Societies for the use of magnetic resonance imaging in daily life clinical practice of multiple sclerosis patients. Neurological Sciences, 34(12), 2085–2093.	Source: Pubmed Excluded: -Does not address rehabilitation
García-Merino, A., Fernández, Ó., Montalbán, X., De Andrés, C., Oreja-Guevara, C., Rodríguez-Antigüedad, A., & Arbizu, T. (2013). Documento del Grupo de Consenso de la Sociedad Española de Neurología sobre el uso de medicamentos en esclerosis múltiple. Neurología, 28(6), 375–378.	Source: Pubmed Excluded: -Does not address rehabilitation
Krupp, L. B., Tardieu, M., Amato, M. P., Banwell, B., Chitnis, T., Dale, R. C., . . . Wassmer, E. (2013). International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Multiple Sclerosis Journal, 19(10), 1261–1267.	Source: Pubmed Excluded: -Does not address rehabilitation
Yamout, B., Alroughani, R., Al-Jumah, M., Khoury, S., Abouzeid, N., Dahdaleh, M., . . . Bohlega, S. (2013). Consensus guidelines for the diagnosis and treatment of multiple sclerosis. Current Medical Research and Opinion, 29(6), 611–621.	Source: Pubmed Excluded: -Does not address rehabilitation
Shatila, A., Koussa, S., Jabbour, R., Mourad, A., Aouad, A., Sabbagh, G., . . . Tourbah, A. (2013). LSN MS guidelines for the management of multiple sclerosis. Revue Neurologique, 169(12), 950–955.	Source: Pubmed Excluded: -Does not address rehabilitation
Abad P, et al. (2012). LACTRIMS consensus document for the pharmacological treatment of the multiple sclerosis and its clinical variants. Rev Neurol 16;55(12):737-48	Source: Pubmed Excluded: -Article not written in English -Does not address rehabilitation
Kes VB, et al. (2012). Recommendations for diagnosis and management of multiple sclerosis. Acta Clin Croat 51(1):117-35	Source: Pubmed Excluded: -Does not address rehabilitation
Laplaud, D., Bodiguel, E., Bensa, C., Blanc, F., Brassat, D., Magy, L., . . . De Seze, J. (2012). Recommendations for the management of multiple sclerosis relapses. Revue Neurologique, 168(5), 425–433.	Source: Pubmed Excluded: -Does not address rehabilitation
Zéphir, H., Bodiguel, E., Bensa, C., Blanc, F., Laplaud, D., Magy, L., . . . Brassat, D. (2012). Recommendations for a definition of multiple sclerosis in support of early treatment. Revue Neurologique, 168(4), 328–337.	Source: Pubmed Excluded: -Does not address rehabilitation
Ouallet, J., Bodiguel, E., Bensa, C., Blanc, F., Brassat, D., Laplaud, D., . . . Magy, L. (2013). Recommendations for useful serum testing with suspected multiple sclerosis. Revue Neurologique, 169(1), 37–46.	Source: Pubmed Excluded: -Does not address rehabilitation
Ramasubbu R, et al. (2012). The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and select comorbid medical conditions. Ann Clin Psychiatry 24(1):91-109	Source: Pubmed Excluded: -Does not address MS
Zamboni P, et al. (2011). Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound--recommendations for a protocol. Int Angiol 30(6):571-97	Source: Pubmed Excluded: -Does not address rehabilitation
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Scott, T. F., Frohman, E. M., De Seze, J., Gronseth, G. S., & Weinshenker, B. G. (2011). Evidence-based guideline: Clinical evaluation and treatment of transverse myelitis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology, 77(24), 2128–2134.	Source: Pubmed Excluded: -Does not address rehabilitation
Popova NF. (2011). A plan for risk management in the treatment of multiple sclerosis with gilenia (fingolomod). Zh Nevrol Psikhiatr Im S S Korsakova	Source: Pubmed Excluded: -Article not written in English -Does not address rehabilitation
Davydovskaia MV. (2011). A plan for risk management in the treatment of multiple sclerosis with natalizumab. Zh Nevrol Psikhiatr Im S S Korsakova.	Source: Pubmed Excluded:

	-Article not written in English -Does not address rehabilitation
Khachanova NV. (2011). [A plan for risk management in the treatment of multiple sclerosis with movectro (cladribine tablets)]. Zh Nevrol Psikhiatr Im S S Korsakova.	Source: Pubmed Excluded: -Article not written in English -Does not address rehabilitation
Federal service on surveillance in healthcare and social development (Roszdravnadzor). (2011). [Logistics and description of treatment technology (the protocol for using disease modifying drugs--DMD)]. Zh Nevrol Psikhiatr Im S S Korsakova.	Source: Pubmed Excluded: -Article not written in English -Does not address rehabilitation
Federal service on surveillance in healthcare and social development (Roszdravnadzor). (2011). [The technology of treatment of multiple sclerosis with long-term immunomodulating drugs (disease modifying drugs--DMD)--beta-interferons and glatiramer-acetate]. Zh Nevrol Psikhiatr Im S S Korsakova.	Source: Pubmed Excluded: -Article not written in English -Does not address rehabilitation
Ghezzi, A., Grimaldi, L. M. E., Marrosu, M. G., Pozzilli, C., Comi, G., Bertolotto, A., . . . Tedeschi, G. (2011). Natalizumab therapy of multiple sclerosis: recommendations of the Multiple Sclerosis Study Group—Italian Neurological Society. Neurological Sciences, 32(2), 351–358.	Source: Pubmed Excluded: -Does not address rehabilitation
Geurts, J. J. G., Roosendaal, S. D., Calabrese, M., Ciccarelli, O., Agosta, F., Chard, D. T., . . . Barkhof, F. (2011). Consensus recommendations for MS cortical lesion scoring using double inversion recovery MRI. Neurology, 76(5), 418–424.	Source: Pubmed Excluded: -Does not address rehabilitation
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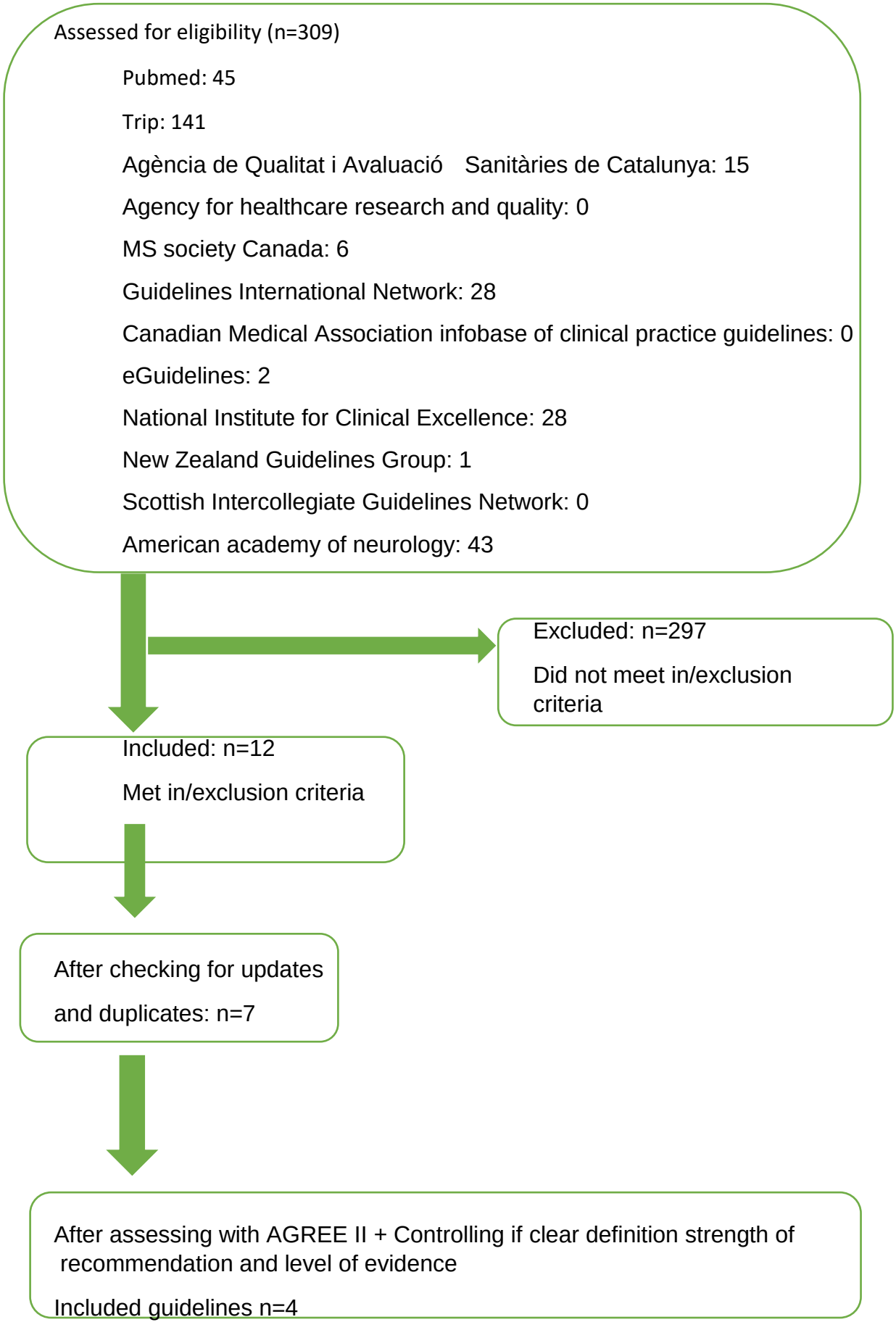
OSTEBA (ES) – Basque Office for Health Technology Assessment. (2009). Análisis de la adecuación de las indicaciones diagnósticas de las siguientes técnicas de aplicación de la RM cerebral: espectroscopia por RM, difusión, perfusión de gadolinio y RM funcional-activación cerebral en el diagnóstico neurológico Avanzado	Source: International Guideline Library Excluded: -Does not address rehabilitation -Not written in English
IQWiG (DE) – Institute for Quality and Efficiency in Health Care. (2014). Addendum zum Auftrag A14-14 (Dimethylfumarat)	Source: International Guideline Library Excluded: -Does not address rehabilitation -Not written in English
NICE guideline. (2014). NICE MS guideline	Source: eGuidelines Excluded: -Does not address rehabilitation
Rashid, Cox, Jackson, McFadden, Merriman and Vernon. (2013). Management of MS in primary care	Source: eGuidelines Excluded: -Does not address rehabilitation
NICE guideline. (2012). Urinary incontinence in neurological disease: assessment and management (CG148)	Source: NICE Excluded: -Does not address rehabilitation -Does not address MS specifically
NICE guideline. (2013). Neuropathic pain in adults: pharmacological management in non-specialist settings	Source: NICE Excluded: -Does not address MS specifically
NICE guideline. (2007). Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management	Source: NICE Excluded: -Does not address MS
NICE guideline. (2018). Dementia: assessment, management and support for people living with dementia and their carers	Source: NICE Excluded: -Does not address MS
NICE guideline. (2018). Renal replacement therapy and conservative management	Source: NICE Excluded: -Does not address MS
NICE guideline. (2006). Obesity prevention	Source: NICE Excluded: -Older than 10 years -Does not address MS
NICE guideline. (2012). Epilepsies: diagnosis and management	Source: NICE Excluded: -Does not address MS
NICE guideline. (2013). Unstable angina and NSTEMI: early management	Source: NICE Excluded: -Does not address MS
NICE guideline. (2013). Falls in older people: assessing risk and prevention	Source: NICE Excluded:

	-Does not address MS
NICE guideline. (2011). Common mental health problems: identification and pathways to care	Source: NICE Excluded: -Does not address MS
NICE guideline. (2016). Autism spectrum disorder in adults: diagnosis and management	Source: NICE Excluded: -Does not address MS
NICE guideline. (2019). Urinary incontinence and pelvic organ prolapse in women: management	Source: NICE Excluded: -Does not address MS
NICE guideline. (2011). Service user experience in adult mental health: improving the experience of care for people using adult NHS mental health services	Source: NICE Excluded: -Does not address MS
NICE guideline. (2009). Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence	Source: NICE Excluded: -Does not address MS
NICE guideline. (2007). Drug misuse in over 16s: psychosocial interventions	Source: NICE Excluded: -Does not address MS
NICE guideline. (2009). Depression in adults with a chronic physical health problem: recognition and management	Source: NICE Excluded: -Does not address MS
NICE guideline. (2011). Coexisting severe mental illness (psychosis) and substance misuse: assessment and management in healthcare settings	Source: NICE Excluded: -Does not address MS
NICE guideline. (2011). Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence	Source: NICE Excluded: -Does not address MS
NICE guideline. (2005). Obsessive-compulsive disorder and body dysmorphic disorder: treatment	Source: NICE Excluded: -Does not address MS
NICE guideline. (2008). Inducing labour	Source: NICE Excluded: -Does not address MS
NICE guideline. (2011). Colorectal cancer prevention: colonoscopic surveillance in adults with ulcerative colitis, Crohn's disease or adenomas	Source: NICE Excluded: -Does not address MS
NICE guideline. (2003). Multiple sclerosis: Management of multiple sclerosis in primary and secondary care	Source: NICE Excluded: -Older than 10 years
NICE guideline. (2019). Antenatal care for uncomplicated pregnancies	Source: NICE Excluded: -Does not address MS
NICE guideline. (2012). Neutropenic sepsis: prevention and management in people with cancer	Source: NICE Excluded: -Does not address MS
NICE guideline. (2014). Transient loss of consciousness ('blackouts') in over 16s	Source: NICE Excluded: -Does not address MS
NICE guideline. (2013). Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease	Source: NICE Excluded: -Does not address MS
New Zealand Guidelines Group. (2018). Hepatitis B	Source: New Zealand Guidelines Group Excluded: -Does not address MS
American Academy of Neurology. (2014). Summary of Evidence-Based Guideline: Complementary and Alternative Medicine in Multiple Sclerosis	Source: American Academy of Neurology Excluded: -Does not address rehabilitation
American Academy of Neurology. (2018). Practice Guideline Recommendations Summary: Disease-modifying Therapies for Adults with Multiple Sclerosis	Source: American Academy of Neurology

	Excluded: -Does not address rehabilitation
American Academy of Neurology. (2018). Stopping DMTs for MS	Source: American Academy of Neurology Excluded: -Does not address rehabilitation
American Academy of Neurology. (2018). Starting DMTs for MS	Source: American Academy of Neurology Excluded: -Does not address rehabilitation
American Academy of Neurology. (2018). Switching DMTs for MS	Source: American Academy of Neurology Excluded: -Does not address rehabilitation
American Academy of Neurology. (2018). Complexity of MS Management	Source: American Academy of Neurology Excluded: -Does not address rehabilitation
American Academy of Neurology. (2002). Disease Modifying Therapies in Multiple Sclerosis	Source: American Academy of Neurology Excluded: -Does not address rehabilitation
American Academy of Neurology. (2003). The Use of Mitoxantrone (Novantrone) for the Treatment of Multiple Sclerosis	Source: American Academy of Neurology Excluded: -Does not address rehabilitation
American Academy of Neurology. (2002). Immunization and Multiple Sclerosis: A Summary of Published Evidence and Recommendations	Source: American Academy of Neurology Excluded: -Does not address rehabilitation
American Academy of Neurology. (2010). Evidence Report: The Efficacy and Safety of Mitoxantrone (Novantrone) in the Treatment of Multiple Sclerosis	Source: American Academy of Neurology Excluded: -Does not address rehabilitation
American Academy of Neurology. (2018). Practice Guideline Recommendations Summary: Disease-modifying Therapies for Adults with Multiple Sclerosis	Source: American Academy of Neurology Excluded: -Does not address rehabilitation
American Academy of Neurology. (2008). The Usefulness of Evoked Potentials in Identifying Clinically Silent Lesions in Patients with Suspected Multiple Sclerosis	Source: American Academy of Neurology Excluded: -Does not address rehabilitation
American Academy of Neurology. (2014). Systematic Review: Efficacy and Safety of Medical Marijuana in Selected Neurologic Disorders	Source: American Academy of Neurology Excluded: -Does not address rehabilitation
American Academy of Neurology. (2011). Update: Plasmapheresis in Neurologic Disorders	Source: American Academy of Neurology Excluded: -Does not address rehabilitation
American Academy of Neurology. (2011). Clinical Evaluation and Treatment of Transverse Myelitis	Source: American Academy of Neurology Excluded: -Does not address MS

Appendix B: Flowchart



Appendix C: Lists of recommendations per ICF domain

Table 4: List of recommendations for Fatigue, therapeutic

	Strength of recommendation	Level of evidence	Guideline
Medication			
Offer amantadine to treat fatigue in people with MS.	strong	moderate	**2**
In MS patients who experience symptoms of fatigue, treatment with amantadine is recommended.	Weak	Low	**1**
In multiple sclerosis patients with fatigue: amantadine may be offered	Weak	level I	**3**
In MS patients with symptoms of fatigue, It is NOT recommended to start treatment with methylphenidate.	weak against	/	1
In MS patients who experience symptoms of fatigue, treatment with modafinil is NOT recommended.	strong against	Low	1
In MS patients who experience symptoms of fatigue, treatment with pemoline is NOT recommended.	strong against	Low	1
Do not use vitamin b12 injections to treat fatigue in people with MS	Strong against	low to very low	2
Education			
Explain that MS-related fatigue may be precipitated by heat, overexertion and stress or may be related to the time of day.	strong	low to very low	2
Advise people that aerobic, balance and stretching exercises including yoga may be helpful in treating MS-related fatigue.	strong	Low to very low	2
Exercise training			
Help the person with MS continue to exercise, for example by referring them to exercise referral schemes.	strong	low to very low	2
If more than one of the interventions recommended for mobility or fatigue are suitable, offer treatment based on which the person prefers and whether they can continue the activity when the treatment programme ends.	strong	low to very low	2
In multiple sclerosis patients with fatigue: energy conservation management should be used	strong	level I	**3**
In patients with MS who experience fatigue symptoms, it is recommended to consider performing energy-saving rehabilitation strategies.	Weak	very low	**1**
Consider mindfulness-based training, cognitive behavioural therapy or fatigue management for treating MS-related fatigue.	Weak	low to very low	**2**
Consider supervised exercise programmes involving moderate progressive resistance training and aerobic exercise to treat people with MS who have mobility problems and/or fatigue.	Weak	low to very low	2
Consider a comprehensive programme of aerobic and moderate progressive resistance activity combined with cognitive behavioural techniques for fatigue in people with MS with moderately impaired mobility (an EDSS score of greater than or equal to 4).	weak	low to very low	2
Consider vestibular rehabilitation for people with MS who have fatigue or mobility problems associated with limited standing balance.	weak	low to very low	2
Consider supervised exercise programmes involving moderate progressive resistance training and aerobic exercise to treat people with MS who have mobility problems and/or fatigue.	Weak	low to very low	2

Table 5: List of recommendations Muscle tone functions, therapeutic

	Strength of recommendation	Level of evidence	Guideline
Observation			
It is important to evaluate the beneficial and/or harmful effects of spasticity from a functional viewpoint as it is not always a disabling symptom/sign. In some cases, spasticity may have beneficial effects and improve the functional status of the patient.	clinical experience	/	1
Medication			
In MS patients who experience spasticity, treatment with oral baclofen is recommended.	weak	low	**1**
Consider baclofen or gabapentins as a first-line drug to treat spasticity in MS depending on contraindications and the person's comorbidities and preferences. If the person with MS cannot tolerate one of these drugs consider switching to the other	weak	low to very low	**2**
In patients with MS and spasticity in treatment with baclofen without clinical improvement or poor tolerance, it is recommended to add or switch to tizanidine.	weak	very low	**1**
Consider tizanidine or dantrolene as a second-line option to treat spasticity in people with MS.	weak	low to very low	**2**
In MS patients who experience spasticity, treatment with gabapentin is recommended.	weak	low	**1**
Consider a combination of baclofen and gabapentin for people with MS if: o individual drugs do not provide adequate relief or o side effects from individual drugs prohibit the dose being increased.	weak	low to very low	**2**
In patients with MS and spasticity where no clinical improvement is seen with oral baclofen or with tizanidine, treatment with diazepam is recommended.	weak	low	1
In MS patients with spasticity where no clinical improvement is seen or with a poor tolerance to the other treatments, treatment with nabiximols is recommended. Discontinuation must be considered if no short-term symptom improvement is seen.	strong	moderate to high	1
In patients with MS and severe spasticity with no response to oral drugs, it is recommended to consider the implantation of an intrathecal baclofen infusion pump. Prior to its indication, its efficacy must evaluated using an intrathecal baclofen test and, in patients with walking ability, this test must be performed by an external pump, that allows the functional performance of the patient to be evaluated.	weak	very low	1
In patients with MS associated with focal spasticity, it is recommended to consider local application of botulinum toxin A.	weak	low	1
Encourage people with MS to manage their own spasticity symptoms by explaining how doses of drugs can be adjusted within agreed limits.	strong	Low to very low	2
Ensure that the person with MS: o has tried the drug at an optimal dose, or the maximum dose they can tolerate. o stops the drug if there is no benefit at the maximum tolerated dose . o has their drug treatment reviewed at least annually once the optimal dose has been reached.	strong	low to very low	2
Consider benzodiazepines as a third-line option to treat spasticity in MS and be aware of their potential benefit in treating nocturnal spasms.	weak	low to very low	2

Do not offer Sativexv to treat spasticity in people with MS because it is not a cost effective treatment.	strong against	moderate to very low	2
Exercise training			
Physiotherapy (passive or active exercise and stretching of spastic muscles), either alone or in combination with other recommended antispastic treatments, can enhance the management of spasticity in patients with MS.	weak	moderate	1
In multiple sclerosis (MS) patients with disabling spasticity: non-pharmacological interventions may be offered as initial treatment, pharmacological intervention may be offered in severe spasticity refractory to non-pharmacological management orthopaedic and neurosurgical procedures may be offered for extreme spasticity, when conservative management fails	weak	level III	3

Table 6: List of recommendations Urinary functions, therapeutic

	Strength of recommendation	**Level of evidence**	**Guideline**
Medication			
In MS patients who experience bladder dysfunction and nycturia treatment with desmopressin is recommended.	weak	low	**1**
In multiple sclerosis, the following medication may be considered: desmopressin for nocturnal diuresis refractory to conservative measures.	weak	Level I	**3**
In MS patients who experience bladder dysfunction (urge incontinence) treatment with oxybutynin is recommended.	weak	low	1
In multiple sclerosis, the following medication may be considered: anti-cholinergics for frequency and urge incontinence.	weak	Level I	3
In multiple sclerosis, the following medication may be considered: alpha blockers for high post-voiding residual volume and urinary retention.	weak	Level III	3
In multiple sclerosis, the following medication may be considered: botulinum toxin type A intravesical injection for urinary incontinence refractory to conservative measures.	weak	Level I	3
Neuromodulation may be considered for the treatment of severe detrussor overactivity refractory to conservative treatment in multiple sclerosis (MS).	weak	Level II-3, III	3
In MS patients who experience bladder dysfunction (urge incontinence), it is recommended to consider treatment with tolterodine.	clinical experience	/	1
Exercise training			
In MS patients who experience bladder dysfunction it is recommended to evaluate the use of pelvic floor rehabilitation.	clinical experience	low to very low	1
Patients candidate for intermittent bladder catheterisation must receive an adequate training in the technique.	Clinical experience	/	1
Surgical			
In multiple sclerosis patients with bladder dysfunction: clean intermittent catheterisation 4 - 6 hourly should be advised in those with high post void residual volume (>100 ml).	strong	Level III	**3**
In multiple sclerosis patients with bladder dysfunction: suprapubic catheterisation is preferred in those with severe refractory urinary symptoms not responding to conservative management	strong	Level III	3
It is recommended to consider the possibility of performing intermittent bladder catheterisation in MS patients who experience bladder dysfunction with increased residual volume.	clinical experience	/	**1**
Bladder augmentation surgery or urinary diversion may be offered in the treatment of severe detrussor overactivity refractory to conservative treatment in MS	weak	Level II-3, III	3

Education			
In multiple sclerosis patients with bladder dysfunction: fluid management, avoidance of caffeinated beverages, timed voiding and pelvic floor muscles exercises may be offered as initial management.	weak	level III	3

Table 7: List of recommendations mental functions, therapeutic

	Strength of recommendation	**Level of evidence**	**Guideline**
Medication			
Consider amitriptylinez to treat emotional lability in people with MS.	Weak	Very low	2
Dextromethorphan/quinidine may be considered in the treatment of multiple sclerosis with pseudobulbar affect	Weak	Level I	**3**
For pseudobulbar affect, a combination of dextromethorphan and quinidine may be considered	Level C	II,III	**4**
In MS patients the use of interferon beta is NOT recommended for the treatment of cognitive deficit.	weak against	low to very low	1
In MS patients the use of glatiramer acetate is NOT recommended for the treatment of cognitive deficit.	weak against	low to very low	1
In MS patients, the use of rivastigmine is NOT recommended for the treatment of cognitive deficit.	strong against	low	1
In MS patients the use of memantine is NOT recommended for the treatment of cognitive deficit.	strong against	very low	1
In MS patients the use of donepezil is not recommended for the treatment of cognitive deficit.	strong against	low	1
Evidence is insufficient to determine the psychiatric effects in individuals with MS of disease-modifying and symptomatic therapies and corticosteroids; risk factors for suicide; and treatment of psychotic disorders	Level U	unproven	4
Exercise training			
In MS patients experiencing cognitive impairment it is recommended to consider performing cognitive rehabilitation addressing the deficit.	weak	moderate to low	**1**
Antidepressants, cognitive behavioural therapy, mindfulness-based intervention or stress management may be offered in multiple sclerosis with depression	weak	level I, II-3	**3**
Clinicians may consider a telephone-administered cognitive behavioral therapy program for treat- ing depressive symptoms	level C	II,III	4
Although pharmacologic and nonpharmacologic therapies are widely used to treat depressive and anxiety disorders in individuals with MS, evidence is insufficient to support/refute the use of the antidepressants and individual and group therapies reviewed herein	level U	unproven	4

Table 8: List of recommendations pain, therapeutic

	Strength of recommendation	**Level of evidence**	**Guideline**
Medication			
In MS patients who present neuropathic pain, treatment with amitriptyline is recommended.	weak	/	**1**
Anticonvulsants or antidepressants may be offered for central neuropathic pain in multiple sclerosis.	weak	level II-2, III	**3**
In MS patients with neuropathic pain, treatment with gabapentin is recommended	weak	very low	1

In MS patients experiencing neuropathic pain, treatment with carbamazepine is recommended.	weak	/	1
In MS patients experiencing neuropathic pain, treatment with pregabalin is recommended.	weak	very low	1

Table 9: List of recommendations mobility, therapeutic

	Strength of recommendation	Level of evidence	Guideline
Medication			
In MS patients with walking impairment, treatment with dalfampridine is recommended provided the current indications established by health authorities are met. Discontinuation must be considered if no shortterm symptom improvement is seen.	strong	moderate to low	**1**
Do not use fampridine to treat lack of mobility in people with MS because it is not a cost effective treatment.	strong against	low to very low	**2**
Exercise training			
Encourage people with MS to keep exercising after treatment programmes end for longer term benefits.	strong	low to very low	2
Consider supervised exercise programmes involving moderate progressive resistance training and aerobic exercise to treat people with MS who have mobility problems and/or fatigue.	weak	low to very low	2
Consider vestibular rehabilitation for people with MS who have fatigue or mobility problems associated with limited standing balance.	weak	low to very low	2

Table 10: List of recommendations seeing functions, therapeutic

	Strength of recommendation	Level of evidence	Guideline
Medication			
Consider gabapentin as a first line drug to treat oscillopsia in people with MS.	weak	very low	2
Consider memantine as the second-line treatment for oscillopsia in people with MS.	weak	very low	2

Table 11: List of recommendations education, therapeutic

	Strength of recommendation	Level of evidence	Guideline
Education			
The consultant neurologist should ensure that people with MS and, with their agreement their family members or carers, are offered oral and written information at the time of diagnosis. This should include, but not be limited to, information about: - what MS is -treatments, including disease-modifying therapies symptom management how support groups, local services, social services and national charities are organised and how to get in touch with them legal requirements such as notifying the Driver and Vehicle Licensing Agency (DVLA) and legal rights including social care, employment rights and benefits.	strong	/	2
Review information, support and social care needs regularly. Continue to offer information and support to people with MS or their family members or carers even if this has been declined previously.	strong	/	2

Explain to people with MS that the possible causes of symptom changes include: o another illness such as an infection o further relapse o change of disease status (for example progression).	strong	/	2
Talk to people with MS and their family members or carers about the possibility that the condition might lead to cognitive problems.	strong	/	2
Discuss the benefits and risks of steroids with the person with MS, taking into account the effect of the relapse on the person's ability to perform their usual tasks and their wellbeing.	strong	/	2
Explain the potential complications of high-dose steroids, for example temporary effects on mental health (such as depression, confusion and agitation) and worsening of blood glucose control in people with diabetes.	strong	/	2
Give the person with MS and their family members or carers (as appropriate) information that they can take away about side effects of high-dose steroids in a format that is appropriate for them.	strong	/	2

Table 12: List of recommendations support and relationships, therapeutic

	Strength of recommendation	Level of evidence	Guideline
Education			
Discuss with the person with MS and their family members or carers whether they have social care needs and if so refer them to social services for assessment. Ensure the needs of children of people with MS are addressed.	strong	/	2
Explain that a relapse of MS may have short-term effects on cognitive function.	strong	/	2

Table 13: List of recommendations ingestion functions, therapeutic

	Strength of recommendation	**Level of evidence**	**Guideline**
Exercise therapy			
Dysphagia therapy may be offered in multiple sclerosis (MS) with swallowing difficulty	weak	level III	3
Speech therapy interventions maybe offered in multiple sclerosis with speech difficulty	weak	Level III	3
Medication			
Botulinum toxin A injection may be offered in dysphagic MS patients with upper oesophageal sphincter hyperactivity.	weak	level III	3

Table 14: List of recommendations muscle functions, therapeutic

	Strength of recommendation	**Level of evidence**	**Guideline**
Exercise therapy			
In MS patients with weakness and paralysis resulting in abnormal gait pattern, physiotherapy intervention, use of walking aids and pharmacological treatment may be offered.	weak	level III	3
Medication			
Carbamazepine, gabapentin or pregabalin may be used in multiple sclerosis with paroxysmal symptoms	weak	level II-3, III	3

Table 15: List of recommendations on procreation function

	Strength of recommendation	**Level of evidence**	**Guideline**
Education			
Pre-pregnancy counselling should be given to women with multiple sclerosis (MS) in the childbearing age	strong	level III	3
Medication			
Steroids should be avoided in the first trimester of pregnancy of MS patients; however the benefit and risk need to be carefully assessed.	strong against	level III, II-2	3
Methylprednisolone may be offered to MS patients with acute relapse in second and third trimesters.	weak	level III	3

Table 16: List of recommendations on fatigue, diagnostic

	Strength of recommendation	Level of evidence	Guideline
Assessment			
Assess and offer treatment to people with MS who have fatigue for anxiety, depression, difficulty in sleeping, and any potential medical problems such as anaemia or thyroid disease	strong	low to very low	2

Table 17: List of recommendations on muscle tone functions, diagnostic

	Strength of recommendation	**Level of evidence**	**Guideline**
Assessment			
In people with MS assess and offer treatment for factors that may aggravate spasticity such as constipation, urinary tract or other infections, inappropriately fitted mobility aids, pressure ulcers, posture and pain.	strong	low to very low	2

Table 18: List of recommendations on urinary functions, diagnostic

	Strength of recommendation	Level of evidence	Guideline
Assessment			
Bladder diary, urine analysis and culture, and post void residual volume should be performed in patients with multiple sclerosis and symptoms of bladder dysfunction. ¡ Ultrasound kidney-urether-bladder and video-urodynamic studies may be considered in those with severe refractory symptoms.	weak	level III	3

Table 19: List of recommendations on mental functions, learning and applying knowledge, general tasks and demands, diagnostic

	Strength of recommendation	**Level of evidence**	**Guideline**
Assessment			
Be aware that the symptoms of MS can include cognitive problems, including memory problems that the person may not immediately recognise or associate with their MS.	strong	low to very low	2
Be aware that anxiety, depression, difficulty in sleeping and fatigue can impact on cognitive problems. If a person with MS experiences these symptoms and has problems with memory and cognition, offer them an assessment and treatment	strong	low to very low	2
Testing			
Clinicians may consider using the Center for Neurologic Study Emotional Lability Scale to screen for pseudobulbar affect.	level C	II, III	4

Clinicians may consider the Beck Depression Inventory and a 2-question tool to screen for depressive disorders and the General Health Questionnaire to screen for broadly defined emotional disturbances	level C	II, III	4
Evidence is insufficient to support/refute the use of other screening tools, the possibility that somatic/neurovegetative symptoms affect these tools' accuracy, or the use of diagnostic instruments or clinical evaluation procedures for identifying psychiatric disorders in MS	level U	unproven	4

Table 20: List of recommendation on pain, diagnostic

	Strength of recommendation	**Level of evidence**	**Guideline**
Assessment			
Be aware that musculoskeletal pain is common in people with MS and is usually secondary to problems with mobility and posture. Assess musculoskeletal pain, offer treatment to the person and refer them as appropriate.	strong	low to very low	2

Table 21: List of recommendations on mobility, diagnostic

	Strength of recommendation	Level of evidence	Guideline
Assessment			
Ensure people with MS and mobility problems have access to an assessment to establish individual goals and discuss ways in which to achieve them. This would usually involve rehabilitation specialists and physiotherapists with expertise in MS.	strong	low to very low	2

Table 22: List of recommendations on support and relationships, diagnostic

	Strength of recommendation	**Level of evidence**	**Guideline**
Assessment			
Identify whether the person with MS having a relapse or exacerbation needs additional symptom management or rehabilitation.	Consensus	/	2

Table 23: List of recommendations on health services, systems and policies, diagnostic

	Strength of recommendation	**Level of evidence**	**Guideline**
Diagnostic imaging			
After treatment with natalizumab has commenced, periodic controls (clinical and MRI) are required to identify the signs of development of progressive multifocal leukoencephalopathy.	clinical experience	/	1
Assessment			
Ensure all people with MS have a comprehensive review of all aspects of their care once a year.	Consensus	/	2
Ensure the comprehensive review is carried out by healthcare professionals with expertise in MS and its complications. Involve different healthcare professionals with expertise in specific areas of the review if needed.	Consensus	/	2

Tailor the comprehensive review to the needs of the person with MS assessing: MS symptoms o mobility and balance including falls o need for mobility aids including wheelchair assessment o use of arms and hands o muscle spasms and stiffness o tremor bladder (see Urinary incontinence in neurological disease NICE clinical guideline 148), bowel (see Faecal incontinence NICE clinical guideline 49) and sexual function o sensory symptoms and pain o speech and swallowing (see Nutrition support in adults NICE clinical guideline 32) o vision o cognitive symptoms o fatigue o depression (see Depression in adults with chronic physical health problems NICE clinical guideline 91) and anxiety (see Generalised anxiety disorder and panic disorder NICE clinical guideline 113) o sleep o respiratory function. MS disease course o relapses in last year. General health o weight o smoking, alcohol and recreational drugs o exercise o access to routine health screening and contraception o care of other chronic conditions. Social activity and participation o family and social circumstances o driving and access to transport o employment o access to daily activities and leisure. Care and carers o personal care needs o social care needs o access to adaptations and equipment at home.	Consensus	/	2
Ensure people with MS are offered a medication review in line with Medicines adherence (NICE clinical guideline 76).	Consensus	/	2
Ensure people with MS have their bone health regularly assessed and reviewed in line with Osteoporosis: assessing the risk of fragility fracture (NICE clinical guideline 146).	Consensus	/	2
Inspection			
Check people with MS and severely reduced mobility at every contact for areas at risk of pressure ulcers (see the Pressure ulcers NICE clinical guideline 179).	Consensus	/	2
Do not routinely diagnose a relapse of MS if symptoms are present for more than 3 months.	Consensus	/	2

Table 24: List of resommendations on fatigue, managing

	Strength of recommendation	Level of evidence	Guideline
Individualized planning			
Help the person with MS continue to exercise, for example by referring them to exercise referral schemes.	strong	low to very low	2
If more than one of the interventions recommended for mobility or fatigue are suitable, offer treatment based on which the person prefers and whether they can continue the activity when the treatment programme ends.	strong	low to very low	2

Table 25: List of recommendations on functions of the cardiovascular, haematological, immunological and respiratory systems, diagnostic

	Strength of recommendation	Level of evidence	Guideline
Observation			
Due to eventual involvement of the heart rhythm, it is recommended to follow the monitoring guidelines established by the European Medicines Agency after administration of the first dose of fingolimod.	clinical experience	/	1
Mitoxantrone must be administered in patients with a minimum ventricular ejection fraction of 50% and ultrasound monitoring of left ventricular function is required during treatment and subsequently for a period of several years.	clinical experience	/	1
Assessment			
Patients treated with mitoxantrone must undergo periodic haematological controls during treatment and subsequently for a period of several years.	clinical experience	/	1

Table 26: List of recommendations on health professionals, diagnostic

	Strength of recommendation	Level of evidence	Guideline
Assessment			
Offer the person with MS a face-to-face follow-up appointment with a healthcare professional with expertise in MS to take place within 6 weeks of diagnosis.	strong	/	2

Table 27: List of recommendations on muscle tone functions, managing

	Strength of recommendation	Level of evidence	Guideline
Collaborating			
If spasticity cannot be managed with pharmacological treatments, refer the person to specialist spasticty services.	strong	low to very low	2

Table 28: List of recommendations on mental functions, learning and applying knowledge, general tasks and demands, managing

	Strength of recommendation	Level of evidence	Guideline
Collaborating			
Consider referring people with MS and persisting memory or cognitive problems to both an occupational therapist and a neuropsychologist to assess and manage these symptoms.	weak	low to very low	2

Table 29: List of recommendations on pain, managing

	Strength of recommendation	Level of evidence	Guideline
Collaborating			
Treat neuropathic pain in people with MS according to Neuropathic pain – pharmacological management (NICE clinical guideline 173) and refer to pain services if appropriate.	strong	low to very low	2

Table 30: List of recommendations on mobility, managing

	Strength of recommendation	Level of evidence	Guideline
Individualized planning			
Help the person with MS continue to exercise, for example by referring them to exercise referral schemes.	strong	low to very low	2
If more than one of the interventions recommended for mobility or fatigue are suitable, offer treatment based on which the person prefers and whether they can continue the activity when the treatment programme ends.	strong	low to very low	2

Table 31: List of recommendations on support and relationships, managing

	Strength of recommendation	Level of evidence	Guideline
Collaborating			
Ensure people with MS and their family members or carers have a management plan that includes who to contact if their symptoms change significantly.	strong	/	2
When appropriate, explain to the person with MS (and their family members or carers if the person wishes) about advance care planning and power of attorney.	strong	/	2
Identify whether the person having a relapse of MS or their family members or carers have social care needs and if so refer them to social services for assessment.	Consensus	/	2
Individualized planning			
Offer inpatient treatment to the person having a relapse of MS if their relapse is severe or if it is difficult to meet their medical and social care needs at home.	Consensus	/	2

Table 32: List of recommendations on seeing functions, managing

	Strength of recommendation	Level of evidence	Guideline
Collaborating			
Refer the person with MS for specialist advice if there is no improvement of oscillopsia after treatment with gabapentin and memantine or side effects prevent continued use.	strong	very low	2
All patients with isolated optic neuritis should be referred to an ophthalmologist/neurologist for further assessment.	consensus	level III	3

Table 33: List of recommendations on education, managing

	Strength of recommendation	Level of evidence	Guideline(s)
Collaborating			
Non-specialists should discuss a person's diagnosis of relapse and whether to offer steroids with a healthcare professional with expertise in MS because not all relapses need treating with steroids.	strong	low to very low	2

Table 34: List of recommendations on health services, systems and policies, managing

	Strength of recommendation	Level of evidence	Guideline
Individualized planning			
Determine how often the person with MS will need to be seen based on: o their needs, and those of their family and carers and of the frequency of visits needed for different types of treatment (such as review of disease-modifiying therapies, rehabilitation and symptom management).	Consensus	/	2
Collaborating			
Refer people with MS to palliative care services for symptom control and for end of life care when appropriate.	weak	/	2
Refer any issues identified during the review of the person with MS to members of the MS multidisciplinary team and other appropriate teams so that they can be managed.	Consensus	/	2
Discuss the care provided by carers and care workers as part of the person's care plan. Ensure carers know about their right to access a local authority carer's assessment and how to apply for one.	Consensus	/	2
Ensure that the MS multidisciplinary team is told that the person is being treated for relapse, because relapse frequency may influence which disease-modifying therapies are chosen and whether they need to be changed.	Consensus	/	2
Navigating			
Develop local guidance and pathways for timely treatment of relapses of MS. Ensure follow-up is included in the guidance and pathway.	strong	low to very low	2

Table 35: List of recommendations on health professionals, managing

	Strength of recommendation	Level of evidence	Guideline
Collaborating			
Care for people with MS using a coordinated multidisciplinary approach. Involve professionals who can best meet the needs of the person with MS and who have expertise in managing MS including: consultant neurologists MS nurses physiotherapists and occupational therapists speech and language therapists, psychologists, dietitians, social care and continence specialists	strong	very low to low	2
Offer the person with MS an appropriate single point of contact to coordinate care and help them access services.	strong	very low to low	2

Table 36: List of recommendations on procretion function, managing

	Strength of recommendation	Level of evidence	Guideline
Individualized planning			
Adequate pregnancy planning is essential to minimise the risks in MS patients.	clinical experience	/	1
Prescripton			
The early start of immunomodulatory treatment after delivery should be considered in women with a high disease activity prior to or during pregnancy.	weak	low	1
It is recommended to discontinue immunomodulatory drugs when a patient states her wish for pregnancy	weak	low	1
It is recommended NOT to start immunomodulatory treatment (interferon beta or glatiramer acetate) during pregnancy in patients with MS	strong	low	1

Table 37: List of recommendations on self-care, managing

	Strength of recommendation	Level of evidence	Guideline
Prescription			
Do not give people with MS a supply of steroids to self- administer at home for future relapses.	strong against	low to very low	2

Table 38: List of recommendations on defecation functions, managing

	Strength of recommendation	Level of evidence	Guideline
Individualized planning			
Bowel management programme may be offered in multiple sclerosis patients with bowel dysfunction.	weak	level I, III	3

Table 39: List of recommendations on sexual functions

	Strength of recommendation	Level of evidence	Guideline
Individualized planning			
Sexual dysfunction in multiple sclerosis (MS) should be enquired and addressed. Management strategies may be offered to provide symptomatic relief and improve the quality of life of MS patients.	strong	level III	3

Appendix D: A global overview of the amount and type of recommendation across the four guidelines

Table 40: A global overview of the amount and type of recommendation across the four guidelines

Domain	Strong	Weak	Consensus	Strong against	Weak against	Consensus-based against
Muscle tone functions	5	12	1	1		
Muscle functions		2				
Mobility	5	2		1		
Fatigue	9	8		2	1	
Pain	2	5				
Education	8					
Mental functions	2	9	3	3	2	
Support and relationships	4		3			
Urinary functions	2	10	4			
Seeing functions	1	2	1			
Ingestion functions		3				
Defecation functions		1				
Sexual functions	1					
Procreation functions	2	3	1	1		
Functions of the cardio-vascular, haematological, immunological and res-piratory systems			3			
Health services, systems and policies	1	1	12			
Health professionals	3					
Self-care				1		

Appendix E

Average item scores on the AGREE II

		Spanish clinical practice guideline on the management of people with multiple sclerosis (2012)	Multiple sclerosis: Management of multiple sclerosis in primary and secondary care (NICE 2014)	Management of multiple sclerosis (2015 Malaysia)	Canadian Physical Activity Guidelines for adults with Multiple Sclerosis (2011)	Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS (2014)	Recommendations for the detection and therapeutic management of cognitive impairment in multiple sclerosis (2012)	Summary of comprehensive systematic review: Rehabilitation in multiple sclerosis (2015)
Domain 1	1	7	7	7	7	7	7	7
	2	7	7	7	7	7	6,5	7
	3	7	7	7	7	7	7	7
Domain 2	4	7	6	5,5	7	5,5	6,5	7
	5	7	5,5	4	7	1,5	6,5	1
	6	7	7	7	6	6,5	1,5	7
Domain 3	7	6	7	7	7	7	7	7
	8	5	6,5	6,5	7	7	4	6,5
	9	6	7	4,5	7	4,5	5,5	6
	10	7	5,5	4,5	6,5	6,5	6,5	6
	11	6,5	6,5	6	6,5	6,5	5,5	6
	12	7	7	7	7	6	5,5	6
	13	4,5	6	5,5	7	2	5,5	5
	14	7	6	7	7	1,5	1	1
Domain 4	15	7	7	7	7	6,5	6,5	6,5
	16	7	7	6,5	7	6	6,5	6,5
	17	7	6,5	3,5	7	6	6	5
Domain 5	18	5,5	3	5,5	1,5	1	3,5	1,5
	19	5,5	3,5	4	5	1	1	1
	20	6,5	7	4,5	1	1	1	1,5
	21	5,5	4,5	5,5	6,5	1,5	1	1
Domain 6	22	7	1,5	5,5	7	7	7	6
	23	5,5	7	7	7	7	1	6,5
	Total	147,5	138	134,5	145	112,5	109	115

Average AGREE domain scores on each domain of the included guidelines.

Obtained scores		Spanish clinical practice guideline on the management of people with multiple sclerosis (2012)	Multiple sclerosis: Management of multiple sclerosis in primary and secondary care (NICE 2014)	Management of multiple sclerosis (2015 Malaysia)	Canadian Physical Activity Guidelines for adults with Multiple Sclerosis (2011)	Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS (2014)	Recommendations for the detection and therapeutic management of cognitive impairment in multiple sclerosis (2012)	Summary of comprehensive systematic review: Rehabilitation in multiple sclerosis (2015)
Domain 1		42	42	42	42	42	41	42
Domain 2		42	37	33	40	27	29	30
Domain 3		98	103	96	110	82	81	87
Domain 4		42	41	34	42	37	38	36
Domain 5		46	36	39	30	9	13	10
Domain 6		25	17	25	28	28	16	25
Domain score								
Domain 1		100%	100%	100%	100%	100%	97,22%	100%
Domain 2		100%	86,11%	75%	94,44%	58,33%	63,88%	66,66%
Domain 3		85,41%	90,63%	87,50%	97,91%	68,75%	67,71%	73,96%
Domain 4		100%	97,22%	77,77%	100%	86,11%	88,88%	83,33%
Domain 5		79,16%	58,33%	64,58%	45,83%	2,08%	10,42%	4,17%
Domain 6		87,50%	54,17%	87,50%	100%	100%	50%	87,50%

This table shows the average AGREE domain scores on each domain of guidelines found by the search strategy used. The numbers shown in red indicate a percentage <50% on the scaled domain score

Appendix F

Table 41: A list of the definitions of the strength of recommendation of the included guidelines

Spanish clinical practise guideline on the management of people with Multiple Sclerosis (2012)	**Multiple Sclerosis: Management of MS in primary and secondary care (NICE 2014)**	**Management of Multiple Sclerosis (2015 Malaysia)**	**Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS (2014)**
"Strong" recommendations could be made in those cases where, according to the evidence available, the working group was sure that the potential beneficial effects resulting from following the recommendation were greater than the potential harmful effects (strongly in favour) or vice versa, namely that the potential harm outweighed the potential benefits (strongly against). When the information available was not fully reliable in terms of the potential beneficial effects being greater than the potential harmful effects or vice versa, the working group issued "weak" recommendations in favour or against. As such, the adjective strong or weak does not refer to the size of the effect of a given intervention but rather to the degree of reliability in recommending performing a given intervention in the patient or not. Furthermore "good practice points" (√) were issued based on the clinical experience of the coordinating and clinical teams for significant practical issues that should be highlighted and for which there is no supporting scientific evidence.	**Strength of recommendations** Some recommendations can be made with more certainty than others. The Guideline Development Group makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Guideline Development Group is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation). For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also Patient-centred care). **Interventions that must (or must not) be used** We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening. **Interventions that should (or should not) be used – a 'strong' recommendation**	In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations: •Overall quality of evidence •Balance of benefits versus harms •Values and preferences •Resource implications •Equity, feasibility and acceptability For example; A strong recommendation -> is recommended A weak recommendation -> should be considered	**Classification of recommendations** A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)* B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.) C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

	We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most patients. **Interventions that could be used (weak)** We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.		U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

Appendix G

Table 42: A list of the definitions of the level of evidence of the included guidelines

Spanish clinical practise guideline on the management of people with Multiple Sclerosis (2012)	**Multiple Sclerosis: Management of MS in primary and secondary care (NICE 2014)**	**Management of Multiple Sclerosis (2015 Malaysia)**	**Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS (2014)**
The quality of the evidence in the studies for each prioritised outcome was evaluated considering the design, methodological accuracy, consistency and whether the evidence was direct or indirect. To this end, the Grading of recommendation assessment, development and evaluation (GRADE) working group guidelines were also followed. The evidence resulting from RCTs was considered to be of "high quality" and that from observational studies of "low quality". However, there are a number of circumstances that can reduce the quality of RCTs or increase that of observational studies. Thus, the quality of RCTs decreased on the basis of design or performance limitations, inconsistent results, lack of direct scientific evidence, lack of precision and presence of bias (publication or reporting). The quality of observational studies can increase when the observed effect is significant, the presence of a doseresponse gradient is demonstrated, or in cases where it is unlikely that all possible confounding factors could have reduced the association observed. These components allow the quality of the evidence for each outcome to be classified. A high quality means that it is very unlikely that new studies will modify our confidence in the outcome; a moderate quality means that it is likely that new studies can modify the confidence we have in the observed outcome; a low quality means that it is very likely that new studies will have a significant impact on our confidence in the	-High: Further research is very unlikely to change our confidence in the estimate of effect -Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate -Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate -Very low: Any estimate of effect is very uncertain	-Level I: Evidence from at least one properly randomised controlled trial -Level II-1: Evidence obtained from well-designed controlled trials without randomisation -Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group -Level II-3: Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence -Level III: Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees	**Classification of evidence** **Screening articles** -Class I: A statistical, population-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. All patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations. -Class II: A statistical, non-referral-clinic-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. Most patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations. -Class III: A sample of patients studied during the course of the condition. Some patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation by someone other than the treating physician. -Class IV: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion or a case report. **Diagnostic articles** -Class I: A cohort study with prospective data collection of a broad spectrum of persons with the suspected condition, using an acceptable reference standard for case definition.

observed outcome; and a very low quality means that the estimated outcome is uncertain. When there is more than one outcome with different quality, the overall quality of the evidence is evaluated based on the lowest quality level obtained for the key outcomes. If the evidence for all key outcomes favours the same option and there is a high quality evidence for some of them, the overall quality can be considered to be high. Weak evidence concerning risks and unimportant adverse events should not reduce the overall degree of evidence.			The diagnostic test is objective or performed and interpreted without knowledge of the patient's clinical status. Study results allow calculation of measures of diagnostic accuracy. -Class II: A case control study of a broad spectrum of persons with the condition established by an acceptable reference standard compared to a broad spectrum of controls or a cohort study where a broad spectrum of persons with the suspected condition where the data was collected retrospectively. The diagnostic test is objective or performed and interpreted without knowledge of disease status. Study results allow calculation of measures of diagnostic accuracy. -Class III: A case control study or cohort study where either persons with the condition or controls are of a narrow spectrum. The condition is established by an acceptable reference standard. The reference standard and diagnostic test are objective or performed and interpreted by different observers. Study results allow calculation of measures of diagnostic accuracy. -Class IV: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report. **Therapeutic articles** -Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required: a. concealed allocation b. primary outcome(s) clearly defined c. exclusion/inclusion criteria clearly defined d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias. e. For noninferiority or equivalence trials claiming to prove

			efficacy for one or both drugs, the following are also required*: 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority. 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective). 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment. 4. The interpretation of the results of the study is based upon a per-protocol analysis that takes into account dropouts or crossovers. -Class II: A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a-e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. -Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.** -Class IV: Studies not meeting Class I, II, or III criteria, including consensus or expert opinion. * Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class.

In te vullen door de promotor(en) en eventuele copromotor aan het einde van MP2:

Naam Student(e): Jason Fraipont **Datum:** 27/05/2019

Titel Masterproef: Clinical guidelines for rehabilitation treatment in MS

1) Geef aan in hoeverre de student(e) onderstaande competenties zelfstandig uitvoerde:
   - NVT: De student(e) leverde hierin geen bijdrage, aangezien hij/zij in een reeds lopende studie meewerkte.
   - 1: De student(e) was niet zelfstandig en sterk afhankelijk van medestudent(e) of promotor en teamleden bij de uitwerking en uitvoering.
   - 2: De student(e) had veel hulp en ondersteuning nodig bij de uitwerking en uitvoering.
   - 3: De student(e) was redelijk zelfstandig bij de uitwerking en uitvoering
   - 4: De student(e) had weinig tot geringe hulp nodig bij de uitwerking en uitvoering.
   - 5: De student(e) werkte zeer zelfstandig en had slechts zeer sporadisch hulp en bijsturing nodig van de promotor of zijn team bij de uitwerking en uitvoering.

Competenties	NVT	1	2	3	4	5
Opstelling onderzoeksvraag	0	0	0	0	0	0
Methodologische uitwerking	0	0	0	0	0	0
Data acquisitie	0	0	0	0	0	0
Data management	0	0	0	0	0	0
Dataverwerking/Statistiek	0	0	0	0	0	0
Rapportage	0	0	0	0	0	0

2) Niet-bindend advies: Student(e) krijgt toelating/~~geen toelating~~ (schrappen wat niet past) om bovenvermelde Wetenschappelijke stage/masterproef deel 2 te verdedigen in bovenvermelde periode. Deze eventuele toelating houdt geen garantie in dat de student geslaagd is voor dit opleidingsonderdeel.

3) Deze wetenschappelijke stage/masterproef deel 2 mag wel/~~niet~~ (schrappen wat niet past) openbaar verdedigd worden.

4) Deze wetenschappelijke stage/masterproef deel 2 mag wel/~~niet~~ (schrappen wat niet past) opgenomen worden in de bibliotheek en docserver van de UHasselt.

Datum en handtekening Student(e)	Datum en handtekening promotor(en)	Datum en handtekening Co-promotor(en)
Jason Fraipont 27/05/2019	27/5/2019	

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UHASSELT
KNOWLEDGE IN ACTION

INVENTARISATIEFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
6/11/2018	Bespreking doel masterproef	Promotor: Copromotor/Begeleider: Student(e): Student(e):
5/12/2018	Bespreken zoekresultaten + resultaten kwaliteitsonderzoek	Promotor: Copromotor/Begeleider: Student(e): Student(e):
4/3/2019	Bespreken zoekresultaten en kwaliteitsbeoordeling (2)	Promotor: Copromotor/Begeleider: Student(e): Student(e):
8/3/2019	Bespreking vormgeving resultaten + feedback intro/methodiek	Promotor: Copromotor/Begeleider: Student(e): Student(e):
28/3/2019	Bespreking vormgeving resultaten (2) + feedback intro/methodiek/resultaten	Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):

In te vullen door de promotor(en) en eventuele copromotor aan het einde van MP2:

Naam Student(e): Pieter Haven Datum: 27/05/2019

Titel Masterproef: Clinical guidelines for rehabilitation treatment in MS

1) Geef aan in hoeverre de student(e) onderstaande competenties zelfstandig uitvoerde:
   - NVT: De student(e) leverde hierin geen bijdrage, aangezien hij/zij in een reeds lopende studie meewerkte.
   - 1: De student(e) was niet zelfstandig en sterk afhankelijk van medestudent(e) of promotor en teamleden bij de uitwerking en uitvoering.
   - 2: De student(e) had veel hulp en ondersteuning nodig bij de uitwerking en uitvoering.
   - 3: De student(e) was redelijk zelfstandig bij de uitwerking en uitvoering
   - 4: De student(e) had weinig tot geringe hulp nodig bij de uitwerking en uitvoering.
   - 5: De student(e) werkte zeer zelfstandig en had slechts zeer sporadisch hulp en bijsturing nodig van de promotor of zijn team bij de uitwerking en uitvoering.

Competenties	NVT	1	2	3	4	5
Opstelling onderzoeksvraag	●	0	0	0	0	0
Methodologische uitwerking	0	0	0	0	●	0
Data acquisitie	0	0	0	0	●	0
Data management	0	0	0	0	●	0
Dataverwerking/Statistiek	0	0	0	0	●	0
Rapportage	0	0	0	0	●	0

2) Niet-bindend advies: Student(e) krijgt toelating/~~geen toelating~~ (schrappen wat niet past) om bovenvermelde Wetenschappelijke stage/masterproef deel 2 te verdedigen in bovenvermelde periode. Deze eventuele toelating houdt geen garantie in dat de student geslaagd is voor dit opleidingsonderdeel.

3) Deze wetenschappelijke stage/masterproef deel 2 mag wel/~~niet~~ (schrappen wat niet past) openbaar verdedigd worden.

4) Deze wetenschappelijke stage/masterproef deel 2 mag wel/~~niet~~ (schrappen wat niet past) opgenomen worden in de bibliotheek en docserver van de UHasselt.

Datum en handtekening Student(e)	Datum en handtekening promotor(en)	Datum en handtekening Co-promotor(en)
27/5/2019	27/5/2019	

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UHASSELT
KNOWLEDGE IN ACTION

INVENTARISATIEFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
6/11/2018	Bespreking doel masterproef	Promotor: Copromotor/Begeleider: Student(e): Student(e):
5/12/2018	Bespreken zoekresultaten + resultaten kwaliteitsonderzoek	Promotor: Copromotor/Begeleider: Student(e): Student(e):
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8/3/2019	Bespreking vormgeving resultaten + feedback intro/methodiek	Promotor: Copromotor/Begeleider: Student(e): Student(e):
28/3/2019	Bespreking vormgeving resultaten (2) + feedback intro/methodiek/resultaten	Promotor: Copromotor/Begeleider: Student(e): Student(e):
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		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):