Universitat de Girona
Facultat de Medicina

Systematic collection of Patient Reported Outcomes and Experiences in multiple sclerosis: its role on quality of life

AN OPEN-LABELLED CONTROLLED CLINICAL TRIAL

END OF TERM PROJECT

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Author: Ana Belén Cendrero Camacho

Tutor: Dr. René Robles Cedeño

Neuroimmunology and Multiple Sclerosis Unit

Santa Caterina Hospital

A mi ángel de la guarda

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Y gracias a mi madre, por no rendirse nunca y no dejar que yo lo haga. Esto, como todo, como siempre, lo hemos conseguido juntas.

ABSTRACT

BACKGROUND: Multiple sclerosis (MS) is a chronic, immune-inflammatory disease of the central nervous system. It is the main cause of non-traumatic disability in young adults, affecting more than 2 million people worldwide. Despite the research carried out by the scientific community to know the pathophysiology, today it remains uncertain. Therefore, the only treatments currently available are aimed at preventing relapse and stopping the progression of the disease, as well as treating the accompanying symptoms. MS presents a very heterogeneous symptomatology with a great impact on the quality of life of the patient, and this is the main reason why they are not properly collected.

OBJECTIVE: The main objective of this trial is to determine if the proper collection and management of symptoms that afflict MS patients can have a positive effect on their quality of life (QoL). Furthermore, its influence on the quality of care will be evaluated secondarily.

DESIGN: multi-centric, open-labelled, randomized controlled clinical trial.

PARTICIPANTS: 450 patients with an age ranged 18 to 65 diagnosed with MS according to McDonald 2017 criteria that carry out their follow-ups in the Neuroimmunology and Multiple Sclerosis Unit of Santa Caterina Hospital and other reference hospitals of Catalonia.

INTERVENTION: participants will be randomly allocated in two groups of equal size. The members of one group will conduct Patient Reported Outcomes Measures (PROMs) questionnaires during five consecutive visits and the results of each of them will be analysed in real time by the neurologist before consultation. Additionally, in the first and last visit of the study they will have to fill out a QoL form and a Patient Reported Experience Measures (PREMs) questionnaire to assess the quality of care. The other group will only have to fill the QoL and PREMs questionnaires at the beginning and at the end of the study.

KEY WORDS: Multiple sclerosis • PREMs • PROMs • Quality of life • Quality of care

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1 ABBREVATIONS

AEs	Adverse Effects
APC	Antigen-Presenting Cells
BBB	Blood-Brain Barrier
CEIC	Clinical Research Ethical Committee - “Comitè Ètic d’Investigació Clínica”
CIS	Clinical Isolated Syndrome
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DIS	Dissemination in Space
DIT	Dissemination in Time
DMT	Disease-Modifying Treatment
EBV	Epstein-Barr Virus
EDSS	Expanded Disability Status Scale
EP	Evoked Potentials
GA	Glatimer Acetate
HLA	Human Leukocyte Antigens
HRQoL	Health-related quality of life
IFN	Interferon beta
IgG	Immunoglobin G
IM	Infectious Mononucleosis
JCV	John Cunningham Virus
MHC	Major Histocompatibility Complex
MOG	Myelin Oligodendrocyte Protein
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NRL	Neurologist
NRS	Numeric Rating Scale
OCB	Oligoclonal Bands
PI	Principal Investigator
PML	Progressive Multifocal Leukoencephalopathy

PPMS	Primary Progressive Multiple Sclerosis
PRMS	Primary relapsing Multiple Sclerosis
QoL	Quality of Life
RRMS	Relapsing-Remitting Multiple Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis
SS	Statistician
Th1	CD4+ T-helper 1
Th2	CD4+ T-helper 2
UVR	Ultra-Violet Radiation

2 INTRODUCTION

2.1 BACKGROUND

2.1.1 EPIDEMIOLOGY

Multiple sclerosis (MS) is the most common chronic inflammatory demyelinating disease of the central nervous system (CNS) and the main cause of neurological disability in young adults. (1–3)

According to 2013 data 2.3 million people worldwide are diagnosed with MS. It has an irregular geographical distribution, being more prevalent in Europe (108/100,000 population) and North America (140/100,000). Sub-Saharian Africa and East Asia are the regions with lowest prevalence rate of MS. Spain is considered a high incidence area with an estimated prevalence of between 80-125 cases per 100.000 inhabitants and it presents an important variability between regions. Nowadays, the global incidence and prevalence of MS tends to increase affecting mainly Europe and the Mediterranean Basin, although this may be due to a better diagnosis thanks to the use of magnetic resonance imaging (MRI), new diagnostic criteria and new treatments (1,4,5).

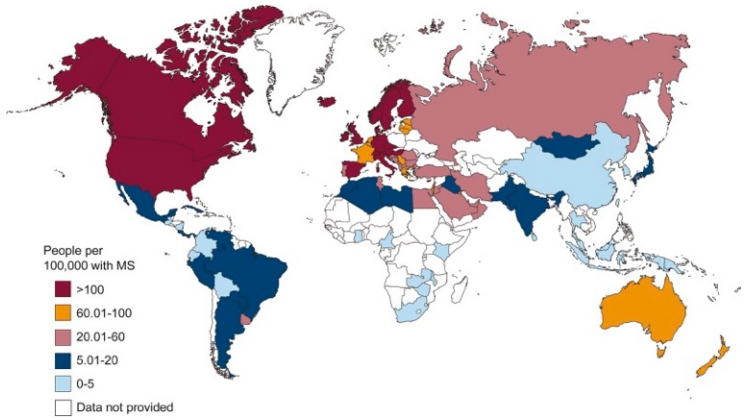


Fig. 1 Map of prevalence of MS by country (4)

This pathology is more frequent in women. Furthermore, the incidence has increase mainly among women and the female-to-male ratio remains around 2:1. This fact can be explained by the ease of women to consult for milder symptoms than men(1). This

difference disappear in older people and the most aggressive forms tend to affect the male (5).

There seem to be two peaks of incidence according to age, the first one at the third decade of life and another around 40 years old. The age of onset is rare before 10 and after 60 (5).

2.1.2 AETIOLOGY AND RISK FACTORS

Even though the aetiology of MS is still unknown, multiple studies point to an autoimmune cause with a multifactor mechanism that is not completely known. Apparently, several environmental factors can cause a dysregulation of the immune system in genetically predisposed individuals (5,6).

2.1.2.1 Genetics factors

MS is not a genetic disorder, but it has a genetic component on its pathogenesis. Therefore, it is not inherited directly from parents to children (5). This can be de explanation of why the prevalence of MS varies within the same geographical latitude, sex or breed.

Several studies support the existence of familial aggregation in MS and higher basal risk within relatives of patients with MS of suffering the disease than the general population (7). The incidence of MS among general population is less than 0,5%, whereas the incidence for first degree relatives is 1,9 to 4,7%. The monozygotic twins display a concordance of 34%, while the concordance rate between dizygotic twins falls to approximately 2% (8). All this can vary depending on the sex of the sibling, parental MS status, and patient onset age (9).

The HLA-DRB1 gene is the strongest genetic factor identified as influencing MS susceptibility, specifically the DRB1*1501 allele of major histocompatibility complex II (MHC) represents approximately 50% of the genetic risk of MS (10). Nowadays, genome wide association studies has identified hundreds of additional variants outside of the MHC that could be involved in the onset of the disease, all of which have modest individual effects (7).

2.1.2.2 Environmental factors

- Geographical latitude– VitD. The incidence of MS increases as one moves away from the equator. This is because the ultra-violet radiation (UVR) exposure and, consequently, the synthesis of VitD is lower in these areas (8,11). VitD deficiency is associated with an increased risk of relapse, increased brain atrophy and a more rapid progression of the disease (12).

VitD modulates the immune response by increasing IL10 production of T cells, causing a change of antigen presenting cells and CD4+ T cells to a less inflammatory profile. Also, it decreases the proinflammatory cytokines and the blood-brain permeability (13). However, different studies have shown contradictory results, so it is believed that VitD and UVR are independently related to MS (8).

People who migrate during the adolescence acquire the risk of developing MS from the area they arrive at, while if they do so later the risk is the same as the population of origin, probably due to childhood infections closely related to MS (9).

- Epstein-Barr virus (EBV). The association between several infectious agents and MS has been studied, but only EBV has been shown to be strongly associated to MS (14). The risk of developing the disease is between 15 and 30 times higher in EBV-positive cases depending of the age of infection, being higher when EVB is acquired during the adolescence when it is presented symptomatically as a painful pharyngitis and fatigue. This is the “kissing disease” or infectious mononucleosis (IM). The probability of triggering MS after IM is 2.17 times higher than when the infection is asymptomatic. The mechanism by which this occurs is not yet clear (15).

- Smoking. It is considered that smoking is a moderate risk factor for the development of MS as for many autoimmune diseases. Also, tobacco smoke exposure during childhood seems to be a risk factor for MS. Smoking can trigger the disease and its course gets worse (8).

2.1.2.3 Other factors

There are many others risk factors related to MS, but its capacity to trigger the disease cannot be demonstrated yet. Some of them are: emotional stress, alteration of microbiota due to the diet or use of high spectrum antibiotics, obesity, age, estrogens level (1,5,8).

2.1.3 PATHOPHYSIOLOGY

Multiple sclerosis is a complex neurodegenerative autoimmune disorder, characterized by inflammation, demyelination and axonal degeneration (1)

2.1.3.1 Immunopathological aspects

The loss of self-tolerance toward myelin and other CNS antigens involves CD4+ myelin-reactive T lymphocytes persistent peripheral activation, spontaneously or by interaction with some exogenous factor (6,16). These cells disrupt the blood-brain barrier (BBB) on their way to the CNS and, once there, they are reactivated by the antigen-presenting cells (APC) , triggering an inflammatory cascade that increases inflation (17). According to different studies, CD4+ T-helper 1 (Th1) cells releasing proinflammatory cytokines, are the main inflammatory mediator. In contrast, CD4+ T-helper 2 (Th2) cells regulate the activity of th1 cells by releasing interleukins. In MS there is a breach of Th1/Th2 balance in favour of Th1 cells (18).

During the process, many other cell lines perform an important role which is not completely known. The difficulty in determining their function suggests the existence of several etiopathogenic pathways that could explain the existence of the different histopathological patterns and evolutionary courses in which the disease occurs (5,18).

One of the most involved cells are the B lymphocytes, which could participate in the process in different ways: by producing antibodies against myelin and axons that would explain the appearance of oligoclonal bands in the cerebrospinal fluid (CSF), as APCs or regulating the inflammatory cascade by recruiting Th2 lymphocytes (19,20).

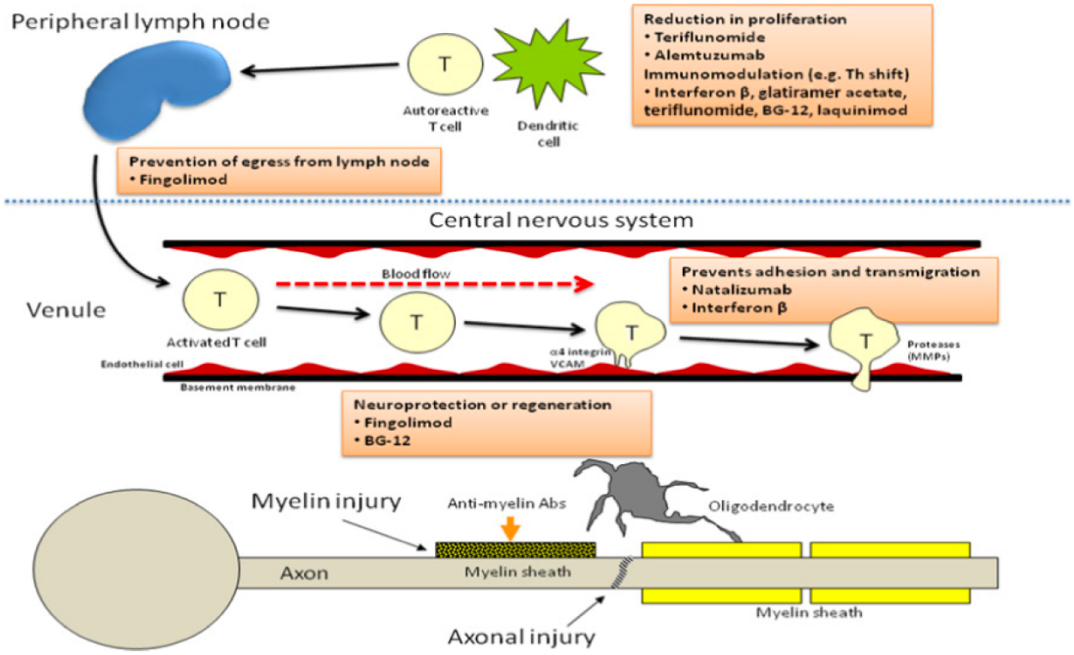


Fig. 2 A model of MS pathogenesis from (21)

2.1.3.2 Histological aspects

MS lesions include breakdown of the BBB, multifocal inflammation, demyelination, oligodendrocyte loss, reactive gliosis and axonal degeneration (22). These lesions can lead to conduction blocks, neuronal hyperexcitability, and generation of ectopic potentials responsible for the patient's clinic (5).

The pathological hallmark of MS is the **demyelination** plaques that appear throughout the CNS, especially in the optic nerves, brainstem, cerebellum, periventricular white matter and spinal cord (17).

MS plaques can be classified histologically as active, mixed and inactive (6,23). The active plaques are characterized by an intense infiltration of activated macrophages loaded with myelin fragments, whereas in the inactive ones the cellular number is low and there are no active fragmentation signs. However, inactive plaques display an intense gliosis and a reduction of the axonal density and the number of oligodendrocytes. Mixed plaques present intermediate characteristics, with a hypocellular centre and a periphery of activated macrophages (5,23).

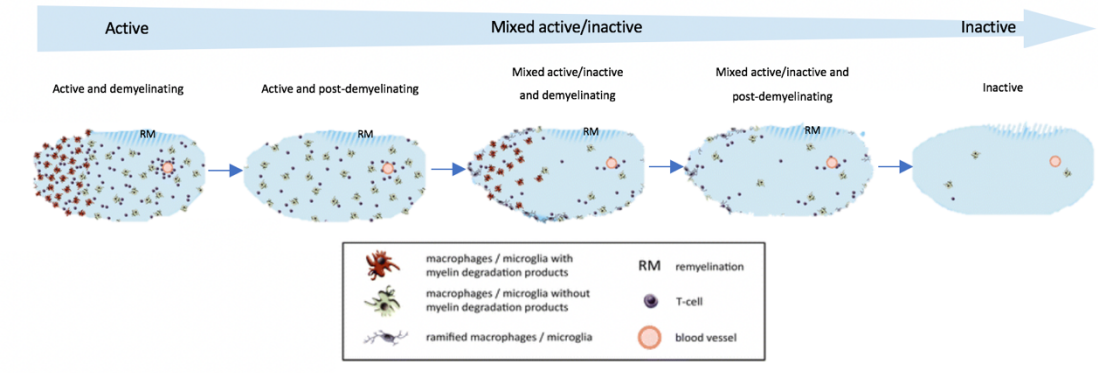


Fig. 3 Temporal devolvement of MS lesions. Adapted from (23)

The plaques vary between patients but remain similar in the same individual. Four patterns are distinguished (5,22):

1. Demyelination associated with macrophages.
2. Antibody mediated demyelination.
3. Demyelination associated with oligodendropathy.
4. Primary degeneration of oligodendrocytes with secondary destruction of myelin.

In some cases, the presence of remyelination is possible. In acute plaques a wide remyelination may occur giving rise to the named “shadow plaques” (6), whereas in chronic or inactive ones remyelination is usually incomplete inducing an axonal depletion (18).

Axonal loss is responsible for the loss of functionality and the degree of disability. It may occur either at the acute point of the outbreak or more slowly on inactive demyelinated plaques. Axonal loss could occur through a specific immunologic attack on the axon or by the activation of substances that weaken and damage demyelinated axons. In addition, these lesions are potential sources of excessive glutamate accumulation that would activate and metabotropic receptors, resulting in toxic cytoplasmic Ca^{2+} accumulation and cell death (22).

2.1.4 SYMPTOMS AND CLINICAL PHENOTYPES

MS is a disease with a very heterogeneous clinical presentation due to the different CNS lesions of sensory, motor, visual, and brainstem pathways (6,16). The type patient is a young woman who presents a visual or sensory disorder of subacute character (24).

The most frequent are:

- Fatigue: it is the physical tiredness that is not correlated with the degree of activity performed. Fatigue is the most frequent symptom of multiple sclerosis and one of the most interfering in the patient daily life, affecting pproximately 90% of patients present it during the course of the disease). It is related to sleep disorders and many other MS symptoms but not to the severity of the disease and it is not considered an outbreak. Fatigue increases with body temperature and during the summer months (24,25).

- Gait difficulties: it is the main cause of disability related to other disease factors like spasticity but, especially, the weakness that preferentially affects the lower extremities, and sensory deficits (26).

- Pain: approximately 70% of patients present neuropathic pain during ongoing disease (24,25). There are studies that suggest that neither the degree of disability, the age of initiation or the time since diagnosis determine which patients suffer pain and which do not (26).

- Mental symptoms: cognitive and emotional changes, memory loss, difficulty concentrating (24).

  More than 50% of patients have some affective syndrome, mostly it is a moderate depression (24). The frequency of depression is independent of the disability degree (25), suggesting that CNS inflammation is a risk factor of depression (26).

  Frank dementia is not very common, however, between 34 and 65% present a cognitive deterioration, especially in advanced cases, that mainly affects recent memory and sustained attention (16).

- Vision problems: optic neuritis, diplopia, oscillopsia, internuclear ophthalmoplegia (24).

  Optic neuritis (inflammation of the optic nerve) is is the first symptom of MS for many people (4,26). It is a unilateral decrease in visual acuity, accompanied by other symptoms such as photophobia, dyschromatopsia and pain that is exacerbated by movements (24). Almost 100% of patients recover completely after 2-6 months of onset (24,26).

  Internuclear ophthalmoplegia is characterized by the loss of unilateral abduction and horizontal nystagmus in contralateral abduction with conserved convergence (24).

- Sensory symptoms: tingling, numbness, burning, tightness (24).

  Vibratory sensitivity is the most affected due to lesions of the posterior cords. The phenomenon of L'hermitte is very characteristic, consisting of an electric shock-like sensation down the spine and into the limbs evoked by neck flexion (16).

- Genitourinary, bowel and sexual symptoms: urinary retention or incontinence, constipation or faecal incontinence, lack of vaginal lubrication, decreased libido, difficulty in erection and ejaculation. Nearly 80 percent of patients will suffer from any of these problems. All of them significantly disturb the quality of life and, in addition, can worsen other symptoms (24,26).

Other less frequent symptoms of MS are: muscular atrophy, speech problems, tremor, seizures, hearing loss.

According to how these symptoms occur, in 1996, four MS disease phenotypes were defined: relapsing-remitting MS (RRMS), primary progressive (PPMS), secondary progressive MS (SPMS) and progressive-relapsing MS (PRMS). Due to advances in diagnostic imaging, this classification was revised and published updated in 2013. New classification is based on central nervous system (CNS) lesion activity, according to clinical relapses and MRI findings, and progression of disability and allows to know the

evolution of the neurodegenerative process, determining in some way the prognosis and the possible therapeutic interventions (27–29) (see ANNEX A).

- **Relapsing-Remitting MS spectrum**: RRMS is the most common clinical form. Approximately 85% of people suffering MS have outbreaks of the disease (4) with full recovery, or with sequelae upon recovery and periods between relapses characterized by a lack of disease progression (6,27).

Clinically isolated syndrome (CIS) is now included in the RRMS disease spectrum. The first clinical manifestation of MS and consistent with MS but isolated in time; may or may not be isolated in space. It affects mainly the optic nerves, brainstem, or spinal cord (6,27,29).

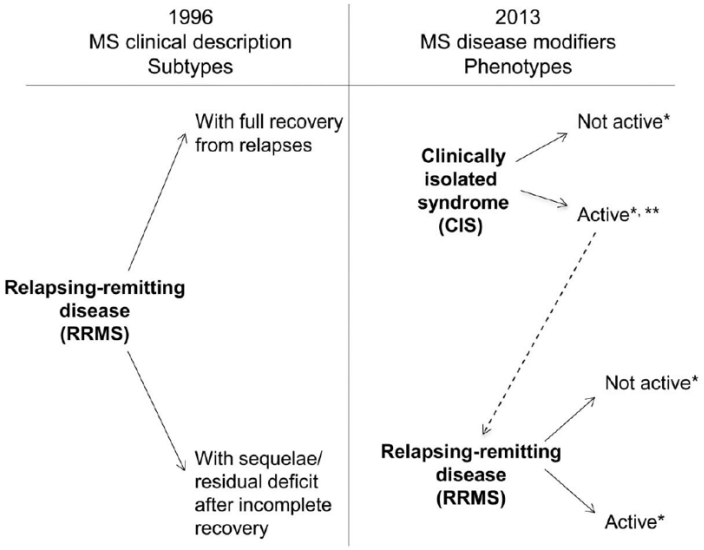


Fig. 4 The 1996 vs 2013 multiple sclerosis phenotype descriptions from (28)

- **Progressive MS spectrum**: includes any form of the disease characterized by continuous worsening of neurological impairment over at least 6–12 months, this is PPMS and SPMS (PRMS has being eliminated of the new classification) (20,27).

- Secondary progressive MS (SPMS): is the second most frequent phenotype of the disease since 80% of patients with RRMS will go on to develop a progressive form (4) with or without relapses. There is no test to determine the transition from RRMS to SPMS (28).

- Primary Progressive MS (PPMS): is the less frequent clinical form of MS, accounting for about 5% of cases (4). Is characterized by a continuous progression of disability from the onset. However, PPMS can present plateaus and temporary minor improvements during it course (2). It usually affects in patients over 40% and there is no distinction by sex (24).

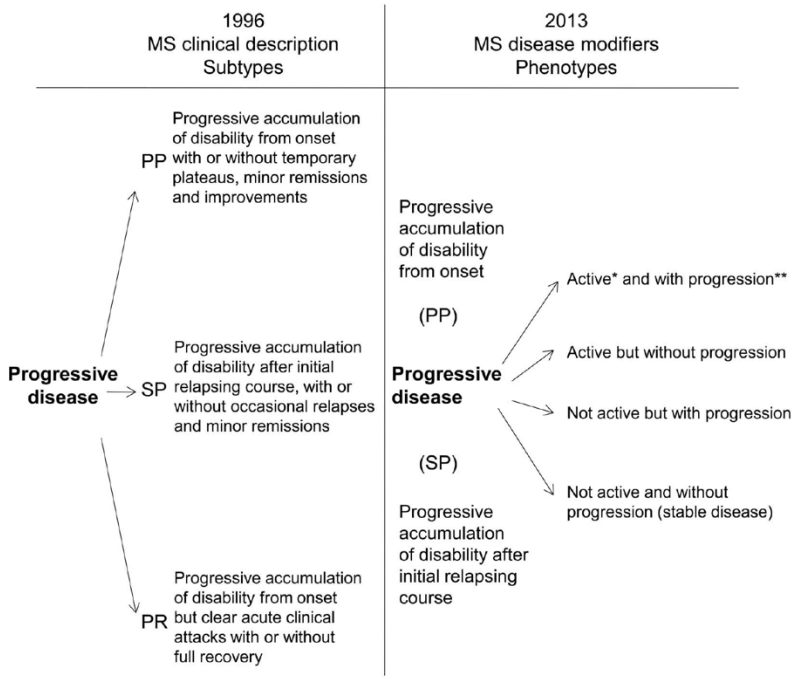


Fig. 5 The 1996 vs 2013 multiple sclerosis phenotype descriptions for progressive disease from (28)

- **Assessment activity**

- Clinically: showing evidence of new relapses or outbreaks, those symptoms or signs of neurological dysfunction that last more than 24 hours or the marked deterioration of a previously stabilized or absent symptom for at least 30 days after excluding any other possible cause (24,25).

  A "pseudo-outbreak" is the one that occurs in the context of fever (Uhthoff phenomenon) or systemic disease with a variable duration from hours to days (24,25).

- Imaging: new gadolinium enhancing lesions and/or new or enlarging T2 lesions on MRI over a specified time period (30).

- **Assessment progression**

At this point it is necessary to differentiate between two concepts (25):

- Worsening: increased disability confirmed over a specified time period as result of a relapse or progressive disease.
- Disease progression: objective worsening of the disease confirmed over certain period of time, with or without relapses. It is only used in cases of progressive-phase disease.

2.1.5 DIAGNOSIS

There is no pathognomonic test for the diagnosis of MS. It continues to be based on the clinical presentation, supported by the results of neuroimaging and, in some cases, by the results of CSF analysis .and evoked potentials studies (6).

Different criteria have been proposed for the diagnosis of the disease. The most used in current clinical practice are the **McDonald criteria** (see ANNEX B). These criteria are based on the demonstration of dissemination in space (DIS) and time (DIT) of neurologic signs and symptoms using clinical, laboratory and/or MRI data (31). It required elimination of other possible diagnoses (32).

Optic neuritis/neuropathy
Inflammatory, neuromyelitis optica (NMO) spectrum disorder, genetic, ischemic
Myelitis/myelopathy—
Inflammatory demyelination—idiopathic, postviral, postvaccinialNMO spectrum disorder, Autoimmune–systemic lupus erythematosus, antiphospholipid antibody syndrome, other systemic autoimmune disorders
Infectious (Lyme disease, HIV, viral, others)
Ischemic/vascular
Others–compressive, nutritional
Brainstem syndrome
Stroke, tumor, vasculitis (lupus, Sjögren's syndrome, Behçet's disease)
Cerebral white matter lesions
Small vessel disease (Leukoaraiosis)
Migraine
Primary CNS vasculitis
Sarcoidosis
CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy)

Fig. 6 Differential diagnosis of MS from (6)

- **Blood test**: there is no definitive serum biomarker for MS, but it may reflect the immune response situation and, what is more important, rule out other possible diagnoses like infections, some hereditary diseases, or collagen-vascular diseases among others that could mimic MS (33) (see Fig. 6). The most studied serum immune biomarkers are immunoglobulin M against extracellular domain of myelin oligodendrocyte protein (MOG) and antibodies specific for myelin basic protein (MBP) (30).

- **Magnetic resonance imaging (MRI)**: it is the most sensitive method that currently exists for the assessment of DIT/DIS and the monitoring of the course of the disease (7,33). Approximately 5 percent of people with MS do not initially show lesions on MRI at the time of diagnosis (33).

MRI is particularly helpful in patients with CIS (33). About 70% of brain lesions and 30% of spinal lesions develop without clinical evidence of relapse. MRI allows us to identify new asymptomatic lesions (radiological relapses) that would confirm diagnosis of early MS (30). In addition, the number of lesions that are seen on the MRI may establish the risk of developing a second attack which allows to diagnosticate a "clinically-definite MS"(30,33).

A brain MRI protocol includes several sequences necessary for the evaluation of the patient with possible (34,35). Spinal cord MRI is recommended in patients with symptoms at the spinal cord level or in patients with focal neurological signs and negative brain MRI if the diagnosis of MS is still being weighed (30,34).

- T1- weighted images the acute lesions appear as hypointense areas. At times they show dark areas called "black holes", that are thought to indicate areas of chronic nerve damage and disability (25). In order to differentiate them, black holes should be persistent for at least 6 months (34). Gadolinium enhanced T1 supplies information about disease activity. When there is active inflammation, the BBB is disrupted and gadolinium can enter and highlight the inflamed areas (7,25,30,33).

- T2-weighted images provide information about the total amount of lesion area, both old and new (33,34).

- FLAIR (fluid attenuated inversion recovery) images are used to better identify brain lesions associated with MS (33).

MS lesions seen on MRI are typically ovoid in shape and small size located mainly in the periventricular white matter, although they can be found in other locations, and usually arranged perpendicularly to the ventricles (7).

Once the disease is diagnosed, annual follow-up MRIs are recommended (33,34).

- **Cerebrospinal fluid (CSF)**: It is obtained through a lumbar puncture and is not specific for MS (31). Further, 5-10 percent of patients with MS never show CSF abnormalities, hence it cannot confirm or rule out a diagnosis of MS by itself (33).

The findings of the CSF analysis that could lead to MS diagnosis are the result of an abnormal immune response. These are (30,33):

- Elevated levels of immunoglobin G (IgG) antibodies and/or
- IgG oligoclonal bands. (OCB)
- Proteins that are the breakdown products of myelin.

- **Evoked potential (EP)**: EP testing has been eliminated from the 2017 revised McDonald criteria for the diagnosis MS (33) but it continues to be done in clinical practice. Up to 50 percent of patients with MS present al slowdown of electrical conduction caused by damage (demyelination) along different sensory pathways (30).

2.1.6 TREATMENT

Due to the wide range of symptoms, the approach has to be multidisciplinary and includes three different aspects (36):

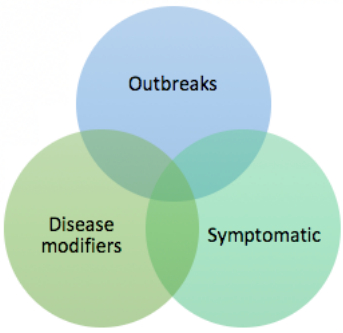


Fig. 7 Scheme of the MS approach adapted from (36)

2.1.6.1 Outbreak treatment

Not all outbreaks require treatment (36). The therapeutic options are:

- Methylprednisolone: high-dose corticosteroids shorten the duration of symptoms and accelerate the recovery of function after relapses, without modifying the progression of the disease (37). Its adverse effects (AEs) are usually mild and transient (euphoria, depression, acne, insomnia, facial flushing, transient HTA, fatigue) (36,38).
- Plasmapheresis: it is used in severe relapses or when there is no response to methylprednisolone (37,39).

2.1.6.2 Disease-modifying treatment (DMT)

MS has no cure (40). The currently authorized treatments only act on the inflammatory phase of MS and their aim is to reduce the activity of the disease, by decreasing the number of relapses and preventing the appearance of new lesions in MRI, and delay the progression of the same (41). To achieve this, it is important that the patient becomes aware of the transcendence of adherence to treatment (25).

- First-line drugs: the effectiveness of these treatments is moderate, but they have a good safety profile (36).

  - Interferon beta (IFN): is obtained through the biotechnological processing of one of the natural interferons, and it acts modulating the activity of T and B cells and reducing the disruption of the BBB by a mechanism that is not known exactly (42). All IFNs are a once or several times a week injectable treatments, subcutaneously (Betaseron® and Rebif®) or intramuscularly (Avonex®) (41), except pegylated form of subcutaneous IFN (Plegridy®), whose long half-life allows administration every 2-4 weeks (43). It is approved for CIS and active progressive forms of MS, decreasing relapse rate by one-third (44). Its main AEs are flu-like symptoms, hepatotoxicity, inflammatory reactions and pain at the injection site, anemia and thrombocytopenia (36).

  - Glatiramer acetate (GA): it is an acetate of synthetic polypeptides that mimic and compete with the myelin basic protein, blocking myelin-damaging T-cells

(41). GA (Copaxone®) is approved for CIS and RRMS with an efficacy similar to IFN (44). It is an injectable solution three times a week with few adverse effects (45). The most common are inflammatory reactions and at the injection site, lipoatrophy and skin necrosis (important to rotate the injection area with each injection) and post-injection reaction (46). Due to its safety profile, it is the most indicated during pregnancy, although none of them is authorized for it (44).

- Teriflunomide (Aubagio®): it is once-daily oral DMT. It has an anti-inflammatory effect by inhibiting a pyrimidine synthesis, which in turn reduces the proliferation of T and B immune cells (47). In general, it is a well-tolerated drug. Its main AEs are: gastrointestinal symptoms, weak hair and analytical alterations (hepatotoxicity and lymphopenia) (48). Aubagio has an efficacy of 34% and it is indicated for patients with relapsing forms of MS as well as for patients with a MS clinical first episode of, but no during pregnancy and lactation due to its prolonged half-life and teratogenicity (41).

- Dimethyl fumarate/BG-12 (Tecfidera®): it is twice-daily oral treatment (41). BG-12 activates the nuclear-related factor 2 transcriptional pathway, which is related to anti-inflammatory and anti-oxidant properties (49). Several studies show an efficiency greater 50% in the treatment of relapsing MS (41). It is a safe DMT with self-limited AEs: gastrointestinal intolerance (nausea, pain, dyspepsia) and flushing (50).

- Second-line drugs: are high-efficacy (60-70%) drugs indicated in case of therapeutic failure of first-line drugs or as first-line therapy for early aggressive MS. These treatments present a slightly more complex security profile (36,41,44).

  - Fingolimod: it is an oral therapy taken once per day (41). Finglolimod (Gilenya®) is a sphingosine 1-phosphate receptor modulator and acts trapping lymphocytes in the lymph nodes. This way, those cells cannot cross the BBB into the central nervous system, thereby reducing inflammatory damage (51). This DMT produces lymphopenia (41), which makes the organism more susceptible to viral

infections, especially varicella zoster. It has a first dose effect consisting of bradycardia that requires clinical observation for 6 hours after (36,41).

- Natalizumab (Tysabri®): it is a humanized monoclonal antibody that blocks α 4-integrine and prevents lymphocytes from attaching to the cerebral vascular endothelium and reaching the CNS (52). This treatment is administered intravenously once a month and have a good safety profile, except for a risk of developing progressive multifocal leukoencephalopathy (PML) in selected cases, an infection of the CNS with the John Cunningham virus (JCV)(53). To know the individual risk of developing PML, a serological anti-JCV test is routinely performed and it is recommended to repeat the test every 6 months(54).

- Alemtuzumab (Lemtrada®): is a humanized monoclonal antibody directed against CD52, a protein on the surface of lymphocytes and monocytes (41). The aim of this intravenous therapy is to "reset" the immune system. The treatment consists of an initial cycle of 5 doses of alemtuzumab and a new cycle of 3 doses one year later. After that, it may be extended annually (55). Up to 20% of patients develop autoimmune thyroid disease and almost 1% have idiopathic thrombocytopenic purpura (41).

- Ocrelizumab (Ocrevus®): it has recently been approved and it is the only DMT that has shown efficacy in the treatment of both the remitting and PPMS forms (56). Ocrelizumab is a humanized monoclonal antibody that targets CD20 positive B lymphocytes similar to rituximab (another anti-CD20 agent)(41,56), but less immunogenic with repeated infusions and with better benefit–risk profile than rituximab (56). Ocrelizumab completely decreases the CD19+ (marker of B-cell counts in anti-CD20-treated patients) B-cell count in blood after 2 weeks and maintains it for 6 to 9 months. It is administered intravenously every 6 months after a second dose in the second week of the start of treatment. More common AEs of this drug are respiratory tract infections and infusion reactions (it is recommended to pre-medicate with methylprednisolone and antihistamine approximately 30 minutes prior to each Ocrevus infusion to reduce the frequency and severity of these reactions) (56,57).

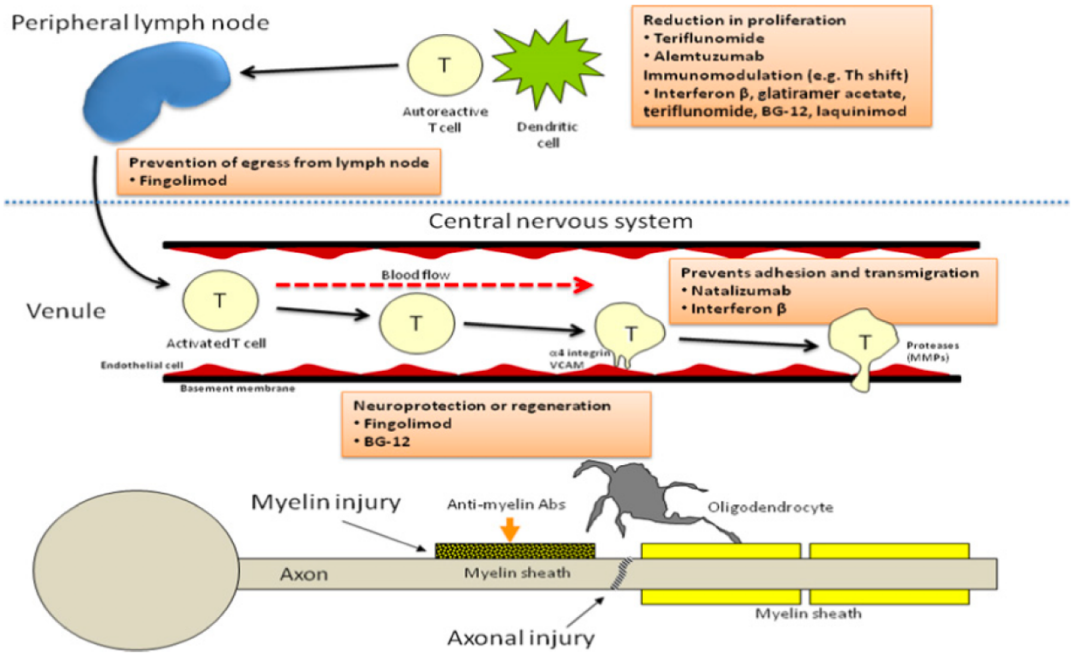


Fig. 8 Immunopathogenic mechanisms in MS and proposed targets of different disease modifying therapies from (6)

- Third-line therapies: in patients not responding to any of the previous treatment lines or in patients with a PPMS form, other strategies can be used, such as rituximab, cyclophosphamide or an autologous hematopoietic stem cell transplantation (36).

The selection of the treatment is based on the consensus developed by the Spanish Society of Neurology in 2016 (44). The main aspects to consider are patient preference, MS activity and the degree of neurological impairment, always bearing in mind the benefit-risk profile of the drug (36,41,44).

2.1.6.3 Symptomatic treatment

The objective is to treat the accompanying symptoms of MS that make the daily life of patients difficult and thus promote well-being and improve their quality of life (QoL) (58).

Fatigue and gait difficulties are the most disabling symptoms of the disease (24). Physical exercise and physiotherapy are baseline to improve the patient autonomy, but it is also important to avoid habits that excessively increase body temperature. If these strategies

fail it will be necessary to resort to pharmacological treatments such as amantadine, modafinil, fluoxetine, fampridine and others (25).

Besides, it is important to avoid the risk factors that intervene in the pathogenesis of the disease. To avoid tobacco and any other toxic substance, control classic cardiovascular risk factors and maintain a diet that follows the recommendations of the Mediterranean diet can positively influence the situation of patients. However, VitD supplementation is not recommended, except in case of deficiency (38).

2.1.7 PROGNOSIS

The great clinical variability of MS prevents knowing the possible evolution of the disease on an individual level (41). Development of a progressive course is the most important factor associated with long-term outcome. The clinical and demographic feature that the patient presents at the onset of the disease can be used as progression predictors (see Table 1), but none of the are able to predict the rate of this progression. Paraclinical tests are the best tool for foretell the risk of CIS conversion into clinically definite multiple sclerosis, relapses, recovery level and later disability. MRI is the most sensitive, but also immunological markers such as OCB and IgM anti-MOG, and EP studies (59).

Table 1 Prognosis factors summary adapted from (1,59)

GOOD PROGNOSIS FACTORS	BAD PROGNOSIS FACTORS
Age < 25	Age > 25
Female	Male
Relapsing-remitting phenotype	Progressive phenotype
Onset: optic neuritis, sensory problems	Onset: motor, cerebellar or spinal problems
Unifocal onset	Polysymptomatic onset
EDDS < 3	EDDS >3
Full recovery from the initial attack	Incomplete recovery from the initial attack
Low relapse frequency in the first 2-5 years	High relapse frequency in the first 2-5 years
Low disability after 5 years	High disability after 5 years
Longer interval between first two attacks	Shorter interval between first two attacks

Two-stage disability progression in MS is defined by using two scores on the Kurtzke Extended Disability Status Scale (EDSS) (see ANNEX C) as benchmarks of neurological impairment accumulation (1,41): an early "phase 1" from onset to irreversible EDSS 3 during which focal inflammatory lessons influence disability progression; and later "phase 2" from EDSS 3 to EDSS 6 during which focal inflammatory lessons influence disability progression and, therefore, independent of "phase 1". Predictive factors of progression only influence first phase (60).

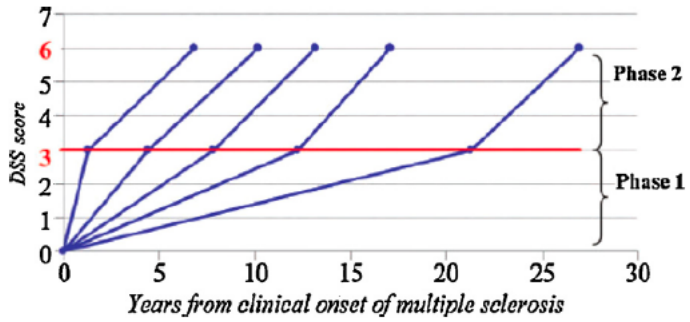


Fig. 9 Two-stage disability progression in MS from(1)

Although patients with MS have a life expectancy similar to that of the general population, especially in the first 20 years of the disease, survival seems to be reduced from 6 to 14 years. The average time from onset of symptoms to death varies from 24 to 45 years (1). Progressive disability leads to severe handicaps, which increase the risk of infections and respiratory-related diseases, first cause of death followed by cardiovascular problems and cancer (38,61). It should also be noted that suicide is from 1.6 to 7.5 times more common than in the general population (62).

2.2 PROMS AND PREMS

Patient reported outcome measures (PROMs) are a tool that provides a quantification of symptoms which cannot be measured objectively using validated generic and MS specific scales (63). They are a method to assess patients QoL identified by themselves (64). Furthermore, PROMs make possible to detect worsening of symptoms, provide information that may have otherwise been missed and enhance shared decision making and patient engagement (65,66).

Some studies also suggest that PROMs improve the quality of health care, care coordination and even reduce costs and increase efficacy (67). In this way, patient reported experience measures (PREMs) reflect patient perception of their experience with health care through questionnaires that evaluate items such as waiting time, quality of communication or knowledge about their own process. At the same time, better experiences seem to associated with better outcomes (68).

2.3 JUSTIFICATION

Multiple sclerosis is an autoimmune demyelinating chronic, and potentially progressive, disorder of the CNS. It has a complex pathophysiological mechanism that is not completely known, which makes it difficult to predict the possible evolution and prognosis of the patient, as well as the formulation of a curative treatment. Its incidence is increasing, especially in developed countries, that affects young people, mainly women, and presents a wide range of symptoms that the patient identifies as disabling and, therefore, with a great impact on his quality of life.

Considering that the MS tends to debut at an early age and that, despite not having curative treatment, life expectancy is close to that of the general population, therapeutic efforts should be directed to try to stop the progression of the disease and normalize the patient daily life as much as possible.

In routine clinical practice, due to the heterogeneity of MS symptoms, many of them are obviated or not picked up correctly. PROMs questionnaires make it possible to collect more quickly and effectively of this information and minimize the burden of data collection during the visit.

This study aims at capturing the symptoms that the patient identifies as more disabling, by using PROMs questionnaires, in order to evaluate how they relate to the patient QoL, and if the correct management of them has a positive impact on the health-related QoL.

According to the literature, electronic systems linked to a registry enable an easier collection of this data and afford timely feedback to clinicians so that could take measures that improve the functionality and quality of life of the patient and,

consequently, improve the quality of care by focusing the visit on the problems that really afflict the patient and promoting a better patient-clinician communication.

3 BIBLIOGRAPHY

1. Leray E, Moreau T, Fromont A, Edan G. Epidemiology of Multiple Sclerosis. Neurol Clin. 2016;34(4):919–39.
2. Pugliatti M, Rosati G, Carton H, Riise T, Drulovic J, Vécsei L, et al. The epidemiology of multiple sclerosis in Europe. Eur J Neurol. 2006;13(7):700–22.
3. Kingwell E, Marriott JJ, Jetté N, Pringsheim T, Makhani N, Morrow SA, et al. Incidence and prevalence of multiple sclerosis in Europe: A systematic review. BMC Neurol. 2013;13.
4. Atlas of MS 2013: Mapping Multiple Sclerosis around the world [Internet]. Sclerosis International Federation. 2013. Available from: www.msif.org
5. Costa-Frossard L. Esclerosis múltiple: introducción, epidemiología, fisiopatogenia. In: Manejo del paciente con esclerosis múltiple en atención primaria: diagnóstico, pronóstico y tratamiento. 2017. p. 5–16.
6. Garg N, Smith TW. An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. Brain Behav. 2015;5(9).
7. Milo R, Miller A. Revised diagnostic criteria of multiple sclerosis. Autoimmun Rev. 2014;13(4–5):518–24.
8. Pantazou V, Schluep M, Du Pasquier R. Environmental factors in multiple sclerosis. Vol. 44, Presse Medicale. 2015.
9. B. K, F.D. L. The genetics of multiple sclerosis. A review. Biomed Pharmacother. 1999;53(8):358–70.
10. Westerlind H, Ramanujam R, Uvehag D, Kuja-Halkola R, Boman M, Bottai M, et al. Modest familial risks for multiple sclerosis: A registry-based study of the population of Sweden. Brain. 2014;137(3):770–8.
11. Gale CR, Martyn CN. Migrant studies in multiple sclerosis. Prog Neurobiol. 47(4–5):425–48.
12. Ascherio A, Munger KL, White R, Köchert K, Simon KC, Polman CH, et al. Vitamin D as an Early Predictor of Multiple Sclerosis Activity and Progression. JAMA Neurol. 2014 Mar 1;71(3):306.
13. Hernández-Pedro NY, Espinosa-Ramirez G, de la Cruz VP, Pineda B, Sotelo J. Initial Immunopathogenesis of Multiple Sclerosis: Innate Immune Response. Clin Dev Immunol. 2013;2013:1–15.
14. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: The role of infection. Ann Neurol. 2007;61(4):288–99.
15. Handel AE, Williamson AJ, Disanto G, Handunnetthi L, Giovannoni G, Ramagopalan S V. An Updated Meta-Analysis of Risk of Multiple Sclerosis following Infectious Mononucleosis. Jacobson S, editor. PLoS One. 2010 Sep 1;5(9):e12496.
16. Hauser SL, Oksenberg JR. The Neurobiology of Multiple Sclerosis: Genes, Inflammation, and Neurodegeneration. Neuron. 2006 Oct 5;52(1):61–76.
17. Mahad DH, Trapp BD, Lassmann H. Pathological mechanisms in progressive multiple sclerosis. Lancet Neurol. 2015;14(2).
18. Yadav SK, Mindur JE, Ito K, Dhib-Jalbut S. Advances in the immunopathogenesis of multiple sclerosis. Curr Opin Neurol. 2015;28(3):206–19.

19. Lehmann Horn K, Kronsbein HC, Weber MS. Targeting B cells in the treatment of multiple sclerosis: Recent advances and remaining challenges. Ther Adv Neurol Disord. 2013;6(3):161–73.
20. Correale J, Gaitán MI, Ysrraelit MC, Fiol MP. Progressive multiple sclerosis: from pathogenic mechanisms to treatment. Brain. 2017;140(3):527–46.
21. Large-scale gene-expression studies and the challenge of multiple sclerosis [Internet]. [cited 2019 Jan 11]. Available from: http://www.mult-sclerosis.org/news/Oct2002/FullTextLargeScaleGeneExpressionStudiesOfMS.html
22. Dutta R, Trapp BD. Relapsing and progressive forms of multiple sclerosis: Insights from pathology. Curr Opin Neurol. 2014;27(3):271–8.
23. Kuhlmann T, Ludwin S, Prat A, Antel J, Brück W, Lassmann H. An updated histological classification system for multiple sclerosis lesions. Acta Neuropathol. 2017 Jan 17;133(1):13–24.
24. Martínez M. Manifestaciones clínicas de la esclerosis múltiple. In: Manejo del paciente con esclerosis múltiple en atención primaria: diagnóstico, pronóstico y seguimiento. Luzán 5; 2017. p. 17–21.
25. Yusta A. Evaluación y control del paciente con esclerosis múltiple. In: Manejo del paciente con esclerosis múltiple en atención primaria: diagnóstico, pronóstico y seguimiento. Luzán 5; 2017. p. 33–41.
26. MS Symptoms : National Multiple Sclerosis Society [Internet]. [cited 2019 Jan 13]. Available from: https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms
27. Klineova S, Lublin FD. Clinical Course of Multiple Sclerosis. Cold Spring Harb Perspect Med. 2018 Sep;8(9):a028928.
28. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014 Jul 15;83(3):278–86.
29. Lublin FD. New Multiple Sclerosis Phenotypic Classification. Eur Neurol. 2014;72(s1):1–5.
30. Karussis D. The diagnosis of multiple sclerosis and the various related demyelinating syndromes: A critical review. J Autoimmun. 2014;48–49:134–42.
31. Kister I, Bacon TE, Chamot E, Salter AR, Cutter GR, Kalina JT, et al. Natural history of multiple sclerosis symptoms. Int J MS Care. 2013;15(3):146–58.
32. National Multiple Sclerosis Society. Updated McDonald Criteria Expected to Speed the Diagnosis of MS and Reduce Misdiagnosis.
33. Diagnosing MS : National Multiple Sclerosis Society [Internet]. [cited 2019 Jan 13]. Available from: https://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-MS
34. Li D, Traboulsee A, Coyle PK, Arnold DL, Barkhof F, Grossman R, et al. Standardized MR Imaging Protocol for Multiple Sclerosis : Consortium of MS Centers Consensus. Am J Neuroradiol. 2006;27(2):455–61.
35. Chen JJ, Carletti F, Young V, Mckean D, Quaghebeur G. MRI differential diagnosis of suspected multiple sclerosis. Vol. 71, Clinical Radiology. 2016.
36. García Domínguez J. Tratamiento de la esclerosis múltiple. In: Manejo del paciente con esclerosis múltiple en atención primaria: diagnóstico, pronóstico y seguimiento. Luzán 5; 2017. p. 23–32.

37. Managing Relapses : National Multiple Sclerosis Society [Internet]. Available from: https://www.nationalmssociety.org/Treating-MS/Managing-Relapses
38. Arrieta E. Comorbilidad en esclerosis múltiple. In: Manejo del paciente con esclerosis múltiple en atención primaria: diagnóstico, pronóstico y tratamiento. Luzán 5; 2017. p. 53–9.
39. Meca-Lallana JE, Rodríguez-Hilario H, Martínez-Vidal S, Saura-Luján I, Carretón-Ballester A, Escribano-Soriano JB, et al. [Plasmapheresis: its use in multiple sclerosis and other demyelinating processes of the central nervous system. An observation study]. Rev Neurol. 37(10):917–26.
40. Huang W-J, Chen W-W, Zhang X. Multiple sclerosis: Pathology, diagnosis and treatments. Exp Ther Med. 2017 Jun;13(6):3163–6.
41. Wingerchuk DM, Carter JL. Multiple sclerosis: Current and emerging disease-modifying therapies and treatment strategies. Mayo Clin Proc. 2014;89(2):225–40.
42. Dhib-Jalbut S. Mechanisms of action of interferons and glatiramer acetate in multiple sclerosis. Neurology. 2002 Apr 23;58(8 Suppl 4):S3-9.
43. Newsome SD, Scott TF, Arnold DL, Nelles G, Hung S, Cui Y, et al. Long-term outcomes of peginterferon beta-1a in multiple sclerosis: results from the ADVANCE extension study, ATTAIN. Ther Adv Neurol Disord. 2018;11:1756286418791143.
44. Garcia-Merino JA. Consenso para el tratamiento de la esclerosis múltiple nola de Neurología 2016. 2017;32(2).
45. Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R, GALA Study Group. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. Ann Neurol. 2013 Jun;73(6):705–13.
46. FDA. COPAXONE HIGHLIGHTS OF PRESCRIBING INFORMATION [Internet]. 2018. Available from: https://www.copaxone.com/Resources/pdfs/PrescribingInformation.pdf
47. Claussen MC, Korn T. Immune mechanisms of new therapeutic strategies in MS: teriflunomide. Clin Immunol. 2012 Jan;142(1):49–56.
48. AUBAGIO® (teriflunomide) | Official Healthcare Professional Site [Internet]. Available from: https://www.aubagiohcp.com/
49. Albrecht P, Bouchachia I, Goebels N, Henke N, Hofstetter HH, Issberner A, et al. Effects of dimethyl fumarate on neuroprotection and immunomodulation. J Neuroinflammation. 2012 Jul 7;9(1):163.
50. FDA. TECFIDERA HIGHLIGHTS OF PRESCRIBING INFORMATION [Internet]. 2017 [cited 2019 Jan 15]. Available from: https://www.tecfidera.com/content/dam/commercial/multiple-sclerosis/tecfidera/pat/en_us/pdf/full-prescribing-info.pdf
51. Cohen JA, Chun J. Mechanisms of fingolimod's efficacy and adverse effects in multiple sclerosis. Ann Neurol. 2011 May;69(5):759–77.
52. Ransohoff RM. Natalizumab for Multiple Sclerosis. N Engl J Med. 2007 Jun 21;356(25):2622–9.
53. Ho P-R, Koendgen H, Campbell N, Haddock B, Richman S, Chang I. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. Lancet Neurol. 2017 Nov;16(11):925–33.

54. Gorelik L, Lerner M, Bixler S, Crossman M, Schlain B, Simon K, et al. Anti-JC virus antibodies: implications for PML risk stratification. Ann Neurol. 2010 Sep;68(3):295–303.
55. FDA. LEMTRADA HIGHLIGHTS OF PRESCRIBING INFORMATION [Internet]. 2001 [cited 2019 Jan 15]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103948s5160_5165lbl.pdf
56. Mulero P, Midaglia L, Montalban X. Ocrelizumab: a new milestone in multiple sclerosis therapy. Vol. 11, Therapeutic Advances in Neurological Disorders. 2018.
57. FDA. OCREVUS HIGHLIGHTS OF PRESCRIBING INFORMATION [Internet]. 2017 [cited 2019 Jan 15]. Available from: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf
58. Dalgas U. Rehabilitation and multiple sclerosis: hot topics in the preservation of physical functioning. J Neurol Sci. 2011 Dec 1;311 Suppl 1:S43-7.
59. Swanton J, Fernando K, Miller D. Early prognosis of multiple sclerosis. In: Handbook of clinical neurology. 2014. p. 371–91.
60. Leray E, Yaouanq J, Le Page E, Coustans M, Laplaud D, Oger J, et al. Evidence for a two-stage disability progression in multiple sclerosis. Brain. 2010 Jul 1;133(7):1900–13.
61. Lalmohamed A, Bazelier MT, Van Staa TP, Uitdehaag BMJ, Leufkens HGM, De Boer A, et al. Causes of death in patients with multiple sclerosis and matched referent subjects: a population-based cohort study. Eur J Neurol. 2012 Jul 1;19(7):1007–14.
62. Scalfari A, Knappertz V, Cutter G, Goodin DS, Ashton R, Ebers GC. Mortality in patients with multiple sclerosis. Neurology. 2013 Jul 9;81(2):184–92.
63. Clark R, Welk B. Patient reported outcome measures in neurogenic bladder. Transl Androl Urol. 2016;5(1):22–30.
64. Giovannetti AM, Pietrolongo E, Giordano A, Cimino V, Campanella A, Morone G, et al. Individualized quality of life of severely affected multiple sclerosis patients: practicability and value in comparison with standard inventories. Qual Life Res. 2016;25(11):2755–63.
65. Worthen VE, Lambert MJ. Outcome oriented supervision: Advantages of adding systematic client tracking to supportive consultations. Couns Psychother Res. 2007;7(1):48–53.
66. Marshall S, Haywood K, Fitzpatrick R. Impact of patient-reported outcome measures on routine practice: A structured review. J Eval Clin Pract. 2006;12(5):559–68.
67. Conway PH, Mostshari F, Clancy C. The Future of Quality Measurement for Improvement and Accountability. J Am Med Assoc. 2013;309(21):2215–6.
68. Black N, Varaganum M, Hutchings A. Relationship between patient reported experience (PREMs) and patient reported outcomes (PROMs) in elective surgery. BMJ Qual Saf. 2014;23(7):534–43.

4 HYPOTHESIS

4.1 MAIN HYPOTESIS

The systematic collection of symptoms related to multiple sclerosis prior to the medical visit and the subsequent evaluation of them improves the quality of life of patients.

4.2 SECONDARY HYPOTESIS

Better management of symptoms allows to improve the quality of care.

5 OBJETIVES

5.1 MAIN OBJETIVES

- Asses which are the symptoms that most affect the quality of life of MS patients in order to treat them.

- Determine if the proper collection and management of symptoms that afflict MS patients can have a positive effect on their quality of life in front of the patients to whom the method is not applied.

5.2 SECONDARY OBJETIVES

- Prove that the analysis of the real-time data improves the quality of medical care.

- Check the feasibility of the method.

- Compare the results obtained between the different subtypes of MS.

6 MATERIALS AND METHODS

6.1 STUDY DESIGN

The aim of the project is to assess which are the symptoms that most affect the quality of life of the patient with MS through a systematic collection of them, to treat them energetically and, in this way, improving the patient daily life.

Thus, the more suitable study design for the consecution of the objectives is a prospective, open-labelled, randomized controlled clinical trial.

Due to the difficulty of recruiting the sample in its entirety in the Multiple Sclerosis Unit of Girona, a multi-centric study will be performed, and data will be collected in the Multiple Sclerosis Unit of different reference hospitals of Catalonia.

6.2 STUDY POPULATION

The population of the study will be patients with an age ranged 18 to 65 diagnosed with MS according to McDonald 2017 criteria that carry out their follow-ups in the Neuroimmunology and Multiple Sclerosis Unit of Catalonia hospitals.

6.2.1 INCLUSION CRITERIA

- Patients with a confirmed diagnosis of MS (any phenotype) following the McDonald Criteria (see ANNEX B).
- People with an age between 18 and 65 years old.
- Individuals who are able to cooperate in the study and sign the consent.
- Patients whose usual follow-up is done every 6 months.

6.2.2 EXCLUSION CRITERIA

- Patients with radiologic isolated syndrome diagnosis.
- Patients with a large cognitive deficit or inability to communicate.
- Institutionalized patients.
- Patients with terminal disease or another disease that could interfere in the study.

6.3 SAMPLE

6.3.1 SAMPLE SIZE

Accepting an Alpha risk of 5% and a statistical power of 80% in a two-sided test, anticipating a moderate effect of the intervention and assuming a drop-out rate of 15%, 225 patients will be needed per arm.

Prof. Marc Saez software, based on the library 'pwr' of the free statistical environment R (version 3.5.1), has been used to define the sample size.

6.3.2 SAMPLING METHOD

Non-probabilistic consecutive sampling method will be performed until getting 450 subjects. Once it has been determined whether patients meet the inclusion and exclusion criteria, they will be randomly assigned in one of two groups according to a 1:1 randomization ratio.

- Group 1: patients on whom the intervention is going to be applied. They will have to fill QoL, PROMs and PREMs questionnaires.
- Group 2: patients on whom the intervention will not be applied and will be used as a control group. They will only have to fill the QoL and PREMs questionnaires.

The initial recruitment of patients will be carried out in the Neuroimmunology and Multiple Sclerosis Unit of Santa Caterina Hospital (Girona). Nevertheless, due to the limited number of patients treated in this unit, the collaboration of other reference hospitals of Catalonia will be requested in order to get the number of subjects needed to carry out this study and obtain statistically significant results.

The number of patients will be proportional to the size of the hospital, and the assignment of patients in each group and the successive follow-up visits, and therefore the data collection, will be performed in each centre where the patients are registered.

Although there are patients who meet criteria, only those who sign the informed consent after reading the information sheet can be part of the study (see section 9).

6.4 VARIABLES

6.4.1 INDEPENDENT VARIABLES

PROMs questionnaires will be used. All of them are validated scales, general or MS specific, of self-evaluation (see ANNEX D).

1. **Pain Numeric Rating Scale** (NRS) (McCaffery): patients will have to choose a number from 0-10 that best describes current pain (0 = “no pain”, 10 = “worst possible pain”).

Score	Classification
0	No pain
1-3	Mild pain
4-6	Moderate pain
7-10	Intense pain

   It is a discrete quantitative variable.

2. **Spasticity 0–10 NRS** (Farrar et al., 2008): this scale allows to quantify how the patient perceives the severity of his spasticity in a range from 0-10 (0 = “no spasticity” and 10 = “worst possible spasticity”). A classification equivalent to that of the pain will be used.
   It is a discrete quantitative variable.

3. **Spasm Frequency Scale** (Penn et al., 1989): it is a self-report measure to assess the frequency of muscle spasms into five different levels.
   It is considered an ordinal qualitative variable.

4. **Sleep Quality 0-10 NRS** (Cappelleri et al., 2009): patients will be asked to choose a number on a scale ranging from 0-10 (0 = “no sleep problems” and 10 = “worst sleep problems you can possible imaging”). Same classification as that of the pain will be applied.
   It is discrete quantitative variable.

5. **Ambulation 0-10 NRS** (Gift et al., 1998): on a scale of 1 to 10 (0 = “no ambulation problems” and 10 = “worst ambulation problems you can possible imaging”), the

patient will be asked to mark how difficult it is for him to walk. A classification equivalent to that of the pain will be used.

It is a discrete quantitative variable.

6. **Modified 10-items Barthel Index** (Mahoney et al., 1965)**:** this scale measures the capacity of the person to develop ten activities of daily life in order to identify the level of independence. The score ranges from 0 to 100 points. The closer to zero, the higher the degree of dependence.

Score	Classification
< 20	Total dependence
21 - 60	Severe dependence
61 - 90	Moderate dependence
91 - 99	Mild dependence
100	Independence

It is a discrete quantitative variable.

7. **Bladder Control Scale** (Turnbull et al., 1992): this four-item instrument evaluates bladder control and the extent to which bladder problems have an impact on everyday activities. Scores can range from 0-22, with higher scores indicating greater bladder control problems.

It is a discrete quantitative variable.

8. **Fatigue Severity Scale** (Krupp et al., 1989): it is a questionnaire to evaluate the impact of fatigue on the patient. It is based on nine statement which can be assessed from 1 to 7 depending on the degree of compliance. Thus, this scale can range from 9-63. If the total score is 36 or higher suggests that a deeper evaluation by a physician is necessary.

It is a discrete quantitative variable.

9. **Sexual Satisfaction Scale** (Nowinski and LoPiccolo et al., 1979): it is an adaptation of the Sexual History Form. Four items about sexual satisfaction were retained, which reflects either male or female global sexual functioning. A score between

0-24 can be obtained. Higher scores indicate greater problems with sexual satisfaction.

It is a discrete quantitative variable.

6.4.2 DEPENDENT VARIABLE

6.4.2.1 Main dependent variable

Health-related quality of life (HRQoL) is the main dependent variable of the trial and It will be evaluated using EQ-5D-5L questionnaire (see ANNEX E). It is a discrete quantitative variable.

EQ-5D-5L provides a profile of HRQoL of the patient that can be used in the clinical and economic evaluation of health care as well as in population health surveys. This questionnaire consists of 2 parts: the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (EQ VAS).

The descriptive system covers 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which has 5 levels (from "no problems" to "extreme problems"). Therefore, a score of 5 to 25 can be obtained. The higher this score is, the worse is the quality of life.

The EQ VAS provides a quantitative measure of how patients judge their own health by a 20 cm visual analogue scale numbered from 1 to 100. Patients will have to mark with an X how healthy they feel that day and, to facilitate the registration of scores, they will have to write the number they marked on the scale in a box.

To convert the EQ-5D-5L descriptive system and the EQ Visual Analogue scale scores into a single value, the "EQ-5D-5L Crosswalk Index Value Calculator" will be used, an Excel file containing the EQ-5D-5L value sets available from the EuroQol web.

6.4.2.2 Secondary dependent variable

Quality of health care is the secondary dependent variable. PREMs questionnaire will be used to measure it. It is composed of polytomous qualitative variables.

There are different PREM tests validated for different situations (hospital, surgical, primary care) but no one specific to this study. Picker patient experience questionnaire (PPE-15) will be use while developing an appropriate questionnaire. It is a fifteen items questionnaire covering eight domains: Information and education, coordination of care, physical comfort, emotional support, respect for patient preferences, involvement of family and friends, continuity and transition, and overall impression (see ANNEX F).

6.4.3 COVARIATES

There are other variables that need to be considered to interpret the outcomes due to their influence on the QoL of any person or specifically on MS patients, being bad prognosis factors. As these variables could act as confounders, to increase the validity of our study, we will have to control them. Besides, these confounder variables will be contemplated as they can better define the population of the study and would make possible a deeper analysis. This confounding effect of these variables can be minimized using a regression analysis.

- Age: generally, the quality of life related to health deteriorates as age increases. It is measures in years, so it is a discrete quantitative variable.
- Gender: male or female, it is a dichotomous qualitative variable. It is demonstrated that, as a general rule, women have a greater predisposition to develop diseases and in the long term shows a higher degree of dependency, what is reflected in their QoL. However, women with MS have a better prognosis than men due to a less disability accumulation.
- Lifestyle: it will be assessed as active or inactive, that is a dichotomous qualitative variable. All people, and specifically MS patients, usually complain less when they keep an active lifestyle.
- Socioeconomic level: education and occupation. Both polytomous qualitative variables.
- MS phenotype: it is a dichotomous qualitative variable, relapsing or progressive. Progressive forms of MS tend to manifest more aggressively than RRMS.

- EDSS: it is considered as a discrete quantitative variable since it measures in numerical form the degree of physical disability.
- Duration of MS: although in the short term an early onset is a factor of good prognosis, the decrease in functionality can be reflected in the QoL. It is measured in years, so it is a discrete quantitative variable.

Some of these variables will be obtained from the clinical history of the patients.

6.5 PROCEDURES

Once the sample has been recruited according to the inclusion and exclusion criteria patients will be asked to sign informed consent as they agree to participate in the study.

At the baseline visit and at the 3 follow-up appointments scheduled for the study, the patients on which the "intervention" will be applied will compile, just before entering the visit, a 10-15 minutes questionnaire consisting of 9 valid self-report scales that evaluate the independents variables described above. For this, an electronic device placed in the waiting room and in the "Hospital de Día" will be used. The information is loaded in real time in the patient clinical history so that the neurologist can analyse and interpret the information prior the visit. Subsequently, patient and neurologist will discuss the results and the necessary measures, satisfactory for both parts, will be taken.

Besides, all selected patients will fill the EQ-5D-5L and PPE-15 questionnaires at the baseline visit prior the meeting (completing the form according to previous visits) and at the last follow-up visit after it. These results will be transferred to a different database to assess whether the routine collection of PROMS could improve HRQoL and health care.

7 STATISTICAL ANALYSIS

7.1 DESCRIPTIVE ANALYSIS

The qualitative variables will be summarized in proportions stratified by the intervention and control group.

The quantitative variables will be summarized as means, standard deviation; medians, interquartile range (IQR), stratified again by the intervention and control group.

The statistics will be accompanied by the appropriate graphs: bar charts for qualitative variables and box plots for quantitative variables.

7.2 BIVARIATE INFERENCE

The difference of proportions of the qualitative variables between intervention and control will be contrasted using Chi-square contrast and Fisher exact test (when the expected frequencies are less than 5).

The difference of means and medians of the quantitative variables between the groups will be tested using the t-Student and the Mann-Whitney U, respectively.

7.3 MULTIVARIATE ANALYSIS

To perform the multivariate analysis the dependent variables will be categorized into two groups, good and rest.

To assess the association between QoL and the different symptoms experienced by MS patients, adjusted by potential confounders described above, it will be performed a multivariate linear regression model.

As It is very possible that the independent variables are tightly related (problem denominated multicollinearity), two logistic regressions, one for categorized EQ-5D-5L and another one for categorized PPE-15, will be necessary to do.

The entire statistical analysis of the variables will be performed using the Statistical Package for the Social Sciences programme (SPSS) 19.0. All tests mentioned above, will be two-sided and p values <0.05 will be considered significant and $p<0.001$ will be considered highly significant.

8 FEASIBILITY

8.1 RESEARCH TEAM

The principal investigator (PI) will be a neurologist from the Santa Caterina Hospital with a great curriculum in the context of research who will coordinate the entire project; participate in the follow-ups of the patients; interpret the statistical analysis; write the final paper and present the results.

Another neurologists (NRL) from the Neuroimmunology and Multiple Sclerosis Unit of different hospitals will participate in the follow-ups.

All the personnel of the Unit will know the operation of the application so that they can explain it to the patients if necessary.

A qualified statistician (SS) who will make the statistical analysis of the results.

8.2 WORK PLAN

8.2.1 STAGE I: Protocol design

This level consists on literature review for the elaboration of the study, the development of the protocol and subsequent presentation to the CEIC for its approval.

The approximate duration of this stage will be about 4 months, varying according to the time that the CEIC ("Comitè Ètic d'Investigació Clínica") takes to approve the protocol.

8.2.2 STAGE II: Preparation and initial coordination

In this stage, the members of the research team will be gathered in the Girona hospital. All the details of the project will be presented so that everyone knows what their role is within the study and and a chronogram will be created to clarify the different phases of the study. All doubts that staff have will be resolved at this time. It will be programmed new meeting during the study to evaluate the problems that have been experienced until the moment and propose potential improvements. All the team will keep in touch via e-mail.

At the same time, the application that is used in the data collection is developed and a database is created for the compilation of information.

This stage will last 3 months, due to the development of the application.

8.2.3 STAGE III: Data collection

It is estimated that this phase will last 2 years and 1 month

8.2.3.1 Sample collection-Screening visit

During a routine visit, the principal investigator and the neurologists of each centre will select patients who meet the inclusion and exclusion criteria. They will be proposed to be part of the study and be explained the purpose of the study and the procedure. At the same time, the information sheet and the consent that must be signed if they agree will be given to the patients.

The collection of the sample will last approximately 2 months, being able to conclude before once it a sufficient number of patients is recruited.

8.2.3.2 Baseline visit and follow-ups

Patients will be cited every 6 months, following the usual schedule of patients with MS.

At the baseline visit, 6 months after the screening visit, the operation of the application will be explained and the questionnaire will be filled for the first time. Patients will be contacted by phone a week before so that they attend the appointment at least 15 minutes in advance (at the baseline visit it has to be earlier). In addition to this visit, the patient will have to answer the questionnaire in 3 more visits, at 12, 18 and 24 months.

Patients who do not receive the intervention will only have to fill out the questionnaires at the baseline visit and at the last follow-up visit.

8.2.4 STAGE IV: Data analysis and article elaboration

Once the data collection is complete, the statistician will analyse the data and present the results to the rest of the research team for its interpretation in a final meeting.

According to conclusion of that meeting, the main investigator will develop the final article.

This stage will take 4 months.

8.2.5 STAGE V: Results publication and dissemination

The final article will be published in a neurology journal in order to properly disseminate the results of the study. Besides, the results will be exhibited in national and international congresses of specialists.

This last stage will last 3 months.

8.3 STUYDY CHRONOGRAM

The full study will last 3 years and 3 months, but may vary depending on the time it takes the CEIC to approve the study and the time it takes to collect the sample (see ANNEX I)

9 ETHICAL CONSIDERATION

The research protocol will be presented for approval by the Clinical Research Ethical Committee (CEIC, "Comitè Ètic d'Investigació Clínica") of every centre participating in the study. All the recommendations of the committee will be considered before the study begins.

This protocol will be carried out in accordance with the ethical principles established by the World Medical Association in the Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects (last updated in October 2013).

Personal and clinical information of patients obtained during the study will be kept confidential and only will be used with the purpose of the research according to "*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales".* Moreover, all the data will be analysed anonymously. Patients will always be allowed to modify or destroy any of their collected data.

Before being included, following the "*Ley 41/2002 Básica Reguladora de la Autonomía del Paciente y de Derechos y Obligaciones en materia de información y documentación clínica"*, the participants will be asked to sign voluntarily the informed consent (see ANNEX H) after receiving appropriate information about procedures through a personal conversation with the research stuff and the information sheet (see ANNEX G). Participants have the right to withdraw the consent without having a negative effect on the relationship with their assigned doctor or treatment received.

No conflicts of interest with any part is related to this study.

10 STUDY LIMITATIONS

In this study there are some potential limitations that have been contemplated to try to minimize them:

- To avoid selection bias caused by the sampling method, exclusion and inclusion criteria will be defined and patients who wish to participate in the study must fulfill them. Also, the sample will be randomized.
- Considering the limited burden of patients followed in the Neuroimmunology and Multiple Sclerosis Unit of Santa Caterina Hospital (Girona), the main centre of the study, to get the sample in an acceptable period of time it has been necessary to carry out a multi-centric study.
- Owing to the characteristics of the intervention, it is impossible to design a blinded study. An open-labelled trial will be carried out, assuming a possible transfer of information between both groups. To minimize it, patients will be asked not to share information among themselves about the questionnaires.
- Another limitation regarding the study design is that it is possible that a Hawthrone effect (information bias) occurs. That is, the patient may change some aspect of his behavior as a result of knowing that he is being studied, not because of any type of intervention relative to the study.
- The first time the patient completes the questionnaire it will be necessary to explain to him how it works with the consequent consumption of nursing time or of the neurologists themselves.
- Patients with large hand disability cannot fill the application form. Patient companion or some team member will have to fill it out.
- The sample is a relatively young population. Because data collection is done electronically, this can pose some difficulty for older people if the intervention becomes part of the usual clinical practice.

- There are unexplored symptoms such as cognitive deficit. Work is being done on recollection of Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ – see ANNEX J) battery (Benedict, et al., 2003).
- There is no specific PREMs questionnaire for this situation. The research team will evaluate which are the most important items that this questionnaire should include to develop it.

11 BUDGET

Many of the activities in this study will not generate any cost. Visits and procedures that are included in the routine clinical practice will not be contemplated in the budget of this study, bibliography research and protocol will be done by the research team that will not receive any compensation for their work.

- PERSONNEL

A qualified analyst will be hired to periodically evaluate the data.

Owing to the requirement to conduct a multicentre study, it will be necessary a data manager to inspect the information.

In addition, the expenses derived from the meetings will be considered. The transfers and the diets of a neurologist for each collaborating center will be included.

- MATERIAL

For the collection of data, electronic devices will be needed. Itis estimated that the desired sample will be obtained with the participation of 3 other hospitals. Approximately 4 devices will be needed per centre.

It is also necessary an application able to dump the data of the patients to the currently used assistance program.

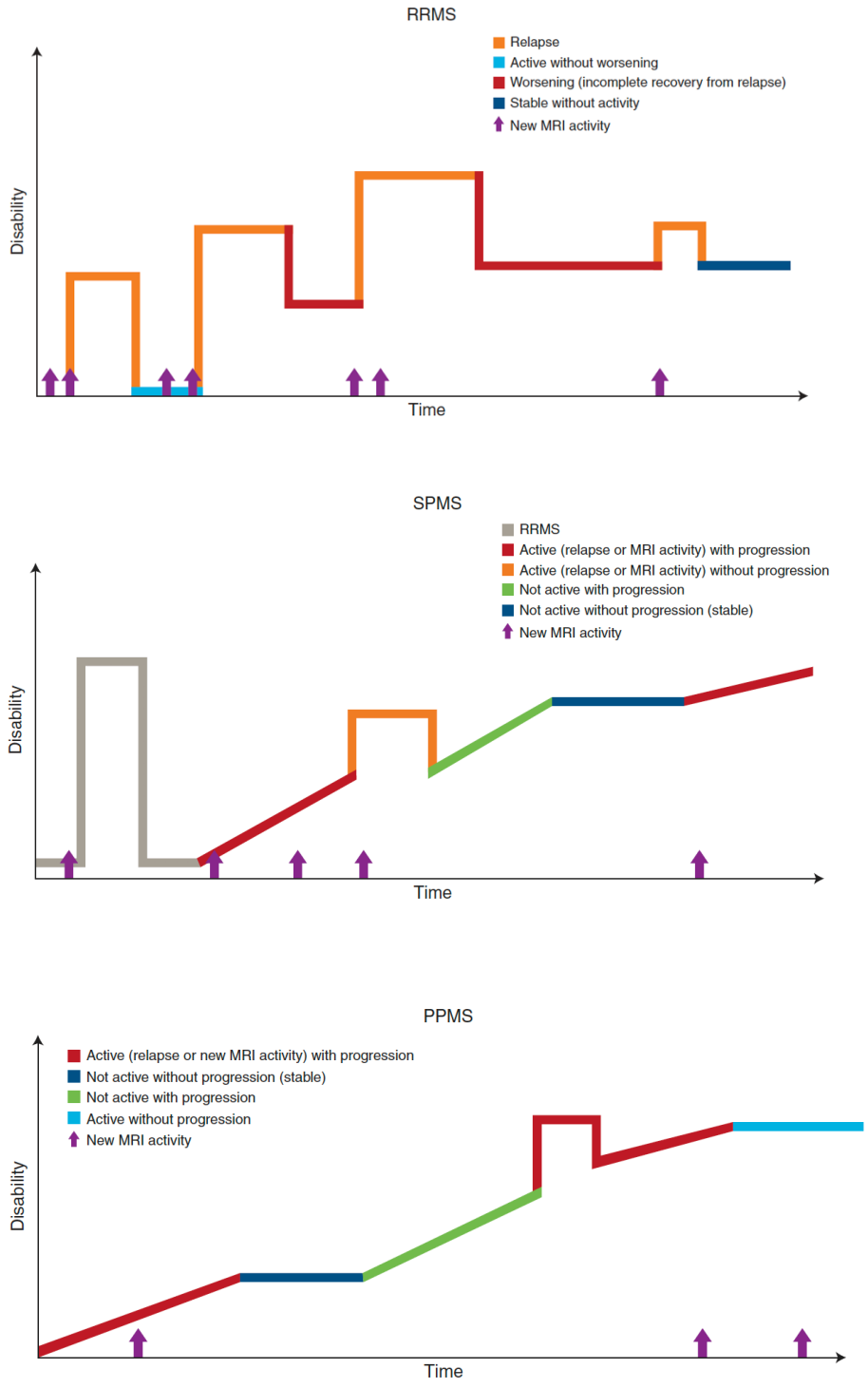
- PUBLICATION AND DISSEMINATION

The publication budget has been estimated as well as the assistance of the research team to conferences and congresses (registration, transport and accommodation included).

	Amount	Price/Unit	Total
PERSONEL			
Statistician	50 hours	30 €/hour	1.500 €
Data manager	3 hours/week x 100 weeks	35 €/hour	10.500 €
Coordination and meetings	3	150 €	450 €
MATERIALS AND SERVICES			
Electronic device	16	94 €	1.504 €
Software	1	3.500 €	3.500 €
PUBLICATION AND DISSEMINATION			
Publication cost	1	800 €	800 €
Conferences and congress	2	1.800 €	3.600 €
		TOTAL	**21.854 €**

12 ANNEXES

ANNEX A. Clinical course of MS



ANNEX B. 2017 McDonald diagnostic criteria

✓ *Requires elimination of more likely diagnoses*
✓ *Requires demonstration of dissemination of lesions in the central nervous system in space and time*

CLINICAL PRESENTATION	ADDITIONAL CRITERIA TO MAKE MS DIAGNOSIS
…in a person who has experienced a typical attack/CIS at onset	
• 2 or more attacks and clinical evidence of 2 or more lesions; OR • 2 or more attacks and clinical evidence of 1 lesion with clear historical evidence of prior attack involving lesion in different location	None. DIS and DIT have been met.
• 2 or more attacks and clinical evidence of 1 lesion	DIS shown by <u>one</u> of these criteria: - additional clinical attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial or spinal cord
• 1 attack and clinical evidence of 2 or more lesions	DIT shown by <u>one</u> of these criteria: - Additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
• 1 attack and clinical evidence of 1 lesion	DIS shown by <u>one</u> of these criteria: - Additional attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial or spinal cord **AND** DIT shown by <u>one</u> of these criteria: - additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
…in a person who has steady progression of disease since onset	
1 year of disease progression (retrospective or prospective)	DIS shown by at least <u>two</u> of these criteria: - 1 or more MS-typical T2 lesions (periventricular, cortical, juxtacortical or infratentorial) - 2 or more T2 spinal cord lesions - CSF oligoclonal bands

DIT = Dissemination in time **CNS** = central nervous system **CSF** = cerebrospinal fluid
DIS = Dissemination in space **T2 lesion** = hyperintense lesion on T2-weighted MRI

ANNEX C. Kurtzke Expanded Disability Status Scale (EDSS)

- ❑ 0.0 - Normal neurological exam (all grade 0 in all Functional System (FS) scores*).
- ❑ 1.0 - No disability, minimal signs in one FS* (i.e., grade 1).
- ❑ 1.5 - No disability, minimal signs in more than one FS* (more than 1 FS grade 1).
- ❑ 2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).
- ❑ 2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).
- ❑ 3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
- ❑ 3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).
- ❑ 4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters.
- ❑ 4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.
- ❑ 5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
- ❑ 5.5 - Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0).
- ❑ 6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).
- ❑ 6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).
- ❑ 7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone).

❑ 7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+).

❑ 8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems).

❑ 8.5 - Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems).

❑ 9.0 - Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+).

❑ 9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+).

❑ 10.0 - Death due to MS.

---

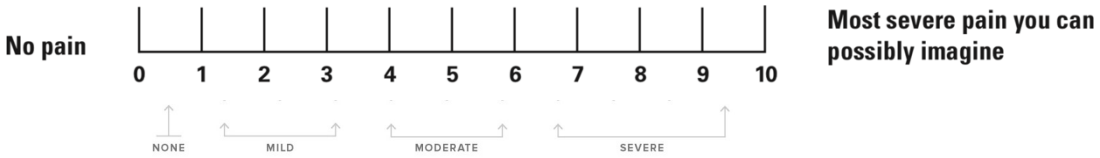
*Excludes cerebral function grade 1.

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the Functional System score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in Functional Systems scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS.

ANNEX D. Patient Reported Outcomes Measures questionnaires

1. 0-10 NUMERIC PAIN RATING SCAL

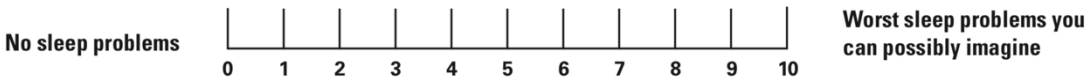


2. 0-10 NUMERIC SPASTICITY RATING SCALE

3. SPASM FREQUENCY SCALE

How often are muscle spasms occurring?	
0	No spasms
1	Spasms induced only by stimulation
2	Spasms occurring less than once per hour
3	Spasms occurring between 1 and 10 times per hour
4	Spasms occurring more than 10 times per hour

4. SLEEP QUALITY SCALE



5. 0-10 NUMERIC AMBULATION RATING SCALE

6. MODIFIED 10-ITEMS BARTHEL INDEX

Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	_____
BATHING 0 = dependent 5 = independent (or in shower)	_____
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	_____
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	_____
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	_____
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	_____
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	_____
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	_____
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	_____
TOTAL (0–100):	_____

7. BLADDER CONTROL SCALE

	None	One	2-4 times	More than one a week but not daily	Daily
How many times have you lost control of urine or had an accidental leak leak?	0	1	2	3	4
How many times have you **almost** lost control of urine or had an accidental leak?	0	1	2	3	4
How many times have you changed your activities due to problems with urine control?	0	1	2	3	4

To what degree have your urine problems limited your quality of life lately?

Nothing									Severely
1	2	3	4	5	6	7	8	9	10

8. FATIGUE SEVERITY SCALE

	Scores 1 = Strongly Disagree; 7 = Strongly Agree						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

9. SEXUAL SATISFACTION SCALE

Do you have sex with your partner? YES = 1 (continue with the questionnaire below)				NO = 0 (it is not necessary to continue the questionnaire)		
	Extremly satisfied	Moderately satisfied	Slightly satisfied	Slightly dissatisfied	moderately dissatisfied	Extremly dissatisfied
How satisfied have you been with the affection expressed physically in your intimate relationships?	1	2	3	4	5	6
How satisfied have you been with the variety of sexual activities with your partner?	1	2	3	4	5	6
How satisfied have you been with your sexual activity in general?	1	2	3	4	5	6
How satisfied do you think your partner has been with your sexual activity in general?	1	2	3	4	5	6

ANNEX E. EQ-5D-5L Health Questionnaire

Figure 1: EQ-5D-5L (UK English sample version)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN / DISCOMFORT

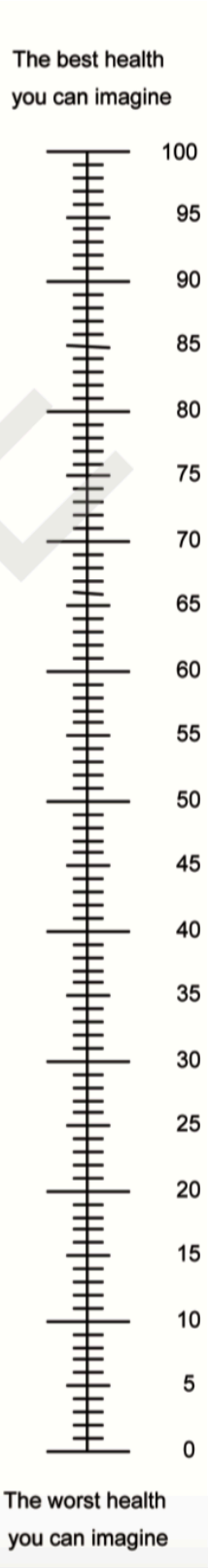
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



ANNEX F. Picker Patient Experience Questionnaire (PPE-15)

Jenkinson C, Coulter A, Bruster S. The Picker Patient Experience Questionnaire: Development and validation using data from in-patient surveys in five countries. Int J Qual Health Care 2002; 14(5):353-58, by permission of Oxford University Press.

The text that follows was pulled directly from the Appendix of the source article indicated above.

1. When you had important questions to ask a doctor, did you get answers that you could understand?

   Yes, always Yes, sometimes No I had no need to ask

2. When you had important questions to ask a nurse, did you get answers that you could understand?

   Yes, always Yes, sometimes No I had no need to ask

3. Sometimes in a hospital, one doctor or nurse wills ay one thing and another will say something quite different. Did this happen to you?

   Yes, often Yes, sometimes No

4. If you had any anxieties or fears about your condition or treatment, did a doctor discuss them with you?

   Yes, completely Yes, to some extent No I didn't have any anxieties or fears

5. Did doctors talk in front of you as if you weren't there?

   Yes, often Yes, sometimes No

6. Did you want to be more involved in decisions made about your care and treatment?

   Yes, definitely Yes, to some extent No

7. Overall, did you feel you were treated with respect and dignity while you were in hospital?

   Yes, always Yes, sometimes No

8. If you had any anxieties or fears about your condition or treatment, did a nurse discuss them with you?

   Yes, completely Yes, to some extent No I didn't have any anxieties or fears

9. Did you find someone on the hospital staff to talk to about your concerns?

   Yes, completely Yes, to some extent No I had no concerns

10. Were you ever in pain?

Yes No

If yes…

a. Do you think the hospital staff did everything they could to help control your pain?

Yes, definitely Yes, to some extent No

11. If your family or someone else close to you wanted to talk to a doctor, did they have enough opportunity to do so?

Yes, definitely Yes, to some extent No No family or friends were involved

My family didn't want or need information I didn't want my family or friends to talk to a doctor

12. Did the doctors or nurses give your family or someone else close to you all the information they needed to help you recover?

Yes, definitely Yes, to some extent No No family or friends were involved

My family didn't want or need information

13. Did a member of staff explain the purpose of the medicines you were to take at home in a way you could understand?

Yes, completely Yes, to some extent No I didn't need an explanation
I had no medicines ---------- Go to question 15

14. Did a member of staff tell you about medication side effects to watch for when you went home?

Yes, completely Yes, to some extent No I didn't need an explanation

15. Did someone tell you about danger signals regarding your illness or treatment to watch for after you went home?

Yes, definitely Yes, to some extent No

ANNEX G. Information sheet for participants

HOJA DE INFORMACIÓN PARA EL PACIENTE

Título del estudio: ensayo abierto aleatorizado para valorar los cambios en la calidad de vida en pacientes con esclerosis múltiple mediante la recogida sistemática de datos en condiciones de práctica clínica habitual.

Nombre del investigador: .....Tfno.:.....

Dirección: .....

Estimado paciente,

Nos dirigimos a usted para informarle sobre el desarrollo de un estudio que se está llevando a cabo en su hospital, al que se le invita a participar.

El estudio ha sido aprobado por el Comité Ético de Investigación Clínica correspondiente y su Comunidad Autónoma y se llevará a cabo de acuerdo con los requerimientos expresados en la Declaración de Helsinki.

Para que pueda tomar una decisión informadas sobre si desea o no participar en este estudio, en este documento se describen sus derechos y obligaciones como paciente, los procedimientos exigidos por el estudio y los posibles beneficios y riesgos de participar. Lea esta hoja informativa con atención, y consulte con las personas que considere oportuno. Nosotros le aclararemos cualquier duda que le pueda surgir.

Participación voluntaria y compensación económica

Debe saber que su participación en el estudio es totalmente voluntaria. Es usted quien decide libremente si participa o no, y su médico no influirá ni juzgará la decisión que tome. Usted puede negarse a participar antes o durante el estudio sin que de ello se derive ningún perjuicio en su tratamiento, ni se vea afectada su atención médica o suponga una pérdida de los beneficios a los que usted tiene derecho. Aunque usted decida participar, también debe saber que su médico del estudio tiene el derecho de retirarle del mismo en cualquier momento con o sin su consentimiento, y usted recibirá una explicación adecuada del motivo que ha ocasionado su retirada.

Usted no recibirá ninguna compensación económica por participar en el estudio.

¿Por qué se hace este estudio?

El estudio ha sido diseñado para evaluar si es posible una mejora de la calidad de vida mediante la recogida sistemática de algunos síntomas de la enfermedad y su manejo correspondiente.

Las complicaciones psicológicas, cognitivas y psiquiátricas que sufren los pacientes con esclerosis múltiple (EM) dan una idea del alcance de esta enfermedad que va mucho más allá del deterioro de la función física y de la discapacidad. Por ello, en los últimos años ha crecido el interés por el estudio de la calidad de vida como una medida que nos va a ayudar en la atención global de nuestros pacientes. Es más, la calidad de vida se considera cada vez más importante en la evaluación de la efectividad del tratamiento y las autoridades sanitarias recomiendan su evaluación como parte de la experiencia del paciente con su enfermedad.

Si atendemos a los síntomas más comunes de la EM tales como la fatiga, depresión, alteraciones cognitivas y disfunción vesical, podemos comprobar que estos síntomas son percibidos por los pacientes como debilitantes, y afectan en gran medida a su calidad de vida más allá del grado de discapacidad en determinados casos.

Sin embargo, en la práctica clínica diaria, es decir, dentro de la atención rutinaria que usted recibe, la evaluación de estos síntomas y de la calidad de vida sigue siendo poco frecuente a pesar de que son importantes predictores del curso de la enfermedad, incluso en estadios tempranos. Es por ello que se necesitan estudios como éste al que se le invita a participar.

Valorar su impacto en la calidad de vida y otros síntomas puede servir para alertar a los médicos sobre aspectos que de otro modo se podrían estar ignorando en la atención de nuestros pacientes.

¿Cuántos pacientes participarán y cuánto durará el estudio?

Se estima que en este estudio participen aproximadamente 450 pacientes diagnosticados de esclerosis múltiple, divididos en dos grupos de igual tamaño. Sobre

un grupo se aplicará la intervención y el otro se utilizará como grupo control (ver más abajo). La duración del estudio será de 3 años y 3 meses.

¿Qué tengo que hacer si decido participar?

Si usted decide participar se le pedirá que firme un formulario de consentimiento informado. Una vez que haya firmado su consentimiento, el médico le evaluará según los criterios de elegibilidad para el estudio y se le asignará de forma aleatoria a uno de los dos grupos. El médico que le trata documentará en su historia clínica su voluntad de participar en el estudio, y conservará un formulario de consentimiento informado original firmado y fechado por ambas partes. Usted recibirá un segundo ejemplar.

Al firmar la hoja de consentimiento adjunta, se compromete a cumplir con los procedimientos del estudio que a continuación se exponen:

- Su participación en el estudio no requerirá la realización de pruebas especiales ni visitas adicionales al médico; tampoco serán necesarios procedimientos terapéuticos fuera de la práctica clínica habitual.
- Si forma parte del grupo de intervención, durante los meses programados de duración del estudio, deberá atender 5 visitas: una visita basal que coincidirá con su inclusión en el estudio y 4 visitas de seguimiento a los 6, 12, 18 y 24meses del inicio. Todas las visitas coincidirán con las que normalmente realiza al especialista para el seguimiento de su enfermedad. En la primera y en la última visita, tendrá que rellenar unos cuestionarios de calidad de vida y calidad asistencial. Además, en cada visita su médico le solicitará que cumplimente varios cuestionarios para valorar ciertos síntomas acompañantes de la enfermedad. No deberá compartir con los demás pacientes información sobre estos cuestionarios para evitar la contaminación de la información. En caso de que no pueda acudir a la cita, deberá ponerse en contacto con el personal del estudio para concertar una nueva.
- Si usted forma parte del grupo control, solo deberá realizar los cuestionarios de calidad de vida y calidad asistencial en la visita basal y a los 24 meses.

Al margen de esto, no tendrá que realizar ningún tipo de seguimiento ni prueba especial y el hecho de entrar en el estudio no modificará el tipo de tratamiento que vaya a recibir posteriormente.

¿Cuáles son los riesgos y beneficios de participar en el estudio?

No tendrá un riesgo adicional diferente al que de por sí tiene con su enfermedad. Sin embargo, su calidad de vida, así como la atención médica pueden mejorar como resultado del análisis de la información que aporta sobre su estado de salud durante el estudio. Si forma parte del grupo control, no habrá beneficios específicos relacionados con su participación. Los beneficios serán, en todo caso, los que se deriven de los resultados del propio estudio en caso de que la información obtenida repercuta positivamente en el manejo de su enfermedad.

¿Qué pasará con los datos que se recogen sobre mí?

Toda la información que se obtenga durante el estudio será confidencial y ni usted ni sus datos, en ningún caso, estarán identificados en cualquier informe que se emita de este estudio. Estos datos se van a incluir en un Fichero de Investigación Clínica del Centro y se manejarán de acuerdo con la Ley Orgánica de Protección de Datos Personales y garantía de los derechos digitales 3/2018, de 5 de diciembre, teniendo usted los derechos que la citada ley le reconoce de acceso, rectificación, cancelación y oposición de los datos. Si decide participar en el estudio, sus datos serán accesibles a las Autoridades Sanitarias, Comités Éticos de Investigación Clínica, auditores y al Promotor, para la verificación de los procedimientos y datos obtenidos durante el estudio, sin violar la confidencialidad de sus datos. Los datos del estudio podrán ser publicados en revistas científicas pero su identidad permanecerá confidencial.

Otra información relevante

El investigador informará a su médico de familia acerca de la participación en el estudio, siempre y cuando esté de acuerdo.

Atención: Deberá quedar constancia en la historia clínica del paciente o en el Consentimiento Informado.

¿Con quién puedo contactar para obtener información adicional sobre el estudio?

Su médico y/o miembros de su equipo están a su disposición para atender cualquier consulta que quiera realizar en relación al estudio. Recibirá una copia de este documento de consentimiento informado y podrá solicitar información adicional contactando con el investigador, Dr._____ en el número de teléfono _____.

[Se dispondrá de otras versiones en diferentes idiomas]

ANNEX H. Informed consent

FORMULARIO DE CONSENTIMIENTO INFORMADO

Título del estudio: ensayo abierto aleatorizado para valorar los cambios en la calidad de vida en pacientes con esclerosis múltiple mediante la recogida sistemática de datos en condiciones de práctica clínica habitual.

Yo (nombre del paciente) _____

con fecha de nacimiento: ___/___/___ y DNI: _____

Declaro que:

- He leído este documento y he comprendido el propósito del estudio y los procedimientos que se realizarán durante el mismo.
- He podido hacer todas las preguntas necesarias respecto al estudio y han sido respondidas de manera satisfactoria.
- He comprendido que mi participación es voluntaria, que puedo retirarme del estudio, y que mi participación en el mismo no conlleva ningún perjuicio para mi salud.
- Otorgo libremente mi consentimiento para participar en este estudio, tal como se me ha descrito en este documento.
- Comprendo que recibiré una copia de este documento cuando esté firmado.

Paciente	**Investigador**
Nombre: Fecha: / / Firma:	Nombre: Fecha: / / Firma:

[Se dispondrá de otras versiones en diferentes idiomas]

ANNEX I Study chronogram

ACTIVITIES	PERSONNEL	2018	2019									2020	2021					2022
		DEC	JAN	FEB	MAR	APL	MAY	JUN	JUL	AUG	SEP- DEC	JAN-DEC	JAN-AUG	SEP	OCT	NOV	DEC	JAN-MAR
STAGE I																		
Literature review	PI																	
Protocol developemet	PI																	
CIEC aprovement	CEIC																	
STAGE II																		
Inital oordiantion	TEAM																	
Database creation																		
Application developement																		
STAGE III																		
Screening	PI and NRL																	
Data collection																		
STAGE IV																		
Statistica analysis	SS																	
Results interpretation	PI																	
Article elaboration	PI																	
STAGE V																		
Publication and dissemination	PI																	

ANNEX J Multiple Sclerosis Neuropsychological Questionnaire (MSNQ)

Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ)

Name: _____

Date: _____

Sex (circle one): Male / Female

INSTRUCTIONS: The following questions ask about problems that you may experience. Rate how often these problems occur **AND** how severe they are. Base your ratings on how you have been over the **last 3 months.** Please check the appropriate box.

	Very often, very disruptive (4)	Quite often, interferes with life (3)	Occasionally, seldom a problem (2)	Very rarely, no problem (1)	Never, does not occur (0)
1. Are you easily distracted?	❒	❒	❒	❒	❒
2. Do you lose your thoughts while listening to somebody speak?	❒	❒	❒	❒	❒
3. Are you slow when trying to solve problems?	❒	❒	❒	❒	❒
4. Do you forget appointments?	❒	❒	❒	❒	❒
5. Do you forget what you read?	❒	❒	❒	❒	❒
6. Do you have trouble describing shows or programs recently watched?	❒	❒	❒	❒	❒
7. Do you need to have instructions repeated?	❒	❒	❒	❒	❒
8. Do you have to be reminded to do tasks?	❒	❒	❒	❒	❒
9. Do you forget errands that were planned?	❒	❒	❒	❒	❒
10. Do you have difficulty answering questions?	❒	❒	❒	❒	❒
11. Do you have difficulty keeping track of two things at once?	❒	❒	❒	❒	❒
12. Do you miss the point of what someone is trying to say?	❒	❒	❒	❒	❒
13. Do you have difficulty controlling impulses?	❒	❒	❒	❒	❒
14. Do you laugh or cry with little cause?	❒	❒	❒	❒	❒
15. Do you talk excessively or focus too much on your own interests?	❒	❒	❒	❒	❒

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