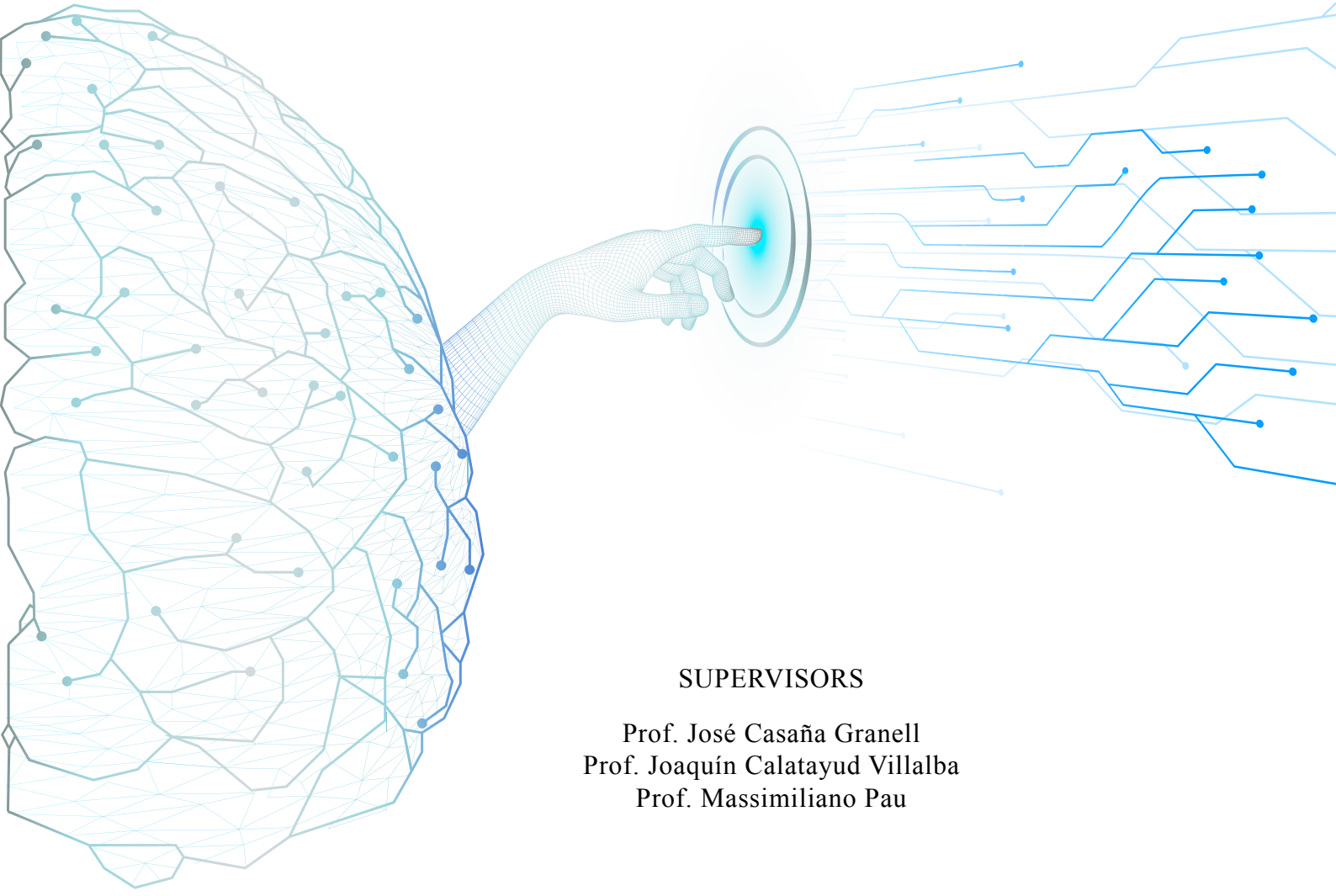
EFFICACY OF AUGMENTED REALITY VERSUS CONVENTIONAL PHYSICAL THERAPY FOR THE IMPROVEMENT OF BALANCE, GAIT, UPPER-LIMB AND DUAL TASK IN PEOPLE WITH MULTIPLE SCLEROSIS

VERÓNICA GEMMA GARCÍA MARTÍ

DOCTORADO EN FISIOTERAPIA
UNIVERSITAT DE VALÈNCIA
JANUARY, 2022



SUPERVISORS

Prof. José Casaña Granell
Prof. Joaquín Calatayud Villalba
Prof. Massimiliano Pau

DOCTORAL THESIS

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Author:
Dña. Verónica Gemma García Martí

Supervisors:
Prof. José Casaña Granell
Prof. Joaquín Calatayud Villalba
Prof. Massimiliano Pau

Valencia, January 2022

A mi familia que, desde arriba,
comparte, con la de abajo,
la felicidad de mis logros.

Prof. José Casaña Granell, Professor at Universitat de València, Physical Therapy department of Universitat de València.

Prof. Joaquín Calatayud Villalba, Professor at Universitat de València, Physical Therapy department of Universitat de València.

Prof. Massimiliano Pau, Professor at Università degli Studi di Cagliari, Department of Mechanical, Chemical and Materials Engineering

CERTIFY:

That this work, entitled "Efficacy of augmented reality versus conventional physical therapy for the improvement of balance, gait, upper-limb and dual task in people with multiple sclerosis" has been carried out under his Direction at the Department of Physical therapy of the University of Valencia and in "Laboratorio di Biomeccanica ed Ergonomia Industriale" from the Università degli Studi di Cagliari (Cagliari, Italy) by Verónica Gemma García Martí, to apply for the degree of Doctor of Phylosophy.

Having concluded, and meeting in his opinion the conditions of originality and rigor scientifically necessary, authorize its presentation so that it can be defended before the corresponding court.

And for the record, they issue and sign this certification in Valencia, on 15 January 2022.

Sig.Jose Casaña Granell.	Sig. Joaquín Calatayud Villalba	Sig.Massimiliano Pau

Acknowledgments

La adversidad es ocasión de virtud.

Lucio Anneo Seneca.

As any PhD candidate knows, it is very difficult to describe what the years writing a PhD thesis means to us. It seems to me that 'adversity' is an apt label for the mix of feelings, experiences, and obstacles faced along the way, resulting in professional and personal lessons.

As it is difficult to settle on a particular order of acknowledgments, I will write them in chronological order.

First of all, I am thankful for the boundless efforts of my parents in every single aspect of my life, which have enabled me to become the person that I am today. They have transmitted to me the importance of doing what I am passionate about, and have motivated me to dream even of what I believed to be unattainable. But above all, I am especially indebted to them for inspiring me never to lose humanity and faith in what I do.

I am grateful to Prof. Roberto Llorens for introducing me to the field of virtual reality in neurorehabilitation as early as my MSc studies.

My deepest and sincerest gratitude goes to my PhD thesis supervisors, Prof. Jose Casaña Granell, Prof. Joaquín Calatayud Villalba and Prof. Masimiliano Pau. For their endless help, dedication, support and patience during all these years in many different aspects, and especially to Massimiliano for introducing me to the field of Multiple Sclerosis, and giving me a way into many other projects and conferences where I have had the opportunity to meet the best researchers in the field.

My appreciation extends to Prof. Eleonora Cocco, since without her help the different studies of this thesis would not have been possible. Also to Patricia, Angela, Cristina, Giancarlo, and Jessica for their help in the recruitment process.

My thanks also go to my lab colleagues Giuseppina and Micaela, for always being there to help me overcome “engineering problems” in the lab, and for their willingness to spend time with me explaining interesting aspects of different technologies.

My infinite thanks go to “my students” Elena and Nicoletta for such beautiful moments shared during the studies – both good and not so good (we all learn from these). Thanks also to Michela for her help with the patient treatments during the studies.

However, my biggest acknowledgement in this thesis is owed to my patients, particularly those who participated in this study and believed in me and in the study since the beginning. I am also grateful to them for sharing with me such good memories during and after the sessions. Even if I was called the motivator, I take the motivation they still give me to go ahead as a must.

Finally, my heartfelt thanks go to all my loved ones, family and friends, from Italy, Spain and Switzerland, and my friends conducting a PhD who have always been there for me and offered to sit down with me for a talk, a videocall, a coffee or a beer anytime I needed to unburden myself and find the strength to keep going.

Preface

Technology has been with us for some years to help us in more and more areas of our society. For more than two decades, the field of physiotherapy and rehabilitation has benefitted from a wide range of technologies, such as robotic systems that have proven to be effective in improving the motor recovery of many patients suffering from neurological damage. However, augmented reality, virtual reality, and even the Metaverse now, are beginning to take center stage in our lives as well as in the field of rehabilitation. But why are they important in the rehabilitation of patients with multiple sclerosis?

Multiple sclerosis is a degenerative disease. Thus, unlike other neurological pathologies, it requires lifelong treatment. Although it is possible to try to stop the development of the pathology, to date there are no treatments that reverse the damage caused by it. This means that patients must stay physically active and attend physical therapy sessions on a regular basis. However, this kind of treatment is not within the reach of all patients, either due to cost, time, or the constraints posed by constant travel, since, unfortunately, not all patients have access to a specialized therapy center close by.

Augmented reality, as well as virtual reality, can help patients improve their motor level in non-severe cases. What is more, not only can these technologies be used in rehabilitation sessions by their physiotherapists, but also through telerehabilitation, at the patient's home. In this way, they have the potential to fill the gap in treatment adherence practices, which has always been one of the biggest obstacles in the rehabilitation process.

There are already many large companies worldwide that have echoed this need and are implementing new software developed ad hoc for patients with a wide variety of pathologies. However, the clinical and research figure or manager is crucial for the development of these new programs where the needs of the patient are the priority.

In this thesis, it will be showed how augmented reality can help in the rehabilitation process in multiple sclerosis patients, but also how creativity and a different kind of performance proposed by the therapist in the same game can enhance the functional recovery in gait, balance, the upper limbs and dual task.

Abstract

Introduction: Multiple Sclerosis is a multifocal progressive disorder of the central nervous system, often resulting in diverse clinical manifestations. People with Multiple Sclerosis (pwMS) often suffer from different motor disturbances in balance, gait, and the upper limbs, including while they are performing some daily life activity, which also affects dual tasking. Augmented reality (AR) is becoming a popular training tool for functional recovery in physical therapy (PT).

Therefore, the aim was to demonstrate the efficacy of AR for balance, gait, the upper limbs and dual task, as one more tool in the wide range of possibilities in PT for pwMS.

Methods: 30 pwMS were equally randomized into the augmented reality group (ARG) or the conventional therapy group (CTG). Each group received balance, gait, upper-limb and dual task training sessions for four consecutive weeks, three sessions per week, 45-minute sessions. Clinical tests, instrumented outcome measures, and self-reported questionnaires were collected upon initiation of the intervention programs and at the end.

Outcomes: Final analysis included 23 patients (12F,11M; mean age, (S.D.) = 49.83(10.82) years; mean EDSS (S.D.) = 4.64 (1.15)). ANOVA revealed statistically significant changes in time but not in the time per group interaction. Both groups showed a main effect of time in 36, and only ARG in 7 out of 48 variables considered for the upper limbs, balance, gait and dual task. No statistically significant differences in favor of the ARG were observed

Conclusions: It is demonstrated that upper-limb, balance, gait and dual task training based on AR is an effective method as conventional therapy for pwMS.

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List of acronyms

2MWT 2 Minute Walking Test, 95

6MWT 6 Minute Walking Test, 95

9HPT 9 Hole Peg Test, 94

AAROM Active Assistive Range Of Motion, 66

AD Assistive Devices, 60

ADF Ankle Dorsi Flexion, 43

ADL Activities Daily Living, 38

AFO Ankle Foot Orthosis, 60

AP Adjustment phase, 103; Antero Posterior, 120

APCOPD Antero Posterio Centre Of Preasure Displacement, 148

APD Afferent Pupillary Defect, 39

APTA American Physical Therapy Association, 93

AR Augmented Reality, 73

ARG Augmented Therapy Group, 83

AROM Active Range of Motion, 66

ATM Acute Transverse Myelitis, 33

BBB Blood Brain Barrier, 25

BBS Berg Balance Scale, 97

BBT Box and Blocks Test, 93

BOS Base Of Sustentation, 64

CI Curvature Index, 126

CIS Clinically Isolated Syndrom, 31

CM Complete Movement, 125

CNS Central Nervous System, 21

COM Centre Of Mass, 43

COP Centre Of Pressure, 64

CSF Cerebro Spinal Fluid, 31

CTG Conventional Therapy Group, 83

DASH Disabilities of the Arm, Shoulder and Hand, 112

DIS Disseminated in Space, 30

DIT Disseminated in Time, 30

DSS Kurtze Disability Status Scale, 36

DT Dual Task, 113
DTM Disease Modifying Therapy, 46
EBV Epstein Barr Virus, 30
EC Eyes Closed, 148
EDSS Expanded Disability Status Scale, 36
EEs Enriched Enviroments, 75
EG ExerGames, 86
FE Flexo Extension, 132
FSST Four Square Step Test, 97
GA Gait Analysis, 98
GCD Gait Cycle Duration, 132
GP Going Phase, 103
GPS Gait Profile Index, 132
HGD Hand Grip Dynamometer, 111
HTM Hand To Mouth, 99
ICF Classification of Functioning, Disability and Health, 95
IMU Inertial Measurement Unit, 108
LL Lower Limb, 43
MAM-36 Manual Ability Measurement, 112
MIF Maximum Isometric Force, 111
ML Medio Lateral, 120; Motor Learning, 71
MLCOPD Medio Lateral Centre Of Preasure Displacement, 148
MR Magnetic Resonance, 26; Mixed Reality, 73
MRI Magnetic Resonance Imaging, 31
MS Multiple Sclerosis, 21
MSFC Multiple Sclerosis Functional Composite, 96
MSWS-12 Twelve Item Walking Scale, 112
OE Open Eyes, 148
ON Optic Neuritis, 32
PF Plantar Flexion, 43
PPMS Primary Progressive Multiple Sclerosis, 32
PROM Passive Range Of Movement, 66
pwMS People with Multiple Sclerosis, 25
QOL Quality Of Life, 56
RCT Radomized Control Trial, 83
RIS Radiologically Isolated Syndrome, 32

RM Repetition Maximum, 62

ROM Range Of Motion, 44

RP Returning Phase, 103

RRMS Relapsing Remiting Multiple Sclerosis, 32

SA Sway Area, 104

SCWT Stroop Color Word Test, 113

SF-36 Short Form Health Survey of the Medical Outcomes Study, 113

SPMS Secondary Progressive Multiple Sclerosis, 32

SUS System Usability Scale, 114

T25FW Timed 25 Foot Walk, 96

TUG Timed Up and Go, 108

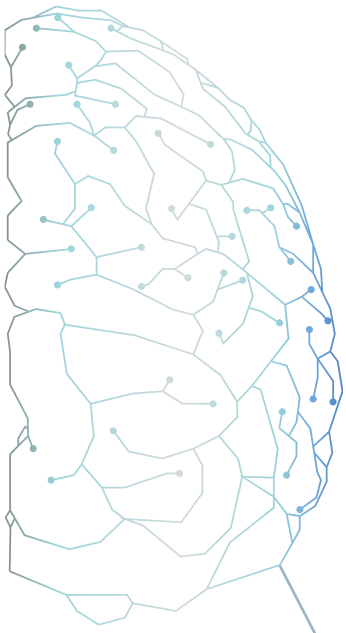
UL Upper Limb, 44

VEs Virtual Enviroments, 74

VR Virtual Reality, 73

Chapter 1

Rehabilitation in Multiple Sclerosis



1 INTRODUCTION

1.1 Multiple Sclerosis

Multiple Sclerosis (MS) has a recent recognition because, even if it makes a fleeting appearance in the early 19th century defined as a "remarkable lesion of the spinal cord accompanied with atrophy"[1], it was not until 1860s when flourish centre stage as clinical neurology[2].

Many definitions are currently available by many authors. For a pathologist, MS is a disorder of the central nervous system (CNS) manifesting as acute focal inflammatory demyelination and axonal loss with limited remyelination, culminating in the chronic multifocal sclerotic plaques from which the disease gets its name. For the patient, MS threatens an apparently infinite variety of symptoms but with certain recurring themes and an unpredictable course. For the neurologist, MS is a disorder of young adults diagnosed on the basis of clinical a paraclinical evidence for at least two demyelinating lesions, affecting different sites within the brain or spinal cord, separated in time. For the clinical scientist, MS is the inflammatory autoimmune disease prototype of the CNS in which knowledge gained across a range of basic and rational strategies for treatment [3].

In summary, MS is an acquired inflammatory and neurodegenerative[4] immune-mediated disorder of the CNS, characterized by inflammation, demyelination and primary or secondary axonal degeneration[5] being the major cause of non-traumatic disability in young adults[6].

1.1.1 Epidemiology

The global distribution of MS can be generalised as increasing with distance north or south of the equator, but that summary conceals many places with disproportionately high or low frequencies[2].

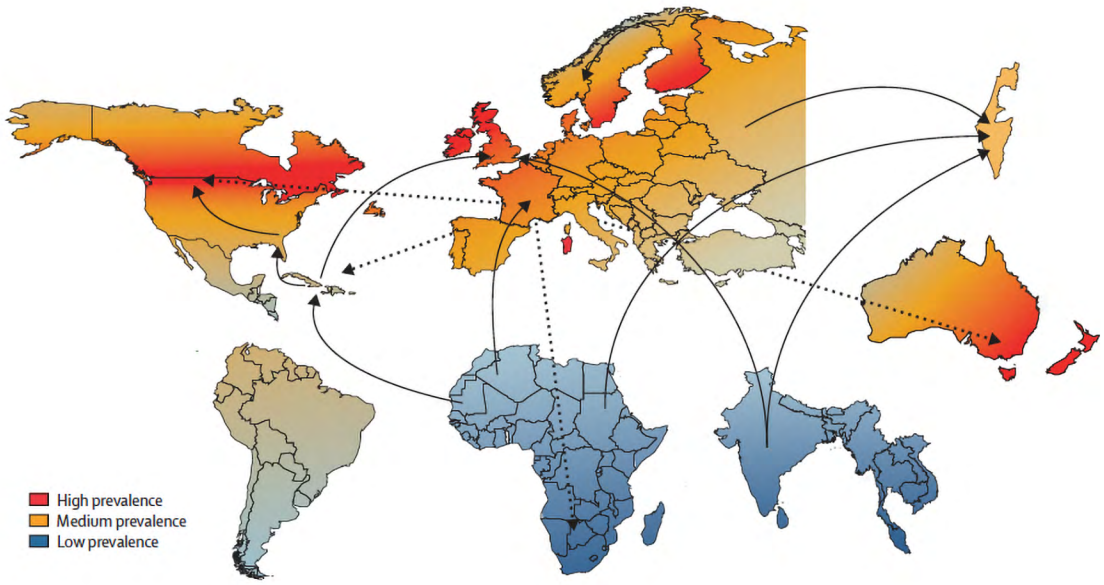


Figure 1. Geography of multiple sclerosis and migrations.

The five continents are depicted to show medium prevalence of multiple sclerosis (orange), areas of exceptionally high frequency (red), and those with low rates (grey-blue). Some regions are fairly uncharted and these colours are only intended to provide an impression of the geographical trends. Major routes of migration from the high-risk zone of northern Europe, especially including small but informative studies, are shown as dotted arrows. Studies involving migrants from low-risk to high-risk zones are shown as solid arrows.
Source: [2]

In the last most complete metanalyses in 2019[7] an estimated 2221188 people worldwide had MS, corresponding to a prevalence of 30:1 cases per 100000 population **(Figure 2)**. Age-standardised prevalence estimates increased by 22:47 cases per 100000 population or 10:4% between 1990 and 2016. Globally there were 18932 deaths due to MS in 2016. Between 1990 and 2016 the age-standardised mortality rate for MS decreased by 11-5%. However, changes by region and country were mostly not significant because of the wide uncertainty intervals.

It is also found a significant association between prevalence and latitude **(Figure 2)**. There is an almost nine times difference in prevalence between countries at the equator and the highest population-weighted average latitude of 74-7°.

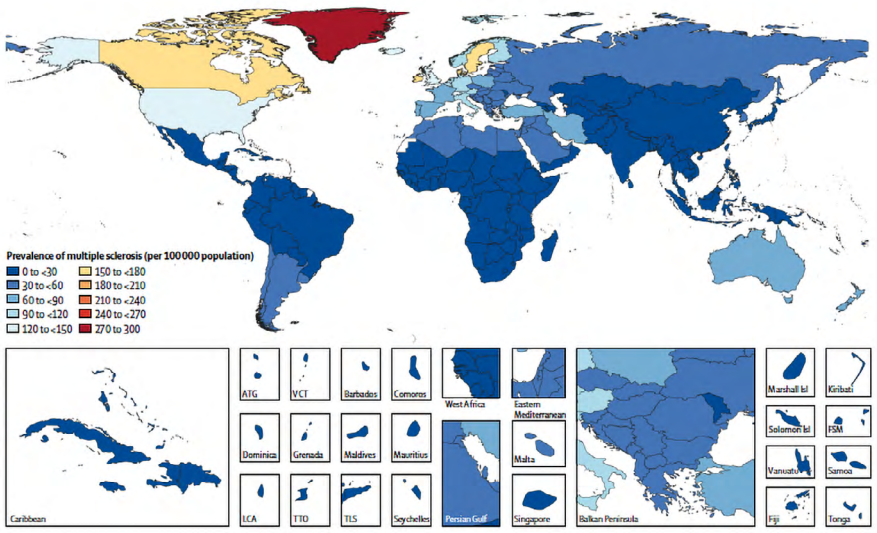


Figure 2. Age-standardized multiple sclerosis prevalence per 100 000 population in 2016 for both sexes, by location.

ATG=Antigua and Barbuda. Isl=Islands. LCA=Saint Lucia. VCT=Saint Vincent and the Grenadines. TTO=Trinidad and Tobago. TLS=Timor-Leste. FSM=Federated States of Micronesia

Source: [8]

The global prevalence of MS differs substantially by sex **(Figure 3)**. Among preteen children, the prevalence of MS is similar in boys and girls. During adolescence, the curves start to diverge, with the prevalence increasing more among girls than boys. This pattern continues until around the end of the sixth decade of life, when the ratio is 2:1 in favour of women. In older people, prevalence generally continues to climb form women, but a slow attenuation in prevalence is seen for men **(Figure 4)**.

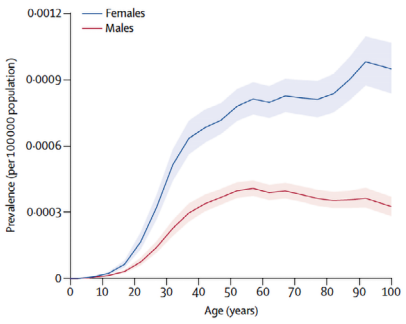


Figure 3. Age-standardized prevalence of multiple sclerosis in 2016, by age and sex.

Shading shows 95% uncertainty intervals.

Source: [8]

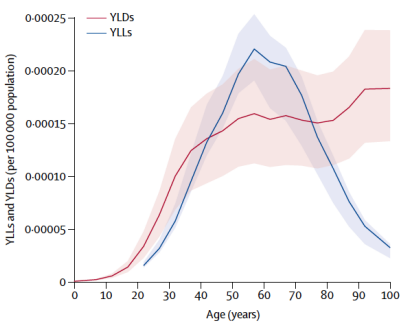


Figure 4. YLDs and YLLs due to multiple sclerosis in 2016, by age.

Shading shows 95% uncertainty intervals. YLDs=years lived with disability. YLLs=years of life lost.

Source: [8]

The effect of years of life lost due to premature death and disability was greatest in the sixth decade of life rising steeply beforehand and dropping substantially afterwards. For years lived with disability the curve rises to a peak at age 55 years, stabilises, then climbs slightly higher during the eight decade of life and more steeply thereafter.

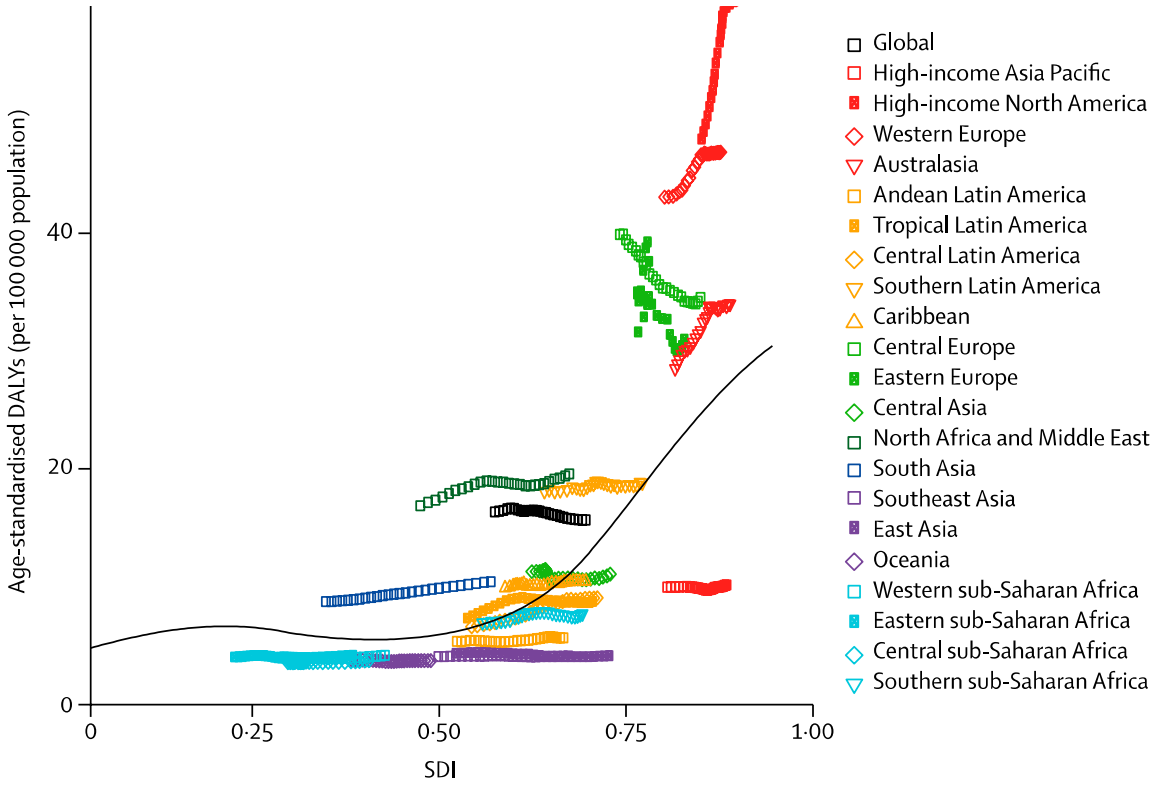


Figure 5. Age-standardised DALYs for multiple sclerosis by SDI, 1990–2016, and expected value-based SDI.

The black line represents the average expected relationship between SDI and DALYs for multiple sclerosis based on values from all countries over the 1990–2016 estimation period. DALYs= disability-adjusted life-years. SDI = Socio-demographic Index.

Source: [8]

Focusing on western Europe, prevalence of MS has been rising. From 1990 to 2016 were 4795 deaths (3451 to 5482) with a percentage of -2.1% (-40.2 to 8.6), a prevalence of 543862 (493933 to 597684) with a percentage of 26.1% (23.3 to 28.7) and the disability adjustive life years 262909 (214047 to 3098869) with a percentage of 8.9% (-8.7 to 16.9) [8] **(Figure 5)**.

In more detail, Spain had 215 deaths (166 to 280) with a percentage of -1.1% (-41.1 to 18.6), a prevalence of 43867 (39811 to 48085) with a percentage of 47.3% (27.5 to 56.9) and the disability adjustive life years 17272 (13654 to 2185) with a percentage of 24.9% (-4.7 to 40.9) [8]. In addition, the distribution by disease severity has been multiply assessed, 58-80% of cases being estimated to be mildly, 15-29% moderately, and 5-18% severely disable[9].

A neighbour country of Spain as it is Italy had similar but more worried data: 318 deaths (280 to 475) with a percentage of -2.0% (-40.0 to 14.5), a prevalence of 72352 (64659 to 80555) with a percentage of 31.7% (23.2 to 40.6) and the disability adjustive life years 29059 (22643 to 35453) with a percentage of 14.7% (-1.1 to 29.8)[8].

A reasonable justification of more prevalence in Italy than Spain could be the inclusion of Sardinian Island in the statistics. Even if MS prevalence follows a latitudinal gradient increasing with latitude; Sardinia represents an exception because represents a high-risk area in spite of its geographical location. Actually, a geoepidemiology study carried out in Sardinia confirmed it as an "hot spot" for MS showing one of the highest prevalence in the world[10]. Environmental factors already associated with the disease in other populations seem to have a role also in the island. However, a creation of a multifactorial (genetic and environmental) predictive model was proposed for future studies.

Therefore, Sardinia seems to be an ideal setting to study MS considering the high homogeneous genetic background and the numerous environmental peculiarities[10], that is the reason why this study was carried out in this Mediterranean island.

1.1.2 Aetiology

The hallmark of demyelinating disease is the sclerotic plaque formation, which represents the process end stage of involving inflammation, demyelination and remyelination, oligodendrocyte depletion, astrocytosis and neural and axon degeneration[2].

Myelin is synthesised by mature oligodendrocyte, each of which contacts short segments of 20-40 juxtaposed axons in white-matter tracts of the CNS. Developmental processes are regulated by defined growth factors that orchestrate proliferation, migration, differentiation, and survival of oligodendrocyte precursors into myelinating cells[11], [12]. The elongated oligodendrocyte processes contact nearby axons and form a cup at the point of contact that encircles the axon, thereafter, extending along the nerve fibre to form an internodal myelinated segment. With maturation, Sodium (Na) channels are retained along the myelinated axon but replaced by Na 1.6 channels as the intervening nodes of Ranvier where electrical resistance is low, thereby facilitating depolarisation, generating electrical current and in turn, triggering saltatory conduction[13].

As far as the pathophysiology its understood at the moment, MS is a T cell mediated autoimmune disease in which myelin-specific autoreactive T cells are activated outside the CNS, followed by proliferation and upregulation of chemokines and adhesion molecules[4]. Those mechanisms allow T cells to transmigrate through the Blood-Brain-Barrier (BBB) and enter the perivascular space. The transition from physiological surveillance to a pathological cascade arises from regulatory defects that allow these cells to set up an immune response within the brain. Regulatory lymphocytes from people with multiple sclerosis (pwMS) fail to suppress effector cells. These autoreactive cells do not effectively

apoptose on stimulation, because of overexpression of B-arrestin 1, which is the key promoter of naive and activated CD4+ T-cell survival. Presumably, failure of local regulatory mechanisms within the brain accounts for the particular sites of inflammation. However, it has recently been shown that besides the inflammatory demyelination, axonal aetiology in the early phase, correlates with the number of infiltrating immune cells and critically contributes to disease severity. Actually, axonal damage was first mentioned by Jean-Martin Charcot, who in the late 19th century described MS as an independent neurological disease. The spectrum of neuronal demise patterns in the white matter and the cortex, ranging from direct cell death to subtle neurodegenerative changes such a loss of dendritic ramification, was described in detail soon after. Indeed, there is a substantial loss of both myelin and axons early in disease process. Moreover, studies based on Magnetic Resonance (MR) spectroscopy showed that in MS the concentration of N-acetylaspartate, which serves as an indicator of neuronal integrity, is reduced at early stages of the disease. The underlying mechanisms have not yet been elucidated. How an immune attack which targets the myelin sheath leads to neuronal damage? It has been suggested that axonal damage is either induced by inflammation itself or is a consequence of demyelination, and that neuronal death could occur secondarily to axonal damage or primarily during inflammation. The precise sequence of the damage-mediating events is crucial not only for MS but also for other, primarily noninflammatory neurological diseases: CNS inflammation has been recognised as a pacemaker of pathogenesis in classical neurodegenerative diseases such as Alzheimer's disease, and to contribute to the process occurring in stroke.

However, investigators have recently discovered that the key role assigned historically to T-Helper 1 (Th1) (interferon-Y secreting) cells in experimental allergic encephalomyelitis was misplaced. Rather, inflammation is driven by a newly designated T-lymphocyte subtype that secrets interleukin-17 under interleukin-23 control. Interleukins 17 and 22 disrupt the human BBB allowing efficient penetration of the Th17 cells into the brain where can kill human neurons.

The antigen specificity of these immune responses is unresolved, not least because many autoreactive lymphocytes can be detected in healthy individuals. Originally, myelin proteins were favoured as candidates for initiation of the disease process in MS, but other specificities are now also implicated. For example, it is suggested that the autoimmune response against alfa beta crystalline prevents physiological suppression of inflammation and that antibodies against neurofascin might mediate axonal injury in MS.

The immune cell-mediated axonal injury and neuronal cell death are linked to the inflammatory infiltrates of active and chronic active MS consists mainly of CD4+ T cells, CD8+ T cells and activated microglia and macrophages, in order that the adaptative immune system orchestrates the attack against CNS ells and drives them to attack oligodendrocytes and neurons.

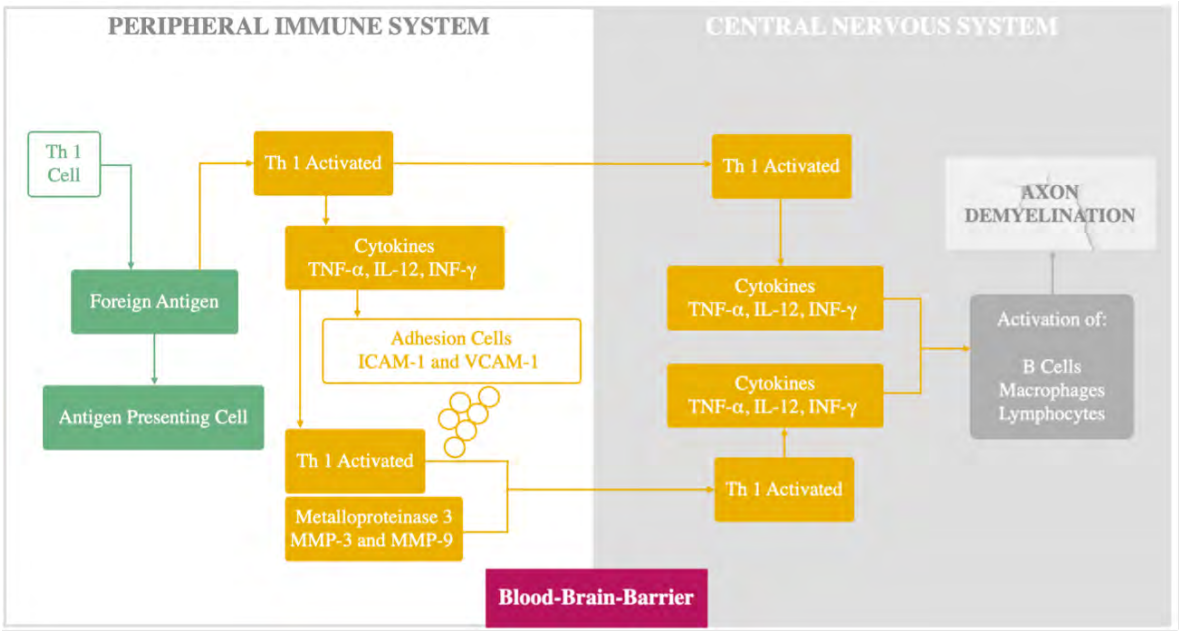


Figure 6. The Pathophysiological mechanisms of Multiple Sclerosis

Source: [14] author's adaptation.

Although, as mentioned before, axonal degeneration is accepted as a major cause of persistent disability in MS, little is known about the mechanisms of how inflammatory demyelination leads to neuronal damage. Furthermore, remyelination accounts for the appearance of shadow plaques. It is most active during the acute inflammatory process coinciding with phagocytic removal of myelin debris, but also occurs in the progressive phase. The mature nervous system maintains a pool of oligodendrocyte precursors that can migrate. Undifferentiated oligodendrocyte precursors surround the lesions of MS and presumably act as the source of cells having the potential to remyelinate naked axons **(Figure 6)**.

Even if in 20% of pwMS, plaques are eventually remyelinated. Nonetheless, remyelination is less successful in other instances, with cycles of demyelination and remyelination apparently exhausting the capacity for tissue repair.

1.1.3 Risk factors

While a definite cause of MS still remains elusive, this makes it difficult to link it to an exclusive cause. Though, many studies have suggested that MS is likely the result of a complex interplay between genetics, nutrition and environment. It is thought that MS may have a geographic connexion. Other risk factors that may interplay with one's genetic susceptibility for MS are vitamin D deficiency, previous injuries, diseases involving a bacterial or viral infection, cigarette smoking and other potential risk factors which will be developed next. The role of additional risk factors such as rural residency and drinking well water are currently under investigation[14].

1.1.3.1 Genetics and family History

Genetic studies have shown that an association exists between first-, second-, and even third-degree relatives. Monozygotic twins have higher overall concordance rates (+25%) for MS that dizygotic twins (5%) and between non-twin siblings (3%)[14].

Even if it is not notable, however, that this genetic predisposition is not hereditary, as no gene specific for MS has yet been identified clinical phenotypic heterogeneity in MS appears to have a genetic basis. Therefore, there are some promising results from different regions and candidate genes of the human genome as:

*1.1.3.1.1 The HLA-DRB1*1501-DQB1*0602*

The HLA-DRB1*1501-DQB1*0602 haplotype on chromosome 6p21 is well accepted as a susceptibility locus for MS. Where HLA-DRB1*15 allele increases MS risk dominantly, HLA-DRB1*03 contributes to a smaller increased MS risk recessively and HLA-DRB1*14 decreases MS risk. There are other potential loci on chromosomes 5q33, 17q23, and 19p13 that show weak linkage with susceptibility to MS.

1.1.3.1.2 The cytotoxic T-lymphocyte antigen-4

The cytotoxic T-lymphocyte antigen-4 is a costimulatory molecule involved in T-cell downregulation on engagement with B7. Which is a key inhibitory molecule involved in the prevention of autoimmunity.

1.1.3.1.3 Interferon-gamma

Interferon-gamma is a cytokine with key regulatory, immunomodulatory and effector roles both in autoimmunity and MS.

1.1.3.1.4 Apoliprotein E

Apoliprotein E is associated with prevention of neurotoxicity and repair processes in a variety of neurological disorders. APOE genotypes have been associated with disease severity in MS in some but not in all studies.

1.1.3.1.5 Interleukin-7 receptor-a

The Interleukin-7 receptor-a is a type I cytokine and is part of the cytokine receptor complex for the ligand IL7 which is involved in proliferation of T and B lymphocytes with n redundancy.

1.1.3.2 Vitamin D deficiency

Worldwide population, further north or south from the equator, have an increased prevalence of MS. In fact, the prevalence rate for MS in populations living at the equator is nearly zero, but at 45º north or south of the equator the prevalence rate jumps up to 50 cases per 1,000,000 people[15]. One possible explanation for this interesting geographical distribution of MS may be a lack of vitamin D in the body. Vitamin D is very important in the maintenance of many body organs and systems, including maintaining the immune system. Vitamin D aids in the maintenance of immunological self-tolerance and is essential for effective immune responses to infectious agents. This is of utmost interest, as an enhanced susceptibility to infection may introduce an unknown foreign antigen into a body that also has a decreased immunological self-tolerance, thus potentially initiating the autoimmune inflammatory response of MS[16]. Many studies have documented vitamin D insufficiency or deficiency in almost 70% of MS patients, as well as an increased risk for bone fractures and a decline in their bone-mineral densities[14].

1.1.3.3 Injury

Extensive injuries that specifically impact the brain or spinal cord have been investigated as potential causative agents of MS. Due to trauma origin, an increase in the permeability of the BBB has placed, facilitating the entry of Th1 cells into the CNS, acting as the trigger factor that initiates the MS inflammatory response[17]. However, not every insult to the CNS will result in the onset of an MS symptom. More scientific research needs to be devoted to the disease[14].

1.1.3.4 Diseases

It has been suggested that bacterial or viral infections may act as trigger factors for the later development of MS in genetically susceptible individuals. Virus such Epstein-Barr virus (EBV) can cause persistent and latent infections in the CNS and immune system, thus delaying the onset of the MS autoimmune response until years later. Moreover, EBV has a protein structure remarkably similar to that of myeline, making easier the myeline attack. Additionally, individuals with an anamnesis of different infections as mumps, measles, rubella or varicella, reported a significantly stronger incidence[14].

1.1.3.5 Cigarette smoking

Heavy smokers, 20-40 cigarettes per day, had a two-fold increased risk of developing MS over those who had never smoked. MS patients experience a deterioration in their upper limb motor performance immediately after smoking[18]. While the mechanisms are still unclear, it is thought that nicotine may interfere with the synaptic transmission of impulses within the CNS. As patients with MS already experience the loss of nerve impulses and electrical signals because of eroded axons, actions that further disrupt synaptic transmissions should be avoid[14].

1.1.3.6 Other potential risk factors

Several recent studies have analysed the relationships between other interesting lifestyle factors and the development of MS. We can find studies which correlate certain environmental agents affect the onset age of MS as well as a correlation between liquid cow milk consumption and MS prevalence[14]. Currently, it is known that a variety of environmental and nutritional factors exist that could serve as the unknown foreign antigen that initiates the entire inflammatory response of the MS disease process[19].

1.1.4 Diagnostic

The diagnosis of MS can only be established with clinical and/or radiological demonstration of lesions in the CNS that are Disseminated In Space (DIS) and in Time (DIT).

Diagnostic criteria for MS combining clinical, imaging, and laboratory evidence have advanced over time. The 2010 McDonald criteria for the diagnosis of MS are widely used in research and clinical practice. However, the International Panel of Diagnoses of MS reviewed in 2017 these last criteria[20]. The 2017 McDonald criteria **(Table 1)** continue to apply primarily to patients experiencing a typical Clinically Isolated Syndrome (CIS), define what is needed to fulfil DIT and DIS of lesions in the CNS, and stress the need for no better explanation for the presentation. The following changes were made in patients with a typically CIS and clinical or Magnetic Resonance Imaging (MRI) demonstration of DIS, the presence of Cerebrospinal Fluid (CSF)-specific oligoclonal bands allows a diagnosis of MS; symptomatic lesions can be used to demonstrate DIS or DIT in patients with supratentorial, infratentorial, or spinal cord syndrome; and cortical lesions can be used to demonstrate DIS.

Table 1. 2017 McDonald diagnostic criteria for Multiple Sclerosis.

Dissemination in space
Presence of at least one lesion in at least two out of four CNS areas:
Periventricular
Cortical or juxtacortical
Infratentorial
Spinal cord
Dissemination in time
A new T2 and/or Gd-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI
Simultaneous presence of asymptomatic Gd-enhancing and nonenhancing lesions at any time
In patients fulfilling DIS, the presence of OB in CSF could demonstrate DIT allowing MS diagnosis

Source: [20] author's adaptation

Prior to the accessibility of MRI, the presence of DIS and DIT was entirely based on clinical findings (Table 2). Fortunately, with the availability of MRI, the most recent criteria incorporate MRI findings to establish the presence of DIS and DIT, which can facilitate earlier treatment, whenever appropriate.

In fact, after the occurrence of a CIS, the diagnoses of MS can be established with a single MRI if it fulfils DIS and DIT criteria[20-21]. Although the McDonald criteria can greatly facilitate the diagnoses of MS, it is essential to note that these criteria are only of utility when applied in the appropriate clinical context. Specifically, the diagnostic criteria should only be applied to patients presenting with typical CIS symptoms and the diagnoses of MS is still considered a diagnosis of exclusion and all alternative diagnoses should be considered and excluded[22].

Table 2. The 2017 McDonald criteria for diagnosis of Multiple Sclerosis in patients with an attack at onset.

	Number of lesions with objective clinical evidence	Additional data needed for a diagnoses of Multiple Sclerosis
≥2 clinical attacks	≥2	None
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location)	None
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI AND Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands

Source: [20] author's adaptation

MRI is the most sensitive tool to detect the presence of brain and spinal cord lesions in MS and is also a helpful to exclude other diseases. Specific guidelines for the clinical implementation of brain and spinal cord MRI in the multiple sclerosis diagnostic process.

1.1.5 Classification

The course of MS cannot be predicted. Some people are minimally affected by the disease, and in others it progresses rapidly towards total disability; but, the majority of those affected, fall between the two extremes. While each person will experience a different combination of MS symptoms, there are several defined modes of presentation and course of MS. Currently MS phenotypic classifications include: CIS, Radiologically Isolated Syndrome (RIS), Relapsing-Remitting MS (RRMS), Primary-Progressive MS (PPMS) and Secondary-Progressive MS (SPMS) **(Figure 7)** [23].

1.1.5.1 Clinically Isolated Syndrome

The category of CIS was added to the new classification scheme, although the term has been in use for many years both in research and clinical practice. CIS represents a patient's initial presentation with clinical symptoms typical for demyelinating event. A patient is classified as having CIS when there is clinical evidence of a single exacerbation and the MRI does not fully meet RRMS criteria[24]. However, clinically isolated idiopathic inflammatory demyelinating diseases, such as optic neuritis (ON), acute transverse myelitis (ATM), and tumefactive demyelinating lesions, have the potential to convert to RRMS. Therefore, it is imperative to understand the risk of conversion from CIS to RRMS due to early treatment is effective at preventing additional relapses. Following an acute episode of ON associated with one or more lesions typical of MS on MRI scanning, 44% of patients still do not develop clinically definite MS by 10 years. Following an episode of partial ATM, which is more characteristically associated with MS than complete ATM, 2o to 60% of patients develop clinical MS within 3 years. Proper recognition of individual idiopathic inflammatory demyelinating diseases has important implications not only for predicting prognosis, but also for response to acute and chronic treatments[25].

1.1.5.2 Radiologically Isolated Syndrome

As MRI has become increasingly widespread, abnormalities suggestive of multiple sclerosis have been noted in patients who have not previously experienced clinical symptoms of the disease. RIS was coined in 2009 and has now been added to the revised multiple sclerosis classification scheme. The current formal diagnostic criteria for RIS required that lesions are ovoid and well circumscribed, not consistent with a vascular pattern, and meet three out of four Barkhof criteria[26]. The findings must be incidental, meaning there must be no history of neurological symptoms suggestive of a demyelinating event and the lesions must not account for functional impairment. Younger age, male sex, and the presence of spinal cord lesions were noted to have predictive value. Currently there exists considerable variability in management, but many clinicians consider the presence of spinal cord lesions, and/or the presence of oligoclonal bands in the CSF in the decision regarding whether to initiate disease-modifying therapy for MS in these patients.

1.1.5.3 Relapsing-Remitting Multiple Sclerosis

The vast majority of pwMS initially follow a relapsing-remitting (RR) course, defined by acute exacerbations from which they typically completely or incompletely recover, with periods of relative clinical stability in between. An exacerbation, also referred to as a relapse or an attack, is defined by the International Panel of Diagnosis of MS as "patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 h, in the absence of fever or infection"[27].

1.1.5.4 Primary-Progressive Multiple Sclerosis

The PPMS classification describes patients with progressive decline in neurological function from the time of disease onset. Patients most often present clinically with a progressive myelopathy although they may also present with a progressive cerebellar syndrome or other progressive symptoms as described as well as at least two of the following: evidence for DIS in the brain (at least one T2 lesion that is periventricular, juxtacortical or infratentorial), evidence for DIS in the spinal cord (at least two T2 lesions in the cord), or positive CSF[24]. As in RRMS, symptomatic lesions are excluded from the MRI DIS lesion count.

1.1.5.5 Secondary-Progressive Multiple Sclerosis

SPMS is defined by gradual progression after an initial relapsing course, occurs in up to 40% of patients by 20 years after the initial event [28]. It is typically characterized by a gradual decline in neurologic functioning, often predominantly involving areas of the CNS previously involved during the relapsing course. The point of transition to SPMS can be difficult to define and is often recognized only in retrospect, at times years after subtle hints of progression first appear [29]. Research regarding potential imaging and laboratory biomarkers that distinguish SPMS from RRMS, better characterized the transition from RRMS to SPMS, is underway although each suggested biomarker currently requires further validation prior to clinical use[30].

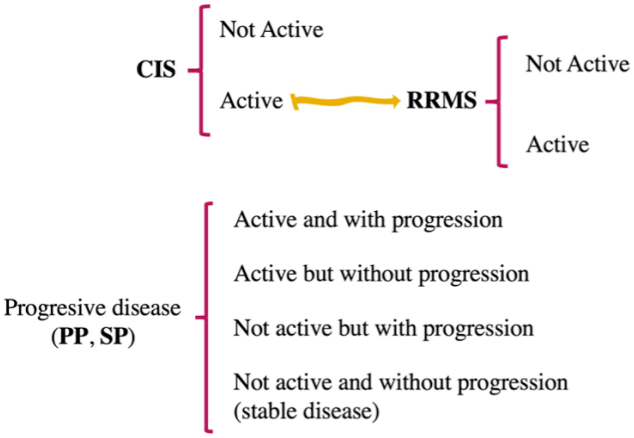


Figure 7. Phenotypes description for Multiple Sclerosis for Relapsing and Progressive disease.

It must be highlighted Progressive-Relapsing MS described in 1996 would now be considered PPMS active (at the time of relapses or new MRI lesions) or not active.

MS is the leading cause of a higher degree of neurological disability in young adults. In its natural evolution, 8 years after its onset, the person with this disease has limitations in walking distances; 20 years after they need some kind of unilateral or bilateral support; And after 30 they can barely take steps but, in addition, numerous functional systems are affected such as: visual, brain stem, cognitive, bladder, intestinal, sexual and sensory, with the consequent poor quality of life[31].

1.1.6 Prognostic

The most common prototypical form of MS is RRMS, which evolves from an isolated demyelinating attack. The disease has an asymptomatic period of unknown duration that precedes the initial presentation with an isolated syndrome. Most patients will continue to have clinical relapses, either with complete remissions or with stepwise accumulation of deficit. Approximately 60% of patients have RRMS, and the reminder have chronic progressive disease. Chronic progression can be either in the form of SPMS or PPMS. There may be rare, interspaced relapses, especially early on, overlapping with progression[25].

The SPMS evolves from RRMS, an evolution widely accepted to be due to superimposed progressive axonal injury exceeding the "clinical threshold". Overall, there is progressively less inflammatory activity in the form of a decreasing number of new relapses and new or enhancing lesions on MRI with progressive brain atrophy. In some patients, despite the appearance of SPMS without any relapses, continued new MRI activity suggesting subclinical inflammatory activity can be detected[25]. Three out of four patients in the population develop SPMS disease course by 25 years; one out of the four remains at the RRMS stage of disease **(Figure 8)**. Early attainment of disability and higher number of attacks of sphincter and motor symptoms predict higher likelihood of conversion to SPMS, whereas frequent attacks of optic neuritis or other symptoms predict a lower likelihood of conversion to SPMS[25].

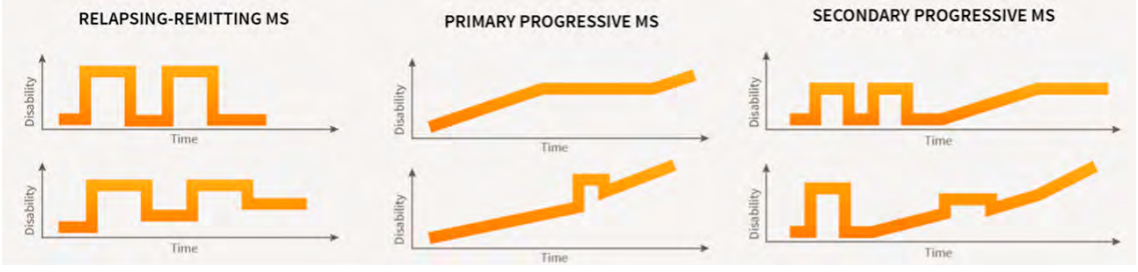


Figure 8. Evolution of MS

Source:[32]

Disease severity can be measured by different tools in MS. The Kurtze's Expanded Disability Status Scale (EDSS) is the standard impairment instrument in MS. The Kurtzke Disability Status Scale (DSS) was developed by Dr. John Kurtzke in the 1950s to measure the disability status of people with MS. The purpose was to create an objective approach to quantify the level of functioning that could be widely used by health care providers diagnosing MS. The scale was modified several times to more accurately reflect the levels of disabilities clinically observed. The scale was renamed the EDSS[33] providing a total score on a scale that ranges from 0 to 10. The first levels 1.0 to 4.5 refer to people with a high degree of ambulatory ability and the subsequent levels 5.0 to 9.5 refer to the loss of ambulatory ability **(Figure 9)**. However, the EDSS is disproportionally affected by ambulation, does not emphasized upper-extremity dysfunction and cognitive defects. That is why is important to include cognitive dysfunction in the assessment. Impairment in attention and information processing speed seems to correlate better with a disease duration longer that 7 years[25].

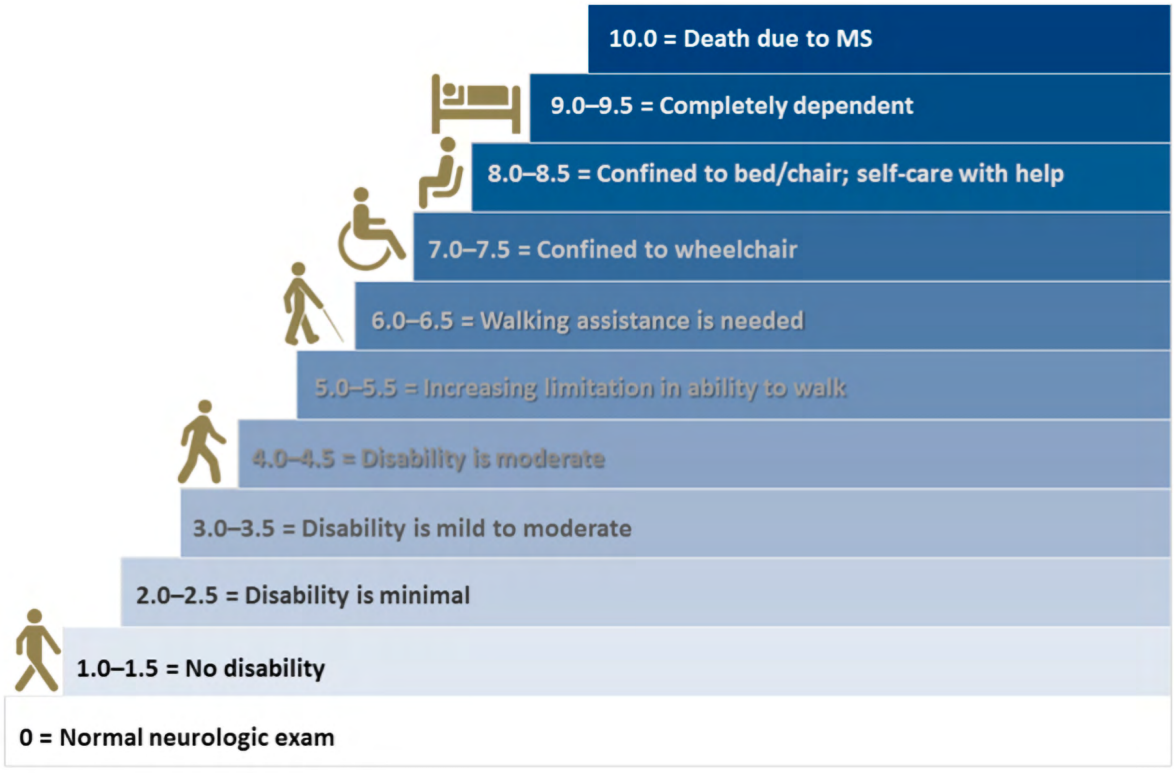


Figure 9. The Extended Disability Status Scale (EDSS).
https://www.nationalmssociety.org/getattachment/Chapters/WAS/Calendar/Programs/Regional-MS-Summit/Bob-Fox-Progressive-MS,-NMSS-Seattle-Program,-6-8-18,-final.pdf?lang=en-US

After 15 years of disease, approximately 50% of MS patients become dependent on at least a walking aid. Median time to having severe disability in the form of being restricted to bed is around 33 years. After 25 years of disease, 10% remain free of major ambulatory disability as measured by EDSS score is 2 or lower for 10 years or longer, there is 90% chance that the disease will continue to remain stable. This latter group constitutes 17% of MS patients and can be designated as "benign" in an ambulatory sense[25].

The prognosis is relatively good when sensory or visual symptoms dominate the course of MS in adults, and there is completely recovery from individual episodes. This pattern is most common in young women. Conversely, motor involvement, especially when coordination or balance are disturbed, has a less positive prognosis. Conversely, poor long-term prognosis has been associated with the following: male sex; older age at onset (>40); motor, cerebellar, or sphincter symptoms at initial presentation; polyregional onset; relatively short time to reach an EDSS level 4; and a progressive course. Moreover, presence of lesions on baseline MRI, presence of CSF-specific oligoclonal bands, and presence of lesions in the spinal cord were predictive of a more active or aggressive disease course[22]. However, 50% of MS patients die from causes others than MS[25].

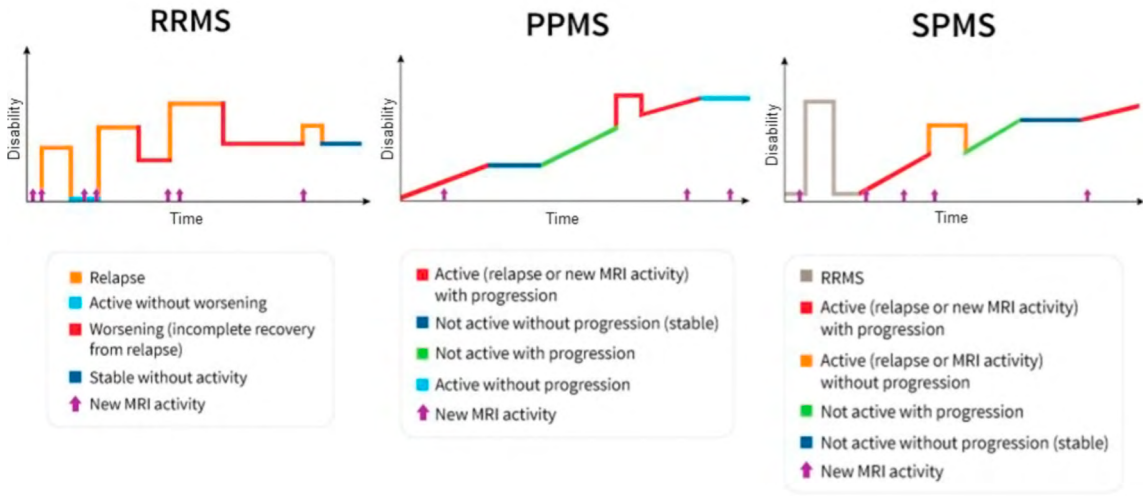


Figure 10. MS progression over time by classification.

Source: Lublin et al., 2014

Both natural history and recent studies have demonstrated that individual patients with CIS, RRMS and PPMS demonstrate striking differences in disease activity and progression. As a result, one of the greatest challenges encountered in clinical practice because of the extreme variability of MS disease course is difficulty with prediction and optimizing treatment at presentation[22]. Although there is not yet a single biomarker that accurately predicts disease course in all patients, at the current time, a combination of these clinical, imaging, and laboratory markers, together with clinical judgment are utilized to influence treatment decisions in clinical practice[22]. Nevertheless, A diagnosis of

progressive MS does not guarantee that the patient will continue to demonstrate ongoing decline. Some patients progress rapidly, some at a slow and steady rate, whereas others seem to reach a plateau **(Figure 10)**[24][34].

Fixed disability in MS is acquired through two distinct mechanisms: incomplete recovery from relapse and disease progression. Patients with relapsing-remitting multiple sclerosis accumulate disability from disease onset more slowly than those with primary progressive MS[3]. Eighty percent of patients present with RRMS typically, the illness passes through phases of relapse with full recovery, relapse with persistent deficit, and secondary progression. In about quarter of patients, MS never affects Activities of Daily Living (ADL); conversely, up to 15% become severely disable within a short time. Episodes happen at random intervals, but initially average about one per year, decreasing steadily thereafter. In 20% of patients, the disease is progressive from onset, hence termed primary progressive affecting the spinal cord and, less frequently the optic nerve, cerebrum, or cerebellum. Disease onset is usually in the third or fourth decade, but 2% of patients with MS present before age 10 years, and 5% before age 16 years[3]. Overall life expectancy is at least 25 years from disease onset with most patients dying from unrelated causes.

1.1.7 Signs and symptoms

The wide range of symptoms and signs is one of the hallmarks of the clinical picture of MS. However we can distinguish two major ways of symptoms manifest: through relapses or progressive disease[35]. MS relapse usually evolve over 24-48 hours and, because of their inflammation, persist for at least 24 hours, often improving gradually over subsequent days and weeks[36], or taking 1-2 years for a relapse to recover to the fullest extent, and sometimes leaving a residual deficit, less than at the peak[35]. Conversely, progressive symptoms are different in that they occur as a result of neurodegeneration and cause gradual worsening occurring over months and years. Although only a minority of new lesions (approximately 1 in 10) in the hemispheric deep white matter is symptomatic. It is also important that, respiratory, urinary or any viral, infections may increase relapse risk. Therefore, relapses must be differentiated from physiological “pseudo-relapses” that may occur in the context of infection-related fever[36].

It must be highlighted the correlation between lesions, as visualized on standard MRI, and clinical manifestations is only approximate. This may be because repair and neural plasticity may compensate for damage and residual function may not parallel changes on MRI images. In addition, recent works showed there is pathology in both white and grey matter not visible on standard MRI[37].

The variability of the most common symptoms in MS can be classified in seven different groups: Visual acuity, genitourinary problems, mood and cognitive disorders, pain, sensory disturbances, fatigue and motor impairments.

1.1.7.1 Visual acuity

Optic neuritis is a common initial clinical presentation which course with loss of visual acuity or colour vision and is usually unilateral and mild to moderate in severity. Patients, generally, experience pain with eye movement and loss of colour discernment, especially in red tones[35].

Examination will reveal 3:4 patients course afferent pupillary defect (APD) and 1:4 papillitis. While in papillitis the lesion is located distally, in APD is usually paracentral in a retrobulbar location. However, the majority of patients recover their vision over a median period of about 8 weeks.

Even if often asymptomatic, patients, may complain of diplopia or blurring of vision on lateral gaze, probably evoking nystagmus affecting the contralateral abducting eye[36].

Nystagmus is commonly seen and represents dysfunction in the vestibulo-ocular tracts. Although pwMS may have different types of nystagmus, pendular nystagmus in particular is characteristic finding. This is sinusoidal in waveform and may be unilateral or bilateral. In some patients, it is hard to detect and may be only found by closely examining the retina[35].

1.1.7.2 Genitourinary problems

The negative impact on quality of life of bladder, bowel and sexual symptoms may be immense, correlating with many aspects on ADL.

Urinary dysfunction can be experience because of detrusor overactivity (frequency, urgency and nocturia), detrusor underactivity (hesitancy and retention) or a mixed picture combining both states which may cause frequent urinary tract infections.

Similarly behaves bowel dysfunction, causing mostly constipation and rarely incontinence. Constipation can go worse with the lack of mobility and dehydration, while incontinence must, understandably, be a large source of anxiety[35].

Lastly, sexual dysfunction can be impaired due to physical and psychological effects. PwMS may struggle with altered body image and personal relationships may be affected by the diagnosis and subsequent illness. PwMS mostly experience altered genital sensation, and disability may affect their ability to engage. Symptoms consist mainly in: decreased libido, erectile dysfunction in men and anorgasmia and vaginal dryness in women[36-37].

1.1.7.3 Cognitive disorders

Psychiatric disorders are common in pwMS. Depression is an early indicator of cognitive impairments[36]. Patients with MS are up to four times more likely to experience at least one major depressive episode than the general population. At some point after an MS diagnosis, up to 50%[6] of patients are also diagnosed of depression. Bipolar disorder, anxiety and suicide are likely increased in MS population, therefore they must treated proactively[35].

Cognitive dysfunction is one of the most challenging. Overall, 35-65% of pwMS experience cognitive dysfunction at some point in the condition[35]. This include: poor concentration, slowed thinking, poor memory, particularly short-term, impaired execution function[36].

It is important to assess and monitor cognition from the time of diagnosis, and practical tools applicable in clinical practice have been developed for this purpose.

Cognitive impairment is a frequent accompaniment of longstanding MS but can begin in the early relapsing phase of the disease in some patients and is a significant contributor to loss of work and income. Patients with MS are particularly vulnerable to "subcortical" deficits in information processing and spatial recall. Recent pathological studies have demonstrated a significant burden of cortical and deep grey matter involvement in MS, even at the CIS stage. Volumetric MRI, which demonstrated both cortical and deep grey matter atrophy in MS, and advanced techniques such as magnetization transfer imaging have confirmed a robust correlation of grey matter pathology and cognitive impairment.

It is important to assess and monitor cognition from the time of diagnosis, and practical tools applicable in clinical practice have been developed for this purpose[36].

1.1.7.4 Pain

Despite the pain linked to spasticity, optic neuritis, inflammatory lesions, or bladder spams, it is important to discriminate, and commonly mistaken, "peripheral" compressive neuropathic syndromes such as carpal tunnel syndrome or lumbosacral radiculopathy with neuropathic pain. Actually, paroxysmal pains, such as trigeminal or glossopharyngeal neuralgia are not uncommon, and their symptoms are usually: neuralgic pain, Lhermitte's phenomenon[1] and pseudoradiculopathies[36].

1 Lhermitte's phenomenon is mostly described as an electric shock like condition by some patients of multiple sclerosis. This sensation occurs when the neck is moved in a wrong way or rather flexed. It was described by Marie and Chatelin and named after Jean Lhermitte.

1.1.7.5 Sensory disturbances

Sensory symptoms are the most common initial MS symptoms. Patients may complain of numbness, paresthesias and dysesthesias. The area of sensory abnormality correlate to lesion location: A brainstem lesion could produce cause in a hemi-facial symptom, while a spinal cord lesion could produce symptoms in a hemi-body, radicular or bilateral (with a level) distribution. Burning discomfort, painful hypersensitivity to touch (allodynia) or temperature frequently occur when demyelination occurs in the spinothalamic pathways[35-36].

Vertigo is a frequent symptom in MS, because vertigo from MS is central, it is often continuous in nature though sometimes worsened by positional change. It may accompany other brainstem symptoms during a relapse[35].

1.1.7.6 Fatigue

Although the pathophysiology of MS fatigue is still understood, this symptom is exceedingly common in MS, affecting up to 80% of patients with MS. For patients, fatigue, is the most disabling features of the condition because increased effort to perform routine tasks, decreased performance or endurance with sustained effort, worsening sensory or motor symptoms with increased body temperature and persistent lassitude[35], [37].

1.1.7.7 Motor impairments

1.1.7.7.1 Movement and paresis disturbances

A motor relapse may rarely involve one limb or cause a hemi or paraparesis. In addition to limb weakness, the examiner may find hyperreflexia and an extensor response. Subtle signs such as mild weakness of the intrinsic hand muscles, pronator drift, and decreased ability to walk on heels or toes may be elicited. Importantly, recovery from even the most severe motor relapse is typically quite good. Motor symptoms are almost, though not always, a feature of progressive MS. In this case, they usually take the course of a gradually worsening hemi-paresis or paraparesis, with the most advanced patients progressing to quadriplegia. In addition to the motor findings above, spasticity is common and worsens as the disease progresses.

The gait may appear wide based and unsteady and the patient will be unable to perform tandem gait. Patients with the most severe cerebellar symptoms may have normal testing, yet the limbs are essentially useless because of severe dysmetria[35]. PwMS may have a spastic gait, a broad based ataxic gait or both, depending on the principal sire (s) of pathology. Balance is commonly affected. Gait abnormalities can be due to cerebellar, visual, motor or sensory dysfunction[36].

Paroxymal short-lived (less than 60 seconds) disorders of posture/movement (Choreo-athetoid/dystonic) may be a sign of an ephaptic discharges ("cross talk"), often localized in the brainstem. These need to be distinguished from epileptic discharges, though both may respond to anticonvulsant therapy. Patients may complain of weakness in either the upper or lower limbs, more commonly the latter. The weakness is typically pyramidal in pattern leading to weaker extensor muscles in the upper limbs and weaker flexor muscle in the lower limbs. Patients may complain of weakness in either the upper or lower limbs, more commonly the latter. The weakness is typically pyramidal in pattern leading to weaker extensor muscles in the upper limbs and weaker flexor muscles in the lower limbs.[36]. Gait impairment is a varying contributions from visual impairment, vestibular symptoms, weakness, spasticity, ataxia, imbalance, sensory loss, pain, and fatigue[37].

1.1.7.7.1.1 Lower-limb

The goal of ambulation is to move from point A to point B in an energetically efficient fashion. Ambulation not only encompasses typical bipedal walking but also includes locomotion via other means such as with a manual or power wheelchair. At a minimum, successful bipedal ambulation requires sufficient antigravity strength to clear the foot during the swing phase of each step together with stability across the ankle, knee, and hip joints.

1.1.7.7.1.1.1 Ankle dorsiflexion

Insufficient Ankle Dorsiflexion (ADF) is the most common manifestation of lower limb (LL) pathology in the MS patient. The most abnormal gait patterns associated with this deficit are the foot slap (Figure 11.a) and steppage gait patterns. In both cases, the usual cause is ADF (tibialis anterior) weakness, but excessive plantar flexion (PF) tone or contracture can also produce these gait patterns. When ADF weakness is mild, a foot slap pattern is observed. In contrast, severe ADF weakness will often present quiet a steppage gait pattern (provided hip flexion strength is preserved). Such ADF weakness may not fully manifest on manual motor testing. Indeed, some patients with full strength on manual motor testing may exhibit a foot slap only after walking for some distance. Suspicion of this type of weakness should be high in a patient who experience actual or near falls when walking, especially when faced with tasks requiring divided attention. It is important to detect it on time in order to avoid the risk for further injury.

1.1.7.7.1.1.2 Knee control

Knee instability secondary to quadriceps weakness (**Figure 11.b**) can also prove challenging to the ambulatory MS patient. In order to compensate for this, the patient will snap the knee backward, at times even hyperextending the knee. This manoeuvre places the ground reaction force closer to the knee axis, increasing stability at that joint. Sometimes, patients will achieve this rapid extension of the knee by keeping the hand in the ipsilateral pocket and providing a knee extension force by pushing back on the femur with the hand. This action can lead to permanent ligamentous laxity, increased risk of degenerative changes within the knee joint, and chronic knee pain.

1.1.7.7.1.1.3 Hip girdle stability

Hip girdle weakness can occur in the pwMS. Hip abduction weakness produces an excessive pelvic drop during ambulation (Trendelenburg sign **Figure 11.c**) and, when severe, can complicate maintenance of balance. To compensate, a patient may throw the trunk toward the side of weakness during stance phase (compensate Trendelenburg). This strategy produces increased stain on the lumbar spine. In the context of normal gait, hip flexor strength is not overly critical because antigravity strength is all that is required. However, in an MS patient who also has ADF weakness, increased hip flexion strength can help with foot clearance. I contrast, hip flexor tightness can be problematic during ambulation as it induces excessive lumbar lordosis, translates the Centre Of Mass (COM) anteriorly, and as a result, increases the muscular forces required to stabilize both the knee and the ankle[38].

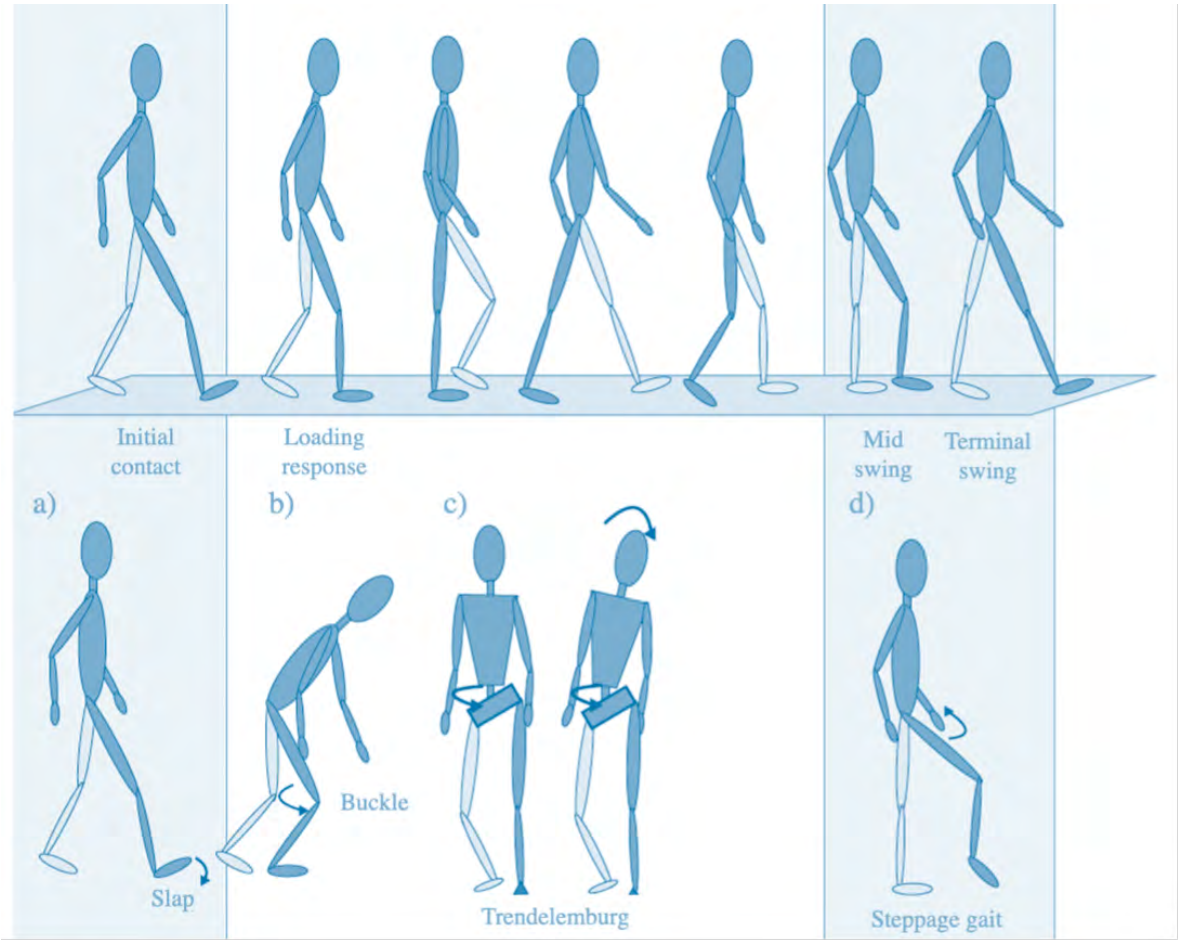


Figure 11. Common gait abnormalities in multiple sclerosis gait.

(a) Foot slap due to mild ADF weakness, (b) knee instability with buckling leading to a fall, (c) Trendelenburg (compensated on the right) finding secondary to hi abduction weakness, and (d) steppage gait with moderate to severe ADF weakness. Each abnormality is aligned with its corresponding phase of gait cycle.

Source:[38]by author's adaptation

1.1.7.7.1.2 Upper-limb

While the LL is or/and are often more severely affected, the Upper Limb (UL) are also at risk in MS, particularly in those with heavy disease involvement of the cervical spine. Particularly disabling is the combination of UL intention tremor and dysmetria. Loss of UL function has greater implications for the performance of ADL, because of the fatigue, limited Range Of Motion (ROM) and weakness.

1.1.7.7.2 Spasticity

Spasticity is defined as velocity-dependent increase in tonic muscle stretch reflexes, resulting from damage to descending motor pathways. Spasticity arises following the loss of inhibitory input from the brain on spinal cord reflexes, resulting in co-contraction of antagonist and agonist muscles. This may manifest as painful spams, cramps, stiffness and clonus. Both weakness and spasticity contribute to the development of disability in 50-70% of patients with approximately one-third reporting that spasticity affected daily activities[37-38].

Regarding the influence of spasticity to its biomechanical effects, insufficiently managed spasticity can make walking energetically costly:

1.1.7.7.2.1 Sural triceps spasticity

PF spasticity is common in pwMS. Excessive plantar flexion spasticity can antagonize ADF during the swing phase of ambulation. Moreover, this could increase the difficulty transferring weight onto the affected leg during the loading response of the gait cycle.

1.1.7.7.2.2 Quadriceps spasticity

Spasticity involving musculature crossing the knee can adversely impact limb clearence during stance phase. Quadriceps spasticity can prevent adequate knee flexion during swing phase making limb clearance more difficult.

1.1.7.7.2.3 Hamstrings spasticity

Hamstring spasticity may prevent adequate knee extension at the terminal portion of swing phase, leading to early weight transfer onto a leg with a bent knee. Landing with an overly bent knee at loading response will not only shorten the step length but also increase the risk of knee buckling and a subsequent fall (Figure 11.d).

1.1.7.7.2.4 Adductors spasticity

At the hip, patients with excessive adductor tone or spasticity may exhibit a scissoring gait. This gait pattern is characterized by a narrow base of support, placing the patient at increased fall risk.

1.1.7.7.3 Tremor

Dysmetria and ataxia both arise secondary to cerebellar pathway dysfunction. Patients may complain of clumsiness, incoordination, and/or tremor. Upon examination, there may be dysmetria with finger-to-nose and heel-to-shin testing, as well as presence of dysdiadichokinesis with rapid alternating movements[35]. Lesions affecting the brainstem and cerebellar pathways are common in patients with MS and can lead to poor coordination. This can be reflected in an ataxic gait, dysarthria or dysmetria[36].

1.1.7.7.4 Speech and swallowing difficulties

Depending on the location, the lesion may have the appearance of an upper motor neuron lesion or a lower motor neuron lesion. Dysguesia, dysarthria and dysphagia may also occur, with the latter two occasionally occurring as a result of a relapse, but more commonly developing insidiously over the course of the disease[35].

1.2 Traditional treatments in MS

The clinical and pathological details of MS had been adequately characterised. Over the past 120 years, ideas have consolidated on the cause and mechanisms of inflammatory demyelination and axonopathy. In the past years, therapies have emerged that modestly affect the course of the illness. Current research is increasingly seen as coherent and focused on the hot topics that need to be solved to limit, repair, and prevent the damage caused by MS[2]. The treatments follow a mechanistic approach rather than clinical pragmatism. The aims of treatment are to:

- Reduce relapse rates
- Prevent fixed disability directly attributable to relapse
- Provide symptomatic management of fixed neurological deficits
- Prevent disabilities acquired through progression
- Treat established progression

Therefore, medical treatment includes a pharmacological and a rehabilitation approach.

1.2.1 Pharmacological treatment

Depending on the aim of the therapy we can subdivide the pharmacological treatment in different groups: Relapses treatment, disease-modifying therapy (DTM) (preventing relapses), immunosuppression therapy, emerging therapies and managing symptoms treatment.

1.2.1.1 Treating relapses

A relapse is a period of acute neurological disturbance that lasts for at least 24 hours and is not attributable to other causes such as infection or changes in core temperature.

1.2.1.1.1 Corticosteroids

Corticosteroids are the mainstay of acute treatment for MS relapses. They are reserved for patients with disabling relapses or patients with an occupational or other need to recover function faster than natural history of the condition allows. However, there are many risks associated in short term (exacerbation of glycemic control, delayed wound healing, skin disorders and infections) and in medium and long term (Hypertension, lipid disorders, osteoporosis, weight gain, cataracts and avascular necrosis of the femoral head).

1.2.1.1.2 Methylprednisolone

Methylprednisolone could be administered intravenously as well as orally. Their side effects include facial flushing, palpitations, insomnia and metallic taste.

1.2.1.1.3 Prednisolone/prednisone

Even if Prednisolone is available as an oral dosing, evidence supports that its used is limited, increasing even the risk of recurrence. Therefore, high-dose oral or intravenous methylprednisolone is preferred for acute relapse[36].

1.2.1.2 Disease modifying therapy

In general, DMTs are used in ambulatory patients with RR MS. In the early 1990s, the first clinical trials immunomodulation produced statistically significant results. Several DMTs are now available and depending on the administration way we can find different drugs.

1.2.1.2.1 Conventional Disease modifying therapy

Here we found interferons and Glatiramer acetate. The mode and frequency of therapy may affect the treatment decision. Interferons are injected intramuscularly weekly or subcutaneously every other day or three times per week while glatiramer acetate is injected only subcutaneously and daily. Redness and swelling skin reactions from the injections could be reduced with intramuscular weekly interferon beta-1a (Avonex). However, up to 35% of patients taking interferon therapy produce neutralizing antibodies against the drug after 2 years of treatment. Therefore, this is an indication to stop the treatment as well as frequent relapses, the continued decline or the intolerable side effects which can reduce the efficacy of the treatment and are an indication to consider alternative treatment options.

1.2.1.2.2 New Disease modifying therapy

New generations therapies are administered intravenous or oral instead of injections.

The intravenous drug more indicated for highly active RRMS is Natalizumab which is a humanized monoclonal antibody against the cell adhesion molecule α4-integrin is ordered to preventing the migration of immune cells into the CNS. Natalizumab had been shown to reduce the annualized relapse rate by 68% and the risk of disability progression sustained for 24 weeks. Alemtuzumab, another highly efficacious treatment, may be an appropriate agent in such patients in the future. Oral therapy includes Fingolimod, Teriflunomide and Dimethyl fumarate. Fingolimod was the first oral agent to be licensed for relapsing forms of MS, and it consists of a novel small molecule modulator of the spingosine 1-phosphate receptor on lymphocytes, preventing their egress from peripheral lymph nodes and reducing the influx of pathogenic inflammatory cells into the CNS. Fingolimod reduces the annualized relapse rate by 54% at 2 ears versus interferon berta-1a at 1 year. However, there are rare and potentially serious side effects, including cardiac rhythm disturbances, macular edema, liver transaminase elevation and increased risk of herpes and zoster viruses. Teriflunomide consists in once-daily oral therapy and is also licensed for use in relapsing forms of MS, already used for rheumatoid arthritis, teriflunomide, selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase, which is required for the novo pyrimidine synthesis in proliferating lymphocytes. Teriflunomide reduced the annualized MS relapse rate by 31.5-36.3% and reduced the risk of sustained disability progression by approximately 25-30%. Common side effects include nausea, diarrhea, hair thinning and elevation of alanine aminotransferase. In last, ingesting Dimethyl fumarate twice daily is an effective oral therapy that shown promise as both a first-line treatment and escalation treatment for MS. Although the precise mode of action is unknown, dimethyl fumarate, activates the nuclear factor pathway, a cellular defense against oxidative stress. It showed a significant reduction in sustained disability progression at 2 years. Even if long-term data in MS patients are lacking the most common side effects is flushing and gastrointestinal.

1.2.1.3 Immunosuppressive therapy

Traditional (cytotoxic) immunosuppressants are now rarely used in the treatment of MS, although they remain an option for those patients with relapsing MS whose condition is not adequately controlled by DTMs. This classification incudes Cyclophosphamide. Azathioprine and Mitoxantrone. Cyclophosphamide is used in patients with highly active RRMS when DMTs are not effective in controlling the disease, and rarely in patients with progressive disease; side effects include bone marrow toxicity, hair loss and nausea/vomiting, besides, long-term side effects include risk of secondary malignancy (leukemia/lymphoma). Mild immunosuppression with oral azathioprine reduces until 30% the annualized relapse rate. However, it may adversely affect the risk profile of subsequently prescribed new generation therapies such as natalizumab. Also, Mitoxantrone effectively reduces relapses and has shown modest efficacy in reducing progressive disability in patients with SPMS. Nonetheless, bone narrow toxicity, dose-dependent cardiotoxicity and life-time risk of acute myeloid leukemia significantly limits its clinical utility. For this reason, Mitoxantrone has largely been supplanted by natalizumab.

1.2.1.4 Emerging therapies

Dramatic advances in molecular and cellular biology over the last two decades have yielded numerous potential therapeutic targets in MS. Immune-directed therapies have little or no impact in the later progressive phase of the disease, which remains a major unmet treatment need. In the last 5-10 years, the emphasis of drug-discovery research in MS has begun to shift toward neuroprotection and the promotion of intrinsic CNS repair mechanisms, some of treatments which are on the horizon are: Monoclonal antibodies, laquiminoids, Stem cell, Vitamin D, Antilingo antibody.

1.2.1.5 *Monoclonal antibodies*

Anti CD52, Anti CD 20, and Anti-CD 25 are the main monoclonal antibodies for treatment in MS. Alemtuzumab, is a monoclonal antibody directed against the cell surface molecule CD52, depletes the circulating lymphocytes (T and B cells) that effect inflammatory demyelination in MS. It is administered intravenously for 5 consecutive days with hospital supervision. Lymphocyte cunts are restored months to years after treatment. Alemtuzumab is most appropriate for patients with highly active disease or those with disease activity despite treatment with other disease-modifying therapies. However, a role for alemtuzumab in natalizumab-leukoencephalotaphy has yet to be defined.

Monoclonal antibody therapies that target the CD20 cell surface molecule include rituximab. ocrelizumab and ofatumumab. These treatments induce prolonged depletion of B-cell precursors, while sparing mature plasma cells. Even their mechanism of action in MS is unknown, they may have effect on B-cell trafficking into the CNS and, indirectly on T-cell responses. Rituximab is often used off-label for the treatment of neuromyelitis optica and an inflammatory demyelinating disease of the CNS with a convincing humoral pathogenesis. Although ocrelizumab trials in rheumatoid arthritis and systemic lupus erythematosus have been discontinued because of an excess of opportunistic infections.

Daclizumab, a humanized monoclonal antibody, which binds to the cell surface molecule CD25, impairs the proliferation of autoreactive T cells, while expanding some natural killer cell populations. Daclizumab reduces the risk and severity of rejection in human organ transplantation and reduces the number of gadolinium-enhancing lesions by 72%. Nevertheless, transient thrombocytopenia, rash, lymphadenopathy and liver dysfunction have been reported.

1.2.1.5.1 Laquinimod

Laquiminoid, is given once daily as oral therapy. In preclinical studies with animal models of neuroinflammation, even if non-significant reduction in annualized relapse rate there is a significant improvement in the progression of disability and whole brain volume loss. The apparent disjunct between an effect on relapses and disability progression/brain volume loss suggests that laquinimod may have a unique mechanism of action, possibly mediated through a direct effort on innate immune cells in the CNS. Long-term side effects are still unknown.

1.2.1.5.2 Stem cell therapy

The application of stem cell therapies to MS is perhaps more frequently raised by patients than their neurologists. However, both conventional (hematopoietic) and novel stem cell approaches offer potential new therapeutic avenues for MS. Autologous hemopoietic stem cell transplantation is in effect a means of "rebooting" the immune system by ablating bone narrow and repopulating it with the patient's own hemopoietic (bone narrow) stem cells. Even if further studies are needed, early studies in MS indicate a greater than 90% reduction in relapse rate. Conversely, mesenchymal stem cell transplantation is a concept of self-renewing multipotent stem cells as the basis for tissue repair in the nervous system, which has a physiologically limited regenerative capacity in adults. Mesenchymal tissue can be harvested from bone marrow, placental or adipose tissue, and multipotent mesenchymal stem cells expanded and purifies in vitro. Evidence from preclinical studies in experimental autoimmune encephalomyelitis models supports both an immunomodulatory and neuroprotective role for mesenchymal stem cells, and there are no serious adverse reactions reported to date.

1.2.1.5.3 Vitamin D

As described in the aetiology (1.1.3.2) low vitamin D levels are epidemiologically associated with an increased risk of developing MS. Several small studies have examined the potential of dietary vitamin D supplementation, to ameliorate relapse frequency in MS and yielded inconsistent results. Studies of vitamin D supplementation in individuals predisposed to MS are also forthcoming.

1.2.1.5.4 Anti-lingo antibody

Promoting repair in MS is, so far, an unexplored sphere of MS therapy. Lingo antagonists promote oligodendrocyte differentiation and myelination in vitro and in animal models of demyelination. Ultimately, therapies that successfully promote remyelination and repair may be applicable across the spectrum of MS subtypes, including progressive form of the disease[36].

1.2.1.6 Managing symptoms

Neuroinflammation and neurodegeneration culminate in a variety of persistent symptoms that are not necessarily related to acute relapse as: visual acuity, bladder, bowel and sexual issues, mood disorders and cognitive dysfunction, pain, sensitivity disorders, fatigue, and motor disturbances.

1.2.1.6.1 Visual acuity

Brainstem/ posterior fossa lesions involving oculomotor pathways can cause diplopia, nystagmus and internuclear ophthalmolegia as well as loss of vision, blurred vision, color desaturation and more rarely, visual field cuts. Chronic stable diplopia may be addressed by prisms. Steroids should be efficacy administered in both oral and intravenous ways for optic neuritis[39]. In some cases, benzodiazepines may be helpful. Only in severe cases is indicated eye muscle surgery.

1.2.1.6.2 Bladder, Bowel and Sexual Issues

Bladder and bowel problems may occur in the context of an MS relapse, and thus management of the relapse can sometimes alleviate associated sphincter dysfunction in the short term.

In general. the non- selective muscarinic agents, such as oxybutynin, tolterodine and trospium, ought to be avoided in patients with cognitive issues since these agents may cross the BBB and exacerbate cognitive deficits; selective muscarinic agents, such as darifenacin and solifenacin, are preferable in patients with cognitive dysfunction[40]. Patients with symptomatic detrusor activity are initially treats with bladder antispasmodics, (oxybutynin, tolterodine and solifenacin). However, the use of these drugs is limited by anticholinergic side effects as dry mouth and constipation. If the patient is still unresponsive botulinum toxin A injections into the detrusor muscle via a cystoscope can be very successful for 5-9 months.

Bowels manage instead even if pharmacological treatment is not the first option as it is bowel routine, dietary changes, adequate hydration, exercise and physical activity and biofeedback; pharmacological agents include stool softeners, laxatives, rectal stimulants such as glycerine suppositories and mini-enemas. Fortunately, very rarely, intractable bowel incontinence causing profound social and physical impairment may necessitate colostomy.

As sexual dysfunction in MS is common in both men and women (40-90%) there are many options as counselling or couple treatment. Nonetheless many of these problems are caused by anticholinergics, in many cases t treats another symptoms as depression, there are available different medicaments focalized in increased libido as flibanserin by binding with serotonin receptors in the brain, or to avoid erectile dysfunctions as sildenafil and tadalafil.

1.2.1.6.3 Mood disorders and cognitive dysfunction

Depression, anxiety and suicide are increased in MS[41-42]. This is the reason why is clinically important treat mood disorders because of the risk of suicide among patients. They could be induced by a high dose of corticosteroids. Bipolar disorders are treated selective serotonin inhibitors, tricycle antidepressants or a dextromethorphan/quindine combination. For depression and in patients with coexisting neuropathic pain, duotoxine or triccles may be useful. Similarly, the anticholinergic effects of tricycles may be useful when there is concomitant detrusor hyperactivity. In addition, medications for cognitive dysfunction include acetylcholinesterase inhibitors, memantine and rivastigmine tartrate even these have shown modest or no effects[43] in pwMS as they have in Alzheimer's disease.

1.2.1.6.4 Pain

Acute pain such as neuropathic pain management consists mainly of the use of anticonvulsant medication. Gabapentin, pregabalin and carbamazepine are considered first-line treatments. Opiates are not recommended because their addictive proprieties and side effects in cognitive and bowel function. in case of migraines pain, caused sometimes by other medications, should be treated with traditional antimigraine drugs, non-steroidal anti-inflammatory drugs and triptans. In chronic pain, tricyclic antidepressant, serotonin-norepinephrine and cannabinoids are also an option.

1.2.1.6.5 Sensitivity disorders

The resultant positive sensory phenomena can range from mild paresthesias to severe sharp electric shock-like pain. Medication options include carbamazepine, phenytoin, pregabalin, gabapentin, tiagabine, levetiracetam, topiramate, duloxetine, or tricycle-antidepressants.

1.2.1.6.6 Fatigue

The management of fatigue is treated pharmacologically with medications in order to increase energy level. These consists of amantadine, selective serotonin reuptake inhibitors, modafinil, which promotes wakefulness, armodafinil and stimulants such as methylphenidate or amphetamine preparation. However, side effects could be irritability, headaches and insomnia. in addition, aspirin reported benefits for MS fatigue[44].

Patients on amantadine should be monitored for livedo reticularis. Patients on modafinil or armodafinil should be monitored for hypertension, headache and weigh loss.

1.2.1.6.7 Motor disturbances

Even if there are many mobility disturbances in pwMS, they can be subdivided the medications sets in three main groups: Spasticity, impaired mobility and tremor.

1.2.1.6.7.1 Impaired mobility

The only available pharmacological treatment for walking difficulty in MS is dalfampridine. It consists in an inhibitor of voltage-sensitive potassium channel that improves impulse conduction in demyelinated nerve fibers, increasing synaptic transmitter release at nerve endings. Fampridine, is an orally administered potassium-channel blocker that improves walking in some pwMS, available for patients between 4.0 and 7.0 of EDSS. Improvements were seen in 25% of pwMS. Even if Fampridine is generally well tolerated, side effects can include neuropathic pain, vertigo, dizziness, nervousness and nausea[45]. More serious adverse events include urinary tract infections and rarely seizures, being this last one a contraindication.

1.2.1.6.7.2 Spasticity

First line medications for spasticity include baclofen, γ-aminobutyric acid agonist, and tizanidine, an α2-adrenergic agonist. Both medications reduce abnormal increased muscle tone[46], and as a consequence can exacerbate or unmask limb weakness, beginning with a low dose and increase it as tolerated. Baclofen may cause bladder symptoms, confusion, somnolence, exacerbation, worsen speech, swallowing and rarely hepatic dysfunction. Even if tizanidine has less tendency to exacerbate weakness and ataxia, it often leads to dry mouth, edema and orthostatic hypotension. Nevertheless, cannabinoids, are currently another option which has been proved to improve self-reported spasticity scores, sleep disruption and the Barthel Activities of Daily Living Index. However, despite of the fact that the psychotropic effects are minimal, cannabinoid therapy detected no improvement for MS-related spasticity as measured by the Ashworth scale[47].

Botulinum toxin type A is considered in severe focal spasticity due to it inhibits acetylcholine release at the neuromuscular junction, reducing muscle contraction for 3-6 months, but with better results in combination with physical therapy. Side effects are usually mild and temporary, predominantly weakness in injected muscles. In case of severe spasticity, the baclofen pump can provide the medication intrathecally, delivering it continuously in small doses, which leads with severe side effects and complications.

Lastly, in bed-bound patients with severe lower extremity weakness and spasticity interfering with positioning and hygiene, surgical rhizotomy is indicated.

1.2.1.6.7.3 Tremor

A variety of medications have been reported to reduce MS tremor, including isoniazid, glutethimide, primidone, gabapentin, levetiracetam, carbamazepine, ondasetron, oral tetrahydrocannabinol, clonazepam, and propranolol.

Stereotactic ablation of the ventrolateral thalamic nucleus or thalamic electrostimulation via implanted electrodes sometimes produces dramatic improvement, but it usually is self-limited[48]. Risks of surgical procedures include weakness, hemorrhage, and infection.

The main treatment options, corticosteroids, plasma exchange, and immunosuppressants, have already been proven effective in acute treatment of MS relapses. Despite the existing therapies focusing on the elimination of future demyelination, direct targeting of demyelinating axons does not prevent long-term disability. The ideal treatment should also enhance remyelination, since lack of remyelination after a clinical or subclinical relapse is the key indicator of long-term disability accumulation in MS. Remyelination is one of the most effective forms of neuroprotection. Future MS treatment strategies should focus particularly on remyelination and axonal repair to achieve full recovery from a relapse and to prevent progressive disease[49].

1.2.2 Rehabilitation treatment

Despite medical and pharmaceutical advances, there is no cure for MS and for that reason rehabilitation practice takes an essential role to handle the majority of signs and symptoms that MS involved and also the medication side effects, remaining the best available way to improve function in MS patients[50]. Rehabilitation is an active, client-centre process that is goal-oriented and empowering. It involves many disciplines, so multidisciplinary team is important, and they should work together to enable the person with MS to:

- Self-manage MS symptoms to minimize their medical role and emotional impact on daily life.
- Maintain current abilities, regain lost abilities, and maximize independence in DLA.
- Enhance participation and autonomy in life roles.
- Self-advocate for necessary services and supports.
- Promote overall health, well-being and life balance[51].

The breadth and depth of MS rehabilitation means that it is delivered across a full range of settings, including inpatient acute care, subacute, inpatient rehabilitation, outpatient rehabilitation, long-term care, home care, and community-based day programs[52-53].

Team members are encouraged to explore alternative solutions to problems and look beyond their own disciplines toward the best and most holistic outcome for the patient[54]. Moreover, the team must review periodically the progress of the patient in order to change some aims if they have not been arisen. Therefore, the ideal rehabilitation program for any given patient is dynamic so as to best address the evolving disease process, secondary complications and changing patient goals.

1.2.2.1 Rehabilitation Team

Currently, is well evidenced that exercise programs improve the Quality Of Life (QOL), increase physical capacity, enhance ADL performance, help with depression and reduce perceived fatigue. However, Physical rehabilitation, and therefore physical therapists must work holistically with other professionals as physicians, occupational therapists, nurses, social workers, speech therapists and psychologists, as well as the family and caregivers.

1.2.2.2 Family and caregivers

Rehabilitation professionals must recognize that the needs identified through their own assessment process may not be the same as those identified by the client or the family. Ensuring that the client's priorities remain central to the rehabilitation effort requires that the client and family/caregivers be active partners in the review of the assessment findings.

Involving clients and families/caregivers in these processes is often referred to as shared decision making, or patient-centred practice[55].

1.2.2.3 Physicians

Several different types of physicians may participate in the rehabilitation process, most common are the neurologist, physiatrist, and the primary care physician, depending on the health care system.

Neurologist is the specialist and expert in neurological diseases and is responsible for making the diagnosis of MS. It involves the neurologist completing a thorough neurological examination, taking a patient and family history, and ordering and interpreting a series of diagnostic tests. After diagnosis, neurologists are also the responsible for selecting and recommending the best DMT for symptom management. So, in brief, neurologist is the responsible for regularly monitoring the patient's neurological status to determine disease progression and the patient response to treatment.

Conversely, the physiatrist is the specialist and expert in physical medicine and rehabilitation, monitoring and managing the overall rehabilitation process, particularly when a patient's issues are complex. Physiatrist must also coordinate the medical treatments and interventions provided by the rehabilitation team that focus on the patient's activity and participation restrictions.

1.2.2.4 Occupational therapists

MS symptoms can restrict engagement in a wide range of occupations at any point in the disease course. Therefore, occupational therapists provide services to people with MS throughout the disease and across a full range of settings including acute care, inpatient rehabilitation, outpatient rehabilitation, day programs, home care and community-based services.

Depending on the patient's interests, needs and goals, occupational therapy intervention may focus on improving the patient's abilities to engage in self-care, mobility (especially upper extremity function), domestic life, leisure activities, or to maintain a productive role.

1.2.2.5 Nurses

There are many roles for nurses in MS care, but there is a particularly important role in creating an environment that supports the rehabilitation process. They are essentials for reliving pain, helping with hygiene and mobilization, providing care to pressure arear to prevent skin breakdown and ulcers, ensuring adequate nutrition, promoting bladder and bowel care and managing incontinence, giving emotional support and providing opportunities for adequate sleep, rest and stimulation. Not less important role for them is addressing patient concerns about sexuality and intimacy.

1.2.2.6 Social workers

Social workers offer counselling, and educational interventions by linking clients to essential community resources that provide employment accommodations, home modifications, disability insurance, long-term care and so on. They often assist family members to identify their feelings and explore ways to engage with each other more comfortably about their concerns[56]. Therefore, the most important goal is to work with patients to advocate for improved access to limited resources.

1.2.2.7 Speech and swallowing therapies

The aim of speech-language pathologist is to assess and manage communication ad swallowing disabilities over the course of the disease process due to the high difficulties reported by pwMS, improving quality of life by enhancing and maintaining communication and swallowing abilities in the context of meaningful life activities and over the course of the disease process. Therapy's goal must facilitate independence and active participation in patient's daily routine, treatment may involve remedial techniques to improve physiology, as strength or ROM or compensatory techniques as exaggerated articulation or modified texture foods. Spoken output may need to be augmented by using non-verbal communications strategies or devices.

1.2.2.8 Psychologists and neuropsychologists

Even if psychology is the health discipline that provides assessment and treatment of cognitive and mental health concerns, a clinical psychologist focuses on mental health while a neuropsychologist focuses on cognition.

Psychologist roles include supporting the work of the other team members, providing direct clinical services to clients, including the assessment of mental health, adjustment, and relationship concerns, and providing therapeutic interventions to address any issues that are identified. Sometimes psychologist refers to, and works collaboratively with, a psychiatrist.

Contrariwise, neuropsychologists treat cognitive dysfunction identifying areas of cognitive strengths and weaknesses, in order to help the patient, make sense of his or her subjective experience and assist and help the patient as well as family and caregivers.

1.2.2.9 Physical therapists

Since many of the common impairments of MS negatively influence movement and function, physical therapists play a critical role on the rehabilitation team throughout the disease course. Physical therapy assessment in MS care evaluated limitations in strength, range of motion, balance,

posture, gait, and transfers and determines their functional impact. Using this information, physical therapists provide treatment aimed at developing, maintaining and restoring minimum movement and function[57].

To address problems in movement and function, a major component of most physical therapy interventions is client-specific exercise prescription. Exercise has been shown to effectively manage many physical symptoms of MS[58–60]. For example, stretching may aid in the management of mild-to-moderate spasticity when done in conjunction with pharmaceutical treatment[61], balance exercises can reduce the risk of falls[62], moderate intensity resistance training can improve muscle strength,41 and cardiovascular endurance can be improved with aerobic exercise[63]. Exercise programs should be a challenge to the patient but not a struggle because for some people, exercising can have temporary negative effects (fatigue, heat intolerance). In general, moderate exertion with a focus in maintaining good quality and consistent movement may be preferable for building strength in pwMS.

Exercise therapy will vary depending on its setting. Programs in an inpatient setting often require that the therapist or therapy assistant provides direct, hands-on assistance and support to the client. When the client returns home, he or she is often able to continue the exercises independently and may start to include community resources.

When gait impairments occur, physical therapists provide gait retraining, which may include prescription and training in the use of orthotic or gait aids. It is common in physical therapists to collaborate with family and care givers on transfers, bed and wheelchair positioning, adaptive equipment, and home modifications, particularly in situations where the client's MS is advanced.

Regardless of the focus of the physical therapy intervention, a strong emphasis is placed on educating the client to self-manage hi or symptoms. For many clients, education focuses on lifestyle changes that support engagement in regular exercise and other modifications to support mobility and function.

When a patient with MS follows through with physical therapy recommendations and exercise programs, he or she can gain a sense of control over MS. Physical therapy is most successful when the therapy goals and interventions are consistent with the client's priorities and ultimately influence functioning positively[51].

1.2.3 Physical rehabilitation

1.2.3.1 Assistive devices

Physiatrists, working together with physical therapists and orthopaedics, are also the responsible of prescribed the Assistive Devices (AD) in order to help ambulatory stability and increasing the patient's base support when required.

1.2.3.1.1 Ankle foot orthosis

To providing an external limit to movement across joints exhibiting instability, bracing can slightly enhance movement in selected directions. For ADS weakness, an Ankle Foot Orthosis (AFO) can provide adequate foot clearance either by fixing the ankle at an angle that will ensure foot clearance or by providing an assistive force to achieve that same foot clearance. If there is additional mediolateral instability of the ankle, the brace should be designed to capture both malleoli so that stability is restored. For individuals with mild quadriceps weakness, the ankle joint of the AFO can be placed in slight plantar flexion, or a ground reaction force model.

1.2.3.1.2 Handheld Assistive devices

A can should be held opposite to the side of greatest weakness. An extended base cane such as a quad cane or a hemi walker can provide even greater unilateral support.

1.2.3.1.3 Bilateral cruces

In bilateral weakness patient or in whom gait instability is not adequately corrected with unilateral device, bilateral cruces are considered. Forearm crutches are preferred over axillary crutches in those who require less weight bearing through the hands.

1.2.3.1.4 Walkers

Walkers are highly customizable with variable height, optional wheels, with or without a seat, with different braking systems, and of different materials of construction. A walker with wheels will require less energy during use because avoids picking up the walker in order to advance forward. A built-in seat provides an instant opportunity for rest, important in patients with fatigue.

1.2.3.1.5 Wheelchairs

Patients with more severe ambulatory dysfunction, wheelchairs are prescribed. A manual chair is good option for individuals with moderate trunk control, sufficient UL strength and coordination, and adequate cardiovascular fitness. Though, a power chair is more appropriate for individuals who lack the either the UL function or cardiopulmonary capacity to propel a manual chair, have reduced trunk control, and/or lack the capacity to perform pressure releases for skin protection. However, power chairs users must have the cognitive ability to drive a chair safely and demonstrate the ability to drive safely[38].

1.2.3.2 Physical exercise

As explained before, MS affects the myelin sheath, which in turns affects the speed with which messages are sent from your brain to you muscles. Less myelin is translated in nerves less efficient in sending messages, muscles becoming weaker experiencing an important loss of strength. Strength training can help prevent contractures, atrophy and fatigue, while improving function[64].

Exercise programs are geared toward improving the patient's intrinsic abilities. A balanced exercise program involves maintenance or pursuit of adequate flexibility, strengthening and cardiovascular fitness. Joint ROM deficits identified on examination should be the focus of targeted stretching programs; this will serve to ameliorate the adverse biomechanical effects of inflexibility. Furthermore, prolonged stretching several times daily is the foundation of a good spasticity management program. Strengthening programs should be designed to correct deficits identified on clinical examination while working toward larger functional goals such as improving balance, increasing independence with transfers, achieving normalization of gait, and increasing stair-climbing tolerance. Cardiovascular fitness ought to be incorporated into every exercise program.

In some individuals, core temperature elevation with exercise may induce Uhthoff's phenomenon, a transient episode of neurologic dysfunction secondary to heat-associated conduction block in previously demyelinated segments. Either internal or external cooling strategies.

Treatment planning and goal setting for each of these aspects of mobility tend to focus on decreasing the need for assistance, increasing efficiency (reducing energy demands), decreasing the time needed to complete a task, or increasing safety during the task. Each of these goals can be pursued by designing treatment plans that include the following:

- Apply the principles of task-specific repetitive training.
- Manage underlying impairments contributing to the restriction of movement, for example, balance, fatigue and weakness.
- Prescribe and then train a client to use adaptative equipment to compensate for difficulties, reduce need for assistance, o improves overall safety.
- Recommend home modifications that reduce the need for assistance or improve overall safety.

1.2.3.2.1 Physical exercise for improving fatigue

Endurance exercise interventions have been performed in people with mild and moderate MS with bicycle ergometry[65], arm/leg ergometry[63], and treadmill walking[66]. While positive changes in endurance after exercise is strong, findings regarding fatigue have been somewhat inconsistent[67]. The lack of change and the fact that fatigue severity did not increase has been suggested to imply that the intervention was well tolerated. Overall, studies reporting positive effects of exercise on perceived fatigue tended to use multidimensional rather than unidimensional fatigue measures.

1.2.3.2.1.1 Endurance exercise

On the basis existence evidence, the recommendations for endurance training in people with mild to moderate MS consist in an initial frequency of 2-3 sessions per week and low-to-moderate intensity of 50-70% of maximal oxygen consumption or 60-70% of maximal heart rate during 10-40 min is optimal. Progression over months is achieved either by longer duration of sessions or by adding an extra session per week. After a period of 2-6 months with exercises on low-to-moderate intensity, a higher intensity can be tested if tolerated[68]. These considerations regarding intensity, frequency and duration are necessary to prevent any increase in intensity or duration of perceived or observed fatigue.

1.2.3.2.1.2 Resistance exercise

Regarding recommendations for progressive resistance training consist in a program of 4-8 exercises in 1-3 sets with intensities of 15 repetition maximum (RM) during the initial sessions is recommended. The intensity can be progressively increased over weeks and months to 3-4 sets of 8-10 RM. Rest periods in the range of 2-4 min between sets and exercises are recommended. The program should contain exercises for the whole body. Larger muscle group exercises should precede smaller muscle group exercises [68].

More research is also needed on the use of exercise to manage MS fatigue, particularly among people with severe disability.

1.2.3.2.2 Physical exercise for improving balance

The general physical condition of pwMS is often poor, which contributes to balance disorders and reduced participation. With emerging evidence of the modulatory role of exercise on neuronal growth factors in reducing damage due to neurodegenerative diseases, exercise activity has become even more important for pwMS[69].

1.2.3.2.2.1 Strengthening exercises

Strength of antigravity muscles is important in postural control and mobility. Strengthening programs for pwMS indicate that functional improvement may be achieved and that neuromuscular capacity in MS can be improved even when there is underlying neurological damage[68], [70-71]. Muscle weakness contributes to impaired mobility and balance disorders, therefore, strengthening exercises in functional contexts may assist in improving balance and also gait.

1.2.3.2.2.2 Endurance Exercise

General deconditioning in people with MS may increase the sensation of fatigue and lead to less efficient sensory-motor control Exercises focusing on endurance for balance relevant tasks may improve balance, reduce exertion, and increase and individual's perception of his or her ability to carry out ADL.

Currently, only few studies have incorporated specific balance training of pwMS in an exercise program[71-72]. All of them share that program must include exercises promoting LL strength training and mobility. Also, functional strengthening, stretching and resistance exercises are required in interventions of a, at least, 12-week program of exercises customized. including always a balance component in each exercise.

Although it is apparent that balance can be positively influenced by exercise ad rehabilitation programs, balance dysfunction and falls remain a major problem for pwMS. There is an urgent need for improved assessment and treatment programs and complementary research programs to address these ongoing problems more adequately. The training must target the functions considered important to the individual and be effective in restoring the function and increasing participation.

1.2.3.2.2.3 Rehabilitation sensory-motor strategies and Balance

Addressing sensory-motor strategies is becoming an integral part of balance rehabilitation. Specific intervention for the improvement of sensory-motor strategies to control static and dynamic balance disorders of pwMS has been implemented with some success. Balance exercises typically include training balance under challenging sensory and dynamic conditions with the goal of improving sensory strategies so that the patient can maintain balance in different environmental contexts. Exercises can include balancing under conditions altered somatosensory input (foam or cushions under feet), reduced visual input (moving eyes with head still, closing eyes), or with the stimulation of vestibular system (exercise done with head turning). The tasks can be more challenging by reducing the base of sustentation (BOS), increasing the number of segments to control, exercising in quiet or busy environmental conditions, and using static or dynamic balance exercise. Dynamic balance training includes walking with head turns looking at a stationary target, walking with horizontal or vertical eye movements, or performing a secondary motor task while walking. Adding secondary cognitive tasks can further challenge dynamic balance. Often by inhibiting the use of other systems during balance exercises aims to facilitate the use of the impaired system in balance control.

Depending on the goal of training sensory strategies, there are different methods available:

1.2.3.2.2.3.1 Reducing dependence on visual information for balance control:

The manipulation of visual information can be achieved by:

- Varying visual conditions: eyes open, closed, dim lighting, glasses that reduces sight or visual motion.
- Creating conflict of information between perception of movement of the retina and somatosensory and vestibular information.
- Varying head orientation and movement.
- Asking the person with MS to follow moving objects with the eyes.

1.2.3.2.2.3.2 Reducing dependence on information from somatosensory system for balance control

The manipulation of somatosensory information can be achieved at the sole and ankle level by:

- Varying surface conditions: carpet, foam, incline, and tilting surfaces. These alternate surfaces reduce the reliability of the information from ankles and soles about the Centre of Pressure (COP) and create a conflict with other incoming sensory information.
- Using vibrating stimulators that can alter proprioceptive information.

1.2.3.2.2.3.3 Reducing dependence on information from vestibular system for balance control:

The manipulation of vestibular information is more complicated than manipulating that from the visual or proprioceptive systems:

- Varying the head orientation and movement can challenge these receptors although the vestibular system is relatively functional also at high rotational frequencies.

Community-based programs such as tai chi, yoga, aquatics and Feldenkrais and hippotherapy improve balance in pwMS[51].

1.2.3.2.3 Physical exercise for improving mobility

Muscle strength, tone and coordination are among the main determinants of a person's ability to perform voluntary movements, and to function in the environment. Therefore, the lack of three of them can be translated into a weakness mobility. Fortunately, interventions and treatments are available to remediate, albeit partially, some of these impairments. Thus, it is essential to assess each impairment separately and to integrate impairment-specific interventions into individualized treatment and rehabilitation planning.

1.2.3.2.3.1 Muscle Tone

Owing to the heterogeneous and unpredictable nature of MS, a variety of muscle tone disorders can be encounters. Hypotonia (which can result from cerebellar dysfunction), extrapyramidal hypertonia (characterized by cogwheeling and rigidity), and dystonia (consisting of abnormal sustained or intermittent muscle contractions with twisting movements and abnormal postures) are not common. Spastic hypertonia is by far the most frequent disorder f muscle tone in MS and will be the focus of our discussion.

Despite the pharmaceutical treatment for spasticity has already been explained as a important treatment for severe spasticity, exercise became the best option for focal or focally bothersome spasticity.

1.2.3.2.3.1.1 To improve passive movement

To improve ROM and reduce deformity, to decrease resistance to passive mobilization. This goal can be attained in many pwMS but often requires daily stretching and the use of orthotics, for which treatment adherence can be a problem.

1.2.3.2.3.1.2 To improve active function

Controlling spasms and reducing the co-contraction of antagonist muscles to a desired movement or function. Examples include reducing plantar flexor tone to improve foot clearance while walking or reducing finger flexor tone to facilitate the release of objects. This proves to be the most challenging goal to attain because there is often significant loss of motor power "underneath the spasticity" and because many other impairments can contribute to the loss of function.

1.2.3.2.3.2 Muscle strength

Strength training during periods of MS relapse should be done with caution. Overtraining during this period can be exhausting and lead to short-term functional decline if a client is pushed to a point of muscular fatigue. Instead, gentle progression of exercise is more beneficial and does not impair short-term function. The concept of "start slow, go slow" is most effective during this stage **(Table 3)**.

The typical progression of exercise in the presence of limited active ROM presented below[68] has been found to be an effective intervention strategy for improving walking and functional ability in moderately pwMS **(Figure 12)**.

1.2.3.2.3.2.1 Active assistive range of motion

Begin passive ROM (PROM) until full ROM is achieved. Active Assistive ROM (AAROM) may be incorporated in the pain-free ROM.

1.2.3.2.3.2.2 Active assistive range of motion

One PROM is within expect limits, begin Active ROM (AROM) in addition to AAROM.

1.2.3.2.3.2.3 Isometric exercises

Once AROM can be completed through the expected ROM without pain, isometric strengthening of surrounding muscle groups can begin. Isometric exercises are static exercises against stable resistance that offer strengthening of the muscle groups surrounding the joint while providing stabilization and protection to the joint because there is negligible joint movement while the exercise is being performed.

1.2.3.2.3.2.4 Isotonic concentric exercises

Once isometric strengthening can be performed without pain, isotonic and isokinetic strengthening can begin. These are typically done in a concentric (muscle contraction while shortening) manner. With isotonic exercises, the tension in the muscle remains constant despite a change in muscle length. Isotonic exercises are typically performed in concentric (muscle contraction while the muscle lengthens) fashion. These exercises involve dynamic

muscle activity performed at a constant angular velocity while torque and tension remain constant as the muscles shorten or lengthen. Isokinetic strengthening exercises typically involve the use of a machine to isolate a specific joint movement.

1.2.3.2.3.2.5 Isotonic eccentric exercises

Eccentric training (muscle contraction while lengthening) may begin for specific tasks that require eccentric control to be performed properly. For example, a patient who has difficulty descending stairs, they may drop abruptly to the next lowest stair due to weakness in the knee extensors, hip extensors, or in the ankle plantar flexors of the stance leg. Repetitive eccentric training of these muscles, using handrails for safety and control, is a task-specific method of using eccentric contractions to achieve a functional goal. Eccentric strengthening should be performed with caution in MS as excessive strain can quickly cause muscle fatigue. For this reason, fewer repetitions and more sets with short breaks in between can help reduce muscular fatigue. Excess muscle soreness or evidence of weakening are indicators to stop.

1.2.3.2.3.2.6 Functional training

Functional training, activity-specific training, or sport-specific training. Increasing difficulty and adaptability with proprioception stimulus and weights or resistances[51].

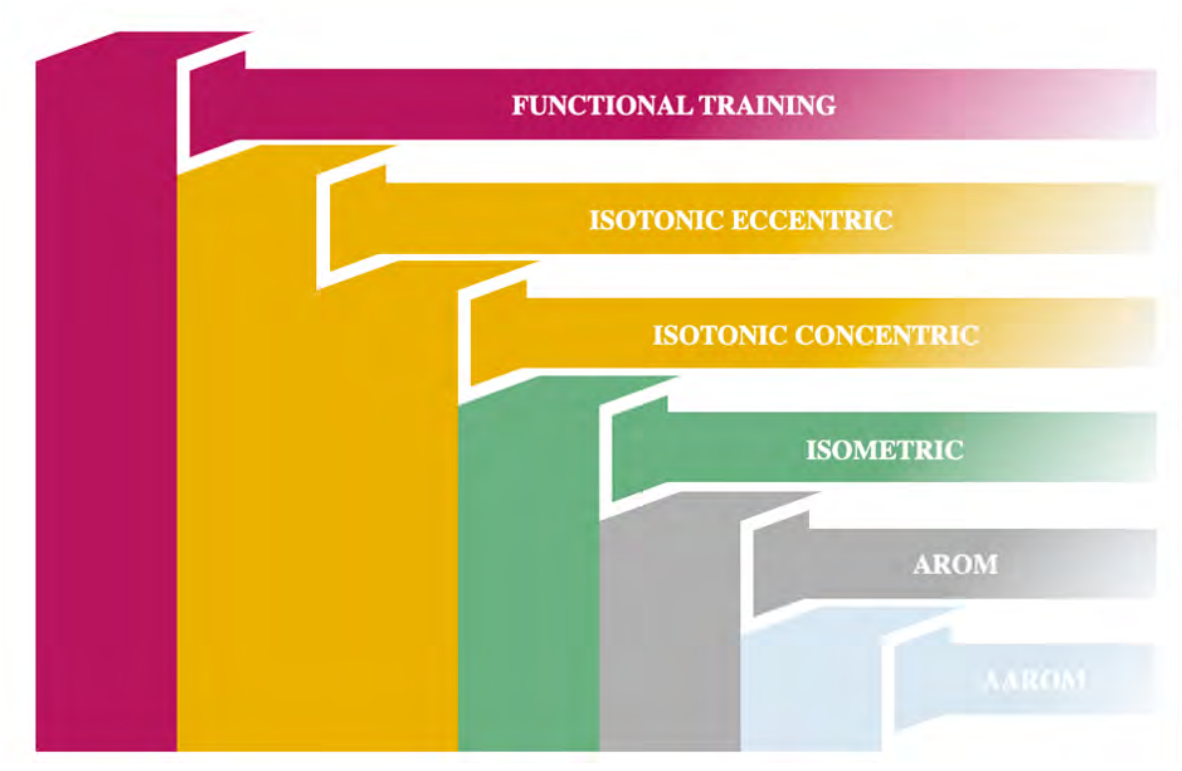


Figure 12. Muscle strength rehabilitation treatment progression.

Table 3. Strength training guidelines in Multiple Sclerosis

• Begin strength training at 70% of a 10 RM. When 25 repetitions at his weight can be performed for two consecutive sessions, increase the weight by 10%.
• Training should be performed two to three times per week, for three sets, 8-12 repetitions per set, 10-15 min per session.
• Do not strength-train the same muscle groups on consecutive days.
A variety of equipment can be used, depending on the levels of balance/coordination, plasticity/tremor, strength and/or fatigue:
• Free weights
• Isokinetic machines
• Stretch band exercises
• Sandbag weights
• Water resistance exercises

RM: repetition maximum.
Source: Strength training guidelines in multiple sclerosis [Internet]; c2007 [cited 2010 July 1]. Available from: http://www.ncpad.org/disability/fact_sheet. php?sheet=79&section=595.

1.2.3.2.3.3 Coordination

1.2.3.2.3.3.1 Ataxia

Exercise programs for the treatment of ataxia typically focus on weight-bearing activities that provide distal stabilization while promoting proximal control. For example, quadruped exercises may be performed, which stabilize the joints distally and allows the therapist to target proximal muscle groups. Alternative positions include, but are not limited to, standing with arms stabilized against a wall, sitting with arms outstretched against a mat table, tall kneeling with arms stabilized against a fitball, or half kneeling with arms stabilized against a wall. It is important to understand that proximal control and stability are required to foster an improvement in distal coordination, but, in the case of the ataxic patient the proximal control must be combined with distal stabilization.

1.2.3.2.3.3.2 Upper-limb

For UL incoordination strengthening exercises can be very beneficial in maintaining strength and preventing disuse weakness. However, strengthening will not reduce tremor. The most practical physics approach is to apply a several-pound weight to the UL, increasing the mass, which consequently decreases the excursion produced by any given force applied. Weakness can be an obstacle to the use of weights, especially for repetitive movements. Along the same line, weighted objects, such as weighted utensils, pens, or cups, may be used for mild tremors. For more severe tremors, the UL may be stabilized distally to minimize the magnitude of the tremor.

1.2.3.2.3.3.3 Lower-limb

For LL loss of coordination, few rehabilitation techniques have been proposed. Assistive devices for mobility, such as canes or walkers, can be helpful in broadening the base of support.

1.2.3.2.4 Physical exercise for improving upper-limb

even though there is more lack of evidence in UL rehabilitation than LL, the strategies for UL have been applied to improve the UL function in pwMS ranging from resistance and endurance training on body functions and structures level to task-oriented training on activity level[73]. Resistance and/or endurance training seem to improve UL strength[63], [74] and endurance on body functions and structures level, while task-oriented training, constraint-induced movement therapy[75], focused on activity level and thus improved capacity and performance on activity level. Sensory training [76] in turn seemed to improve sensory function in the hand on body functions and structures level and UL capacity on activity level. In summary, this indicates the importance of selecting a training program in function of the desired improvements (resistance training to improve strength or task-oriented training to improve UL capacity and performance in daily life).

Conversely, there is no consensus about dosage: training duration, frequency of training sessions duration of a single training session, and intensity of training. Even there is more standardized dosages in other pathologies like stroke, in MS there is no attention for the therapy dosage of UL rehabilitation. Most studies had an intervention duration of 8 weeks or more. The frequency of training ranged from 2 to 5 days per week while the duration of a training session ranged from 30 to 60 minutes.

1.2.3.2.5 Physical exercise for improving neuroplasticity

Lastly, significant levels of disability do not necessarily preclude exercise. With a little bit of creativity, an exercise program can be created for most individuals. Overall the benefits of exercise extent beyond physical fitness and increased functional capacity, there is evidence to support a positive impact on both mood and fatigue[77].

1.3 New technologies for neurorehabilitation in MS

The motor practice seems to be determinant to induce neuroplastic changes and motor recovery. More recently these findings have been extended to MS, in particular, it has been hypothesized that disease progression, functional reorganization and disability are mutually related. For this reason, neuroplasticity -based technologies and interventions have been rapidly introduced in MS rehabilitation. Constraint-induced movement therapy, robotics and virtual training are new rehabilitative interventions that deliver an intensive e task-specific practice, which are two critical factors associated with functional improvements and cortical reorganization[49].

Recently, it has been demonstrated how the cerebral cortex might adopt functional reorganization mechanisms that might prevent functional loss and maintain the ability to learn a motor task [78]. It could be hypothesized that clinical progression partially occurs when the mechanisms above mentioned fail. This new approach leads to the application of rehabilitative interventions that might promote functional reorganization and recovery. Functional recovery in MS is achieved by the resolution of inflammation and the development of functional reorganization processes. Evidence supports and adaptative role of functional reorganization mechanisms that might limit the adverse effects of MS on motor behaviours [79-80].

New insights and findings in neuroscience fields lead to a paradigm shift in neurorehabilitation. Actually, new evidence that the human brain can change and modulate that the human brain can change and modulate itself according to external experiences and behaviours, leading to physiological and anatomical changes[81-82]. Bottom-up and top-down approaches have been described to enhance cortical reorganization and motor recovery. The former included multimodal, external inputs that act at a peripheral level (bottom) with the aim of influencing CNS and neuroplastic changes. They are mainly represented by sensory-motor training. The letter use brain functions and post-lesional reorganizations mechanisms to drive rehabilitative interventions [83]. The bottom-up approach is based on the belief that postlesional CNS might regain functions and motor skills and that behavioural experiences and exercises might shape it. However, the underlined paradigms are still unclear, and the dose, type, and modality of exercises are far to be out-lines.

1.3.1 Functional recovery in multiple sclerosis

Evidence from brain systems supports an adaptative role for neuroplastic changes in MS despite the widespread pathology. Specifically, it may limit the negative effects of MS on behaviour[84-85]. The extent and type of neuroplastic changes vary across phases and stages of the disease [86]. Patients with CIS presented in a study a more widespread recruitment of the contralateral hemisphere (local cortical reorganization) during a simple motor task (fingers flexion-extension). Conversely, in a RRMS and some disability, an activation of the ipsilateral sensorimotor networks occurs (lateralization shift). As the disease advances toward secondary progression, patterns of functional reorganization show an increasingly bilateral distribution and, even for simple motor tasks, involve higher control sensorimotor areas that are recruited for a novel or complex task in healthy subjects (association areas). The enhancement of cortical excitability due to paired associative stimulation and training-induced improvement are persevered even in disable MS [87]. Furthermore, improvements in both short and long-term motor learning (ML) in MS population, despite the disability level [78]. However, functional reorganization processes could be limited by MS-specific characteristics and the accumulation of structural CNS damage because brain damage, functional reorganization processes, and disability are mutually related throughout the disease progression [88]. Therefore, the effects of neuroplasticity-based technologies and interventions, virtually beneficial for functional recovery, have been poorly tested so far. Recently, UL task-oriented rehabilitation, but nor arm passive motion, has been showed to influence

white matter integrity in the corpus callosum and corticospinal fibber bundles [89]. Limited but clear evidence of functional recovery in MS exists and the developing of therapeutic interventions that induce adaptative plasticity are encouraged.

1.3.2 Principles of use-dependent neuroplasticity

Plasticity refers to "an intrinsic property of the human brain and represents evolution's intervention to enable the nervous system to escape the restrictions f its own genome and thus adapt to environmental pressures, physiologic changes, and experiences"[90]. Neural plasticity is believed to be the basis for both learning in the intact brain and relearning in the damage brain that occurs through physical rehabilitation. It is now well established how experiences and practices play a fundamental role in neural reorganization processes in the healthy and damage brain. Plasticity can be considered multi-levels phenomena that involve: brain (neurons and glia cells), cortical networks (changes in neuronal activation and cortical maps), intra (for example mitochondrial functions), and inter-cellular mechanisms (changes in synaptic strength, including sprouting), genome.

Motor behaviours remarkably adaptative and may change during motor experiences; the components of motor training (skills, strength and endurance) could have specific effects on plasticity-related events. Skill training, which refers to the acquisition of new and complex movements' combination, can induce a substantial cortical network reorganization that leads to a synaptogenesis process with increased synaptic number, an increased synaptic strength, and changes in the cortical topography closely related to the trained movement. It is important to bear in mind that cortical reorganization occurs only if the tasks are challenging and quite new.

Intensive five-fingers "like piano" moto training was able to modify significantly finger cortical motor maps. Although an influence of CNS might be expected even in strength training that preferentially leads to an increased muscle power, it does not result in any form of cortical reorganization [82]. Finally, endurance training, in which motor outputs are prolonged, can induce new angiogenesis and increase cerebral low without any effect on motor maps [91].

Neuroscience research has made significant advances in understanding experience-dependent neural plasticity, and these findings are beginning to be integrated with research on the degenerative and regenerative effects of brain damage. A relevant example of the integration of basic neuroscience rehabilitation practice and research are the ten experience-dependent plasticity principles postulated[92]. These principles should be incorporated in clinical rehabilitation with the aims of improving functional recovery, activities and quality of life.

Table 4. Principles of experience-dependent neuroplasticity.

Principle	Description
Use it or lose it	Failure to drive specific brain functions can lead to functional degradation.
Use it and improve it	Training that drives specific brain function can lead to an enhancement of that function.
Specificity	The nature of the training experience dictated the nature of the plasticity.
Repetition matters	Induction of plasticity requires sufficient repetition.
Intensity matter	Induction of plasticity requires sufficient intensity.
Time matterns	Different form of plasticity occur at different times during training.
Salience matters	The training experience must be sufficiently salient to induce plasticity.
Age matters	Training-induced plasticity occurs more readily in younger brains.
Transference	Plasticity in response to one training experience can enhance the acquisition of similar behaviours.
Interference	Plasticity in response to one training experience can interfere with the acquisition of other behaviours.

Adopted by Kleim and Jones[92]

1.3.3 Virtual reality

Before to go deeper in the different ways of realities, it is important to clarify that augmented, virtual and mixed reality are still terms that did not have a consensus yet to be used. In the literature, Virtual Reality (VR) is the terminology most used even if that includes Augmented Reality (AR) or Mixed Reality (MR). Therefore, in this chapter we do not make a difference between AR and VR as it is presented as a state of the art.

In recent years, VR technologies have begun to be used as a treatment tool in rehabilitation for their low-cost, high portability, off-the-shelf software and devices available and for the chance to deliver an engaged, high-repetitive, standardized, active learning. VR has been defined as the "use of interactive simulations created with the computer hardware and software to present users with opportunities to engage in environments that appear and feel similar to real-world objects and events[93].

Two fundamental concepts in VR are presence and immersion: presence is considered the subjective feeling of being present in a simulated environment, whereas immersion is a measure of the VR platform related to the ability to induce a sensation of the real world in the users[93]. In virtual rehabilitation, simple devices as joysticks, or complex systems using capture motion systems, sensors or haptic feedback are used to interact with the environments. VR scenario usually reproduces real life activities where practice can be adjusted on user's characteristics. More recently, gaming console, as Nintendo wii or Kinect Xbox, have been introduced in clinical and research settings as a low-cost way to deliver virtual reality[94].

1.3.3.1 Presence and embodiment in virtual reality

Even though there is no standardized definition for presence, it can be understood as the psychological state in which an individual is unable to acknowledge that an experience is computer generated [95-96]. There is a consensus to characterize presence as a multicomponent construct [97]. It has been commonly though that presence is the key mechanism that makes VR work. Presence may be especially relevant in a neurologic population, since the subjective perception when interacting with Virtual Environments (VEs) elicited in persons with CNS dysfunction has been shown to be different to that of healthy subjects[98]. Characteristics of both the user and what and how sensory information are presented by the VE determine the level of presence in VR. With regard to the user, the demographic, psychocultutal and also clinical characteristics modulate the perception of the virtual world and the interaction with it. Likewise, a previous experience with VR systems may influence presence[99].

Like presence, embodiment is a multicomponent psychological construct. It has been defined as the sense of one's own body [100], as the bodily self-conscious [101], or as corporeal awareness [102]. All the existing evidence seems to indicate that presence and embodiment are innately linked. This relationship is evidenced by studies showing that the sense of presence can be modulated with avatars that accurately represent the users' actual selves (rather than avatars representing their ideal selves), which can facilitate their embodiment [103].

1.3.3.2 Motor learning principles

Motor learning principles are defined as the set of processes associated with practice or experience that lead to relatively permanent changes in the ability to perform actions[104]. Different principles have been postulated to modulate motor learning after stroke. Salient, goal-directed, task-specific movement and practice of sufficient intensity are important determinants in motor learning in human skill motor learning[105].

1.3.3.2.1 Enriched environments

Preclinical research on enriched environments (EEs) serves as the basis for hypothesizing that enriched VR experiences could serve as rehabilitation tools to promote motor learning[106]. Initial findings shown that EE promote sensorimotor functions and learning after stroke. Neurological patients exposed to EE that motivated exploration, physical training, and social interaction, they increased activity and decreased their alone time[107].

1.3.3.2.2 Intrinsic and extrinsic feedback

Movement performance is informed by both intrinsic and extrinsic feedback. Intrinsic feedback relates to the sensory-perceptual information that is naturally generated during or after a movement. Augmented feedback, also known as extrinsic feedback, is an add-on to the intrinsic feedback with the goal of

providing further information, in the goal of providing further information. Augmented feedback is provided by an external source and not by the movement itself[108]. VEs ca provide augmented feedback through different sensory modalities such as visual and auditory information with audio-visual devices and proprioceptive information through specific interfaces such as a haptic apparatus. Consequently, VR systems capitalize on both intrinsic feedback and augmented feedback[109].

1.3.3.2.3 Task specificity

Task specificity has long been a fundamental requirement for designing recovery of function programs. The principle of specificity suggests that motor learning is more effective when practice includes environmental and movement conditions similar to those required for the execution of the movement[110]. This suggest that the benefit of the practice specificity occurs because motor learning is specific o the information available during the learning process.

1.3.3.2.4 Dosing

The dose of the training has been reported as a central factor in motor learning[111]. Dosing depends on three parameters: training duration and frequency with which he individual performs training and the number of repetitions performed during training. It is known that a sufficient dose of practice needs to be performed in order to produce skilled behavior[112] and neuroplastic changes[92]. VEs are designed to promote repetitive task practice that can be tracked and progressed. Dose alone, however, is not sufficient for motor learning and neural plasticity.

1.3.3.2.5 Adaptability

The repetition of a task is critical for its learning and its refinement. However, the mere repetition of a task has not been shown to induce plastic changes in motor maps. Being exposure to a task that requires little or no learning does not produce changes in motor maps or neural morphology [82]. Based on this principle, rehabilitation interventions should involve motor skills with growing difficulty to always pose a motor challenge.

1.3.3.2.6 Motivation

Motivation can be defined as the set of forces that move an individual to act, which may be extrinsic (prompted by an external reward) or intrinsic (propitiated because the task in inherently pleasurable: curiosity, play, etc). Research has shown that motivation promotes learning[113]. Thus, motivation plays a major role in VE because it persuades patients to accomplish a task and facilitates presence in the virtual world.

1.3.3.3 Motivating through gaming elements in virtual environments

Gaming elements can improve motivation and that, if paired with other activities, they ca be harnessed to engage users and achieve desired outcomes[114]. However, there is no consensus regarding the required essential characteristics of these gaming elements. Many elements have been suggested to be important

for the design of a successful game, such as fun, flow, goals, feed-back, game balance, pacing, interesting choices, and narrative structure among others[115]. Actually, some of the intrinsic characteristics of games that can affect motivation and earning[116], and how those are used in the context of motor rehabilitation, such as goal setting, balancing challenge and reward, overlap with principles of motor learning[117].

1.3.3.4 Virtual reality training results in multiple sclerosis

Effectiveness of VR-based interventions in stroke survivors has been reported. Use of VR and videogaming may be beneficial in improving UL function and ADL function[118] about MS VR have been tested so far for improving balance or gait with inconclusive results [119-123]**.** VR scenario combined with treadmill training on gait , reporting positive results on gait speed and ability in negotiating obstacles [123]. Interactive visual-feedback exercises with Nintendo Wii balance were tested for improving balance and mobility in MS patients with patients with mixed conclusions. Nilsagard et al. reported no significant differences compared to no intervention, even if moderate effect size has been highlighted [119]. Conversely, Brichetto et al postulated that Wii training could be more effective than the current standard protocol in improving balance disorders in MS [120]. Prosperini et al proposed the Wii balance training as a potentially useful home-based treatment [122]. Kramer et al. combined exergames with an unstable platform to improve balance; they found how it was superior to other treatments especially in dual task conditions[121].

Also different metanalysis and systematic reviews concluded that VR is as effective as conventional training for improving balance[124-125] and gait[125] in pwMS, and improving motor function UL despite the no clear consensus on which VR based approaches are the most effective, or the optimum intervention duration and intensity[126]. VR positively affect MS patient's outcomes by boosting motivation and participation with a better response to treatment[127] and representing a motivational and effective alternative to traditional motor rehabilitation protocols with VR and increase the effects of treatment[128].

However is still in conflict due to the lack of argued choices for interventions the design and planning of personalized VR-based treatments[129].

Up to date, it is reasonably demonstrated that functional reorganization processes occur even in MS patients and that they could be positively modulated by motor practice. So far, positive effects of these interventions were documented in arm function, gait, mobility and balance and subsequently on QOL and participation.

1.3.4 BTS NIRVANA

Nirvana is a virtual reality-based medical system to support motor and cognitive rehabilitation in patients with neuromotor pathologies. NIRVANA creates a "sensory room" in which the patient is immersed in different interactive scenarios. It allows the patient's rehabilitation process with a stimulating experience.

The exercises can be modified in real time and adapted to the specific characteristics of each patient treated.

Figure 13. NIRVANA set
Source: https://www.btsbioengineering.com/es/new-nirvana-installation-in-france/

The characteristics of NIRVANA are:

- Customizable clinical exercises

  The core of NIRVANA is the database of exercises, grouped into 6 categories and developed in collaboration with a clinical staff.

- Easy interpretation report

  During the exercise, the system measures and provides significant indices of the patient's progress, through a report **(Figure 14)**.

- Manageable from pc, tablet and smartphone

  In order to access to the system through a web-based application compatible with all popular devices and operating systems.

- Multi-user platform

  The software can be used by multiple users by creating different login accounts (clinician, physiotherapist, occupational therapist).

- Web-based interface

  Rehabilitation sessions can be created or consulted remotely thanks to the web-based software interface, which is innovative and easy to use.

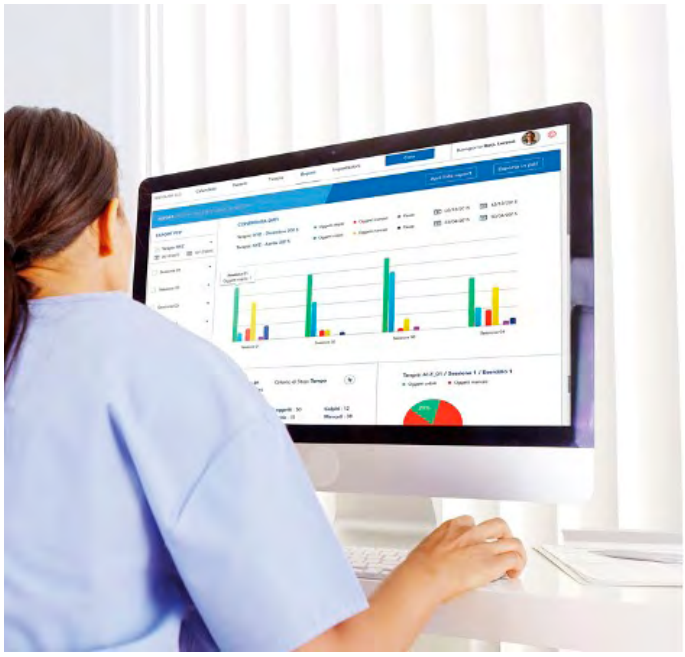


Figure 14. Nirvana report
Source: https://www.btsbioengineering.com/nirvana/it/perche-nirvana/

NIRVANA is preconfigured with a set of exercises that can be customized for levels of difficulty and exercise speed according to the various types of patients. The exercises were developed entirely in collaboration with clinical figures recognized by the international scientific community. The system allows clinicians to rehabilitate multiple patients simultaneously under the supervision of a single therapist.

Moreover, NIRVANA has been already used in different pathologies and for paediatric adults and elderly population, with the aim of improving cognitive deficits, motor impairments and both. However, even it has been proven the efficacy in motor disturbances, there is no study that assess multiple variables with gold standard instruments and neither in pwMS.

1.4 Thesis Overview

1.4.1 Justification

This VR interventions which are based on principles of use-dependent neuroplasticity and mechanisms of motor recovery after CNS lesions are emerging in clinical settings as potential tools for increasing functional recovery[81]. However, well-stablished evidence from large-scale clinical trials and meta-analysis on the efficacy of these interventions are still lacking, and further studies are essential to drive definitive conclusions, especially with exergames developed ad hoc for neurological patients, in this case in pwMS.

Moreover, it is noteworthy that most previous studies on pwMS did not assess the effectiveness of the VR-aided rehabilitation program by means of a combination of objective techniques for human movement analysis together with clinical tests and self-reported questionnaires. Moreover, as mentioned before, it is important to differentiate between VR and AR, although a consensus is still need to clarify. However, as in this thesis will be presented AR and not VR as Nirvana adds elements to a live view, as it is projected on the wall or on the floor. Also, there is a gap in literature about the doses and the type of exercise during the neurorehabilitation treatments as well as for conventional therapy as for exergames.

1.4.2 Hypothesis

The hypothesis of this thesis are:

- The use of AR for motor rehabilitation in pwMS has, at least, the same efficacy as conventional therapy.
- The use of AR in rehabilitation improves the gait kinematics parameters as conventional therapy in pwMS.
- The use of AR in physical therapy treatment achieves better performance in ADL which requires the use of UL as CT in pwMS.
- The use of AR in balance rehabilitation promotes as better performance as CT in pwMS.
- The use of AR for dual task exercises results more significant than conventional therapy treatments in people with MS,

1.4.3 Objectives

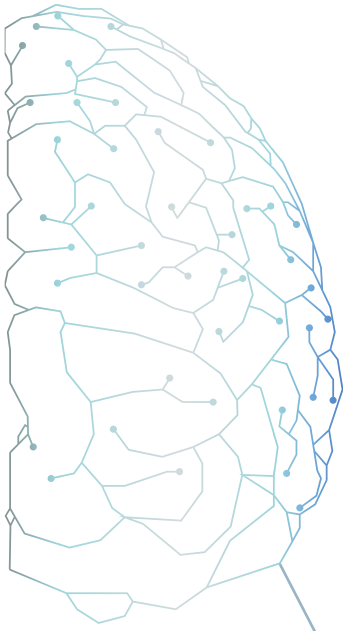
The general objective of this thesis is to evidence the efficacy of AR in motor rehabilitation as one more tool in the wide range of possibilities in physical therapy for pwMS.

The specifics objectives are:

- To demonstrate the efficacy of AR vs CT treatments in pwMS for the upper-limb performance with clinical, instrumental tests and self-questionnaires.
- To prove the efficacy of AR vs CT treatments in pwMS for gait performance with clinical, instrumental tests and self-questionnaires.
- To evidence the efficacy of AR vs CT treatments in pwMS for dual task, in gait with cognitive tasks, execution with gold standard systems for gait analysis.
- To show the efficacy of AR vs CT treatments in pwMS for balance performance with clinical and instrumental tests.

Chapter 2

Material and methods



2 MATERIAL AND METHODS

2.1 Experimental design and procedure

2.1.1 Research design

The studies carried out in this thesis were based on the single-blind Randomized Control Trial (RCT)-Type experimental research design. Patients were randomized in two groups: conventional therapy group (CTG) and augmented reality group (ARG). Both underwent a rehabilitation program of four weeks, three times per week, therefore a total of twelve sessions and each session lasted forty-five minutes. Both groups performed their treatment in the rehabilitation gym of the Centre for Multiple Sclerosis of Sardinia at Binaghi Hospital (Cagliari, Italy) and were assessed twice, before and after the whole treatment **(Figure 15)**.

Figure 15. Visual representation of the different phases carried out during the research.

2.1.2 Participants

In these studies, pwMS referred to the Multiple Sclerosis Centre of Sardinia (Ospedale Binaghi, Cagliari, Italy) were recruited for eligibility. These patients were selected for the study by the following inclusion and exclusion criteria:

2.1.2.1 Inclusion criteria

- Age > 18 years old
- Diagnosis of MS agreeing with modified McDonald's criteria and EDSS between 3.5 and 6.5.

2.1.2.2 Exclusion criteria

- Any other neurologic and orthopaedic condition that could affect balance or gait, in order to perform exercises standed-up.
- Any pharmacological treatment changes in the last two months.

The sample size for each study is similar to those of previous similar studies in the field. Each participant was informed about the study purposes and sign a written informed consent in accordance with Helsinki's Declaration. Groups' characteristics as well as clinical assessment tools used to assess movement disabilities will be extensively described in the sections below.

2.1.3 Interventions

Both interventions with CTG and ARG, were always leaded by a physical therapist and adapted to each patient in order to satisfy two philosophies:

- 1) The specificity and adaptability of the exercises based on each patient's physical capacities.
- 2) Bearing in mind the participated model in order to deliberate together with the patient the expectations of the treatment prioritizing their necessities and preferences.

2.1.3.1 Conventional therapy

CTG's treatment consisted in physiotherapy methods with scientific evidence for the motor treatment of MS including functional training adapted to the necessities of each patient, and different techniques from: Kabat, Perfetti, Bobath and Task Oriented methods. Sessions in CTG were divided in three parts of fifteen minutes each, in order to standardize patient's treatments.

- The first part was performed on the litter to warm-up, mobilizing joints (passive, auto-assisted, active, or against resistance) and analytics movements, with or without resistance, looking for improving strength fundamentally. The material used were mainly elastic bands of different resistance levels, sticks, weights, little balls to through to some basket or Bobath balls under legs during crunches and Kabat diagonals, for example.
- In the second part, performed on the pad area, were added the role of balance and coordination, either on trellises or on the mat, using different objects available, such as pieces to pile in each reach or turn. In addition, to increase difficulty were used also balance disks, under knees in quadruped or on feet in stan-up position, in front of trellises in bipodal or monopodal ways **(Figure 16)(Figure 17)**.

Figure 16. Example of balance exercise on the pad area (I).

Figure 17. Example of a balance exercise on the pad area (II).

- Finally, the third part was performed on treadmill, cycle ergometer or parallels, varying each of the three days of the week. Treadmill and cycle ergometer were chosen looking for a fatigue improvement alike the quality of gait cycle with parallels **(Figure 18) (Figure 19)**, also in combination with ramp mats or obstacles, and Nordic walking, to correct, mainly, ankle and knee ROM while walking.

Figure 18. Example of balance exercise in parallels (I).

Figure 19. Example of balance exercise in parallels (II).

2.1.3.2 Augmented reality

Instead, ARG treatment, as said, also lasted 45 minutes and was divided in four parts of eight minutes each with pauses of 4 minutes in between. The first two parts consisted in two plays projected on the wall and the other two on the floor.

Due to the wide range of exergames (EG) included in Nirvana Software, these were studied to be selected for the study and classified in different groups **(Table 5)**. It had been considered the parameters of each game and the way the physiotherapist could added different objects, to increase difficulty or to adapt the way of playing. Therefore, the same EG could be performed in many different ways (**Figure 20** to **Figure 25**). Besides that, just varying the projection, the way of performance, the limb to use, as well as the objects added, there are a lot of different exercises combinations, what makes impossible to show all the variety of exercises patients carried out in all sessions. However, many ways of playing different EG will be shown and explained below (**Figure 28** to **Figure 37**).

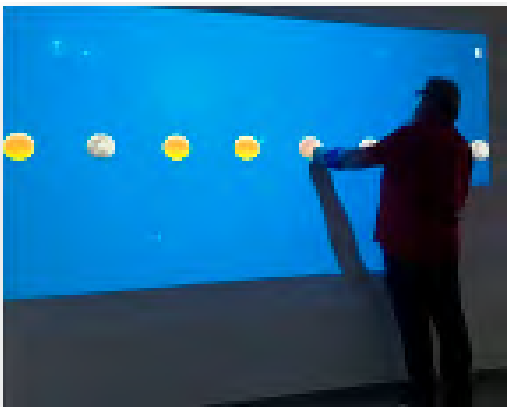


Figure 20. "Moon" (G4) projected on the wall for reaches and weight on the wrists for strengthen upper-limb (I).

Figure 21. "Moon" (G4) projected on the wall for reaches and weight on the wrists for strengthen upper-limb (II).

Figure 22. "Moon" (G4) projected on the floor for opposite lateral reaches and CORE strengthen (I).

Figure 23. "Moon" (G4) projected on the floor for opposite lateral reaches and CORE strengthen (II).

Figure 24. "Moon" (G4) projected on the floor for tandem's balance and upper-limbs and lower-limbs coordination (I).

Figure 25. "Moon" (G4) projected on the floor for heel-tip exercise with weights on ankles for strengthen quadriceps and anterior tibial (II),

2.1.3.2.1. Exercises

Sixteen exergames were selected for the sessions and divided in five groups depending on the way of playing **(Table 5)**. In group 1 (G1) exergames were played on a proprioception table or using different weights on wrists. In the group 2 (G2) patients were asked to overcome some obstacles in order to move along the scenarios to reach the objectives and may also wear weights on the ankles to increase difficulty in the following sessions. In group 3 (G3) exergames were performed wearing weight or an elastic band between ankles, while raising the opposite arm. In group 4 (G4) exergames were performed wearing weight on wrist, using a step on the leg which side is cleaned by hand so as to transfer body weight, adding or not a balance disk on the step, or using a proprioception table.

Finally, group 5 (G5) wore weight on wrists, and an elastic band resistance on the pelvis to increase squat intensity. Contrary, projected on the floor, plays were performed wearing weight on the ankles or an elastic band between them, also raising the opposite arm imitating Nordic walk with the appropriate sticks to work on waists coordination to extrapolate the movement in gait.

Figure 26. "Balloons" (G1) projected on the wall. Patient on a fitball with weight on the wrists for upper-limb and CORE strengthening, balance and coordination.

Figure 27. "Bubbles" (2) projected on the wall. Patient from sitting down with weight on the wrists for upper-limb and quadriceps strengthening.

Figure 28. "Clean window" (G5) projected on the wall. Patient with one foot on a step to weight transfer, upper-limb and quadriceps strengthening and with weights on the wrists upper-limb strength and manual eye coordination.

Figure 29. "Clean window" (G5) projected on the wall. Patient with one foot on an unstable disk on a step to weight transfer, upper-limb and quadriceps strengthening and with weights on the wrists upper-limb strength and manual eye coordination.

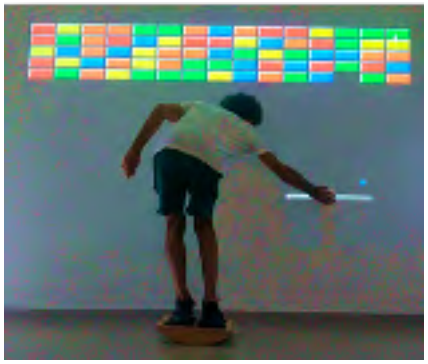


Figure 30. "Arkanoid" (G1) projected on the wall. Patient on an unstable table for balance, manual eye coordination and hemibody weight transfer.

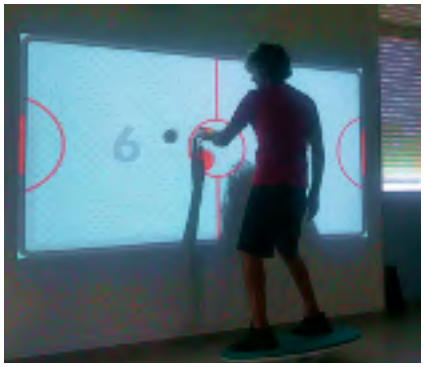


Figure 31." Ice Hockey" (G1) projected on the wall. Patient on an unstable disk for balance, manual eye coordination and hemi body weight transfer.

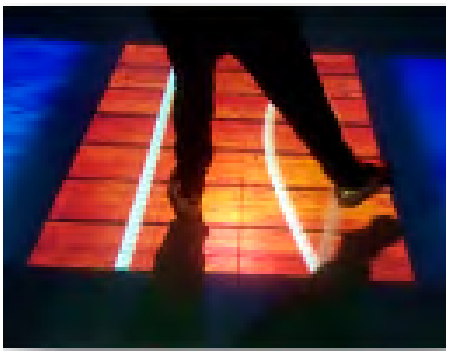


Figure 32. "Bridge" (G3) projected on the floor. Patient with in monopodal balance to strengthening gluteus medius.

Figure 33. "Bridge" (G3) projected on the floor. Patient with theraband between the feet for strength of gluteus medius and monopodal balance (II).

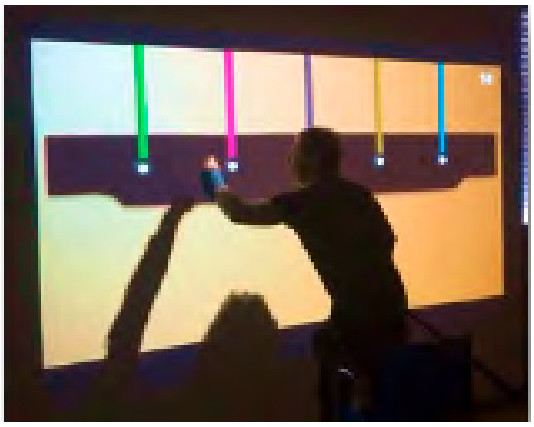


Figure 34. "Guitar" (G4) projected on the wall. Patient sited down on a chair with a theraband on the hip and weights on the wrists for balance and upper-limb, CORE, gluteus and quadriceps strengthening).

Figure 35. "Guitar" (G4) projected on the wall. Patient sited down on a fitball with a theraband on the hip and weights on the wrists for balance and upper-limb, CORE, gluteus and quadriceps strengthening.

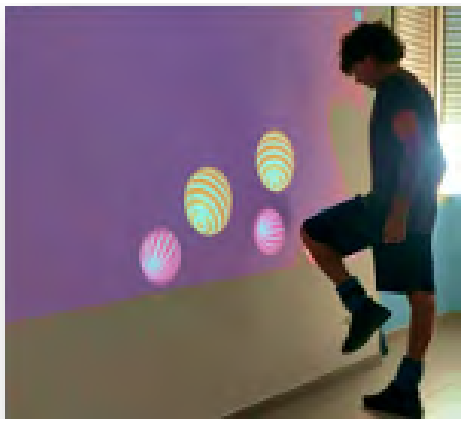


Figure 36. "Balls" (G2) projected on the wall. Patient with weights on the ankles for monopodal balance, quadriceps, gluteus medius and anterior tibial strengthening and knee eye coordination.

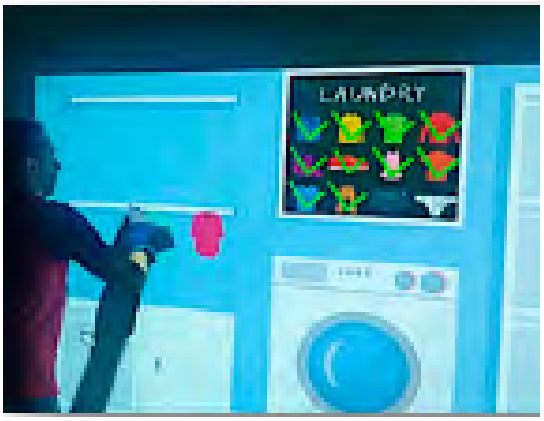


Figure 37. "Laundry" (G5) projected on the wall. Patient wearing weights on the wrists for strengthen upper-limb and manual eye coordination (I).

Figure 38. "Tap the mole" (G3) projected on the floor. Patient performing ankle and hip strategy.

Table 5. Exergames from Nirvana selected and classified for the study.

Group	Exercise name	Description
1	**Balloons** (projected on the wall)	Reach the balloons flying upwards and pop them with the hand
1	**Air Hockey** (projected on the wall)	Grasp the red joystick and push the plate into the goal post to make score.
1	**Arkanoid** (projected on the wall)	Move the boat with the hand to hit the little ball and prevent it from falling on the ground. The aim is to break the bricks.
2	**Balls** (projected on the wall)	Play with the balls to make them bounce on the walls of the screen and never touch on the ground *(touch them with the knees)*
2	**Bubbles** (projected on the wall)	Remove the bubbles from the screen with movement.
3	**Bridge** (projected on the floor)	Walk or try to stay in the center of the path without hitting the boundaries/ raise one leg to make sound the rope of that side/ step strategy: one foot in a rope and the other in the rope in front.
3	**Tap the mole** (projected on the wall and/ or floor)	Catch the mole appearing randomly on the wall/floor.
3	**Trumpets** (projected on the floor)	Play the trumpets touching or stepping on them.
4	**Guitar** (projected on the wall and/ or floor)	Touch all the strings in sequence until they vibrate. Available in different length of the strings.
4	**Moon** (projected on the wall and/ or floor)	Touch each moon in sequence to turn it into sun. Available in different layouts.
5	**Laundry** (project on the wall)	Grasp the clothes appearing on the blackboard and move them into the laundry to wash them.
5	**Memory** (projected on the wall and/ or floor)	Touch the cards to find the object pairs hidden behind the boxes appearing on the screen.
5	**Clean window** (projected on the wall)	Clean the window discovering the background landscape.
5	**Cooking** (projected on the wall)	Grasp the ingredients appearing on the blackboard and move them into the pot, in the correct order.
5	**Discover landscape** (projected on the wall)	Discover the scenario hidden by clouds with your movement.
5	**Supermarket** (projected on the wall)	Grasp the objects appearing on the blackboard of the shopping list and move them into the shopping cart.

Metrics	Parameters	Domain
• Number of hit ballons • Errors • Execution time (s)	• Number of balloons on the scene • Velocity of balloons	Selective attention; Response times; Denomination; Color Recognition; Muscle strengthening; Coordination; Visual Research
• Number of goals • Errors • Execution time (s)	• Velocity of the disk • Dimension of goal area	Attention process and vico-spatial abilities; Problem solving; Response times; Procedural memory; Cycle of the step
• Number hit bricks • Errors • Execution time (s)	• Number of rows • Velocity of ball • Width of puck	Decision making; Sustained and alternate attention; Problem solving; Response times
• Number hit balls • Errors • Execution time (s)	• Number of balls	Problem solving; Decision making; Perception/Gnosis; Spatial cognition; Articular excursion and coordination; Muscle strengthening
• Number of moved bubbles • Execution time (s)	• Number of bubbles • Return time	Sensory-motor integration; Balance; Attention process
• Number hot cords • Execution time (s)	• Width of path	Inhibitory control; Static and dynamic balance; Executive functioning; Cycle of the step come on/back
• Number hit moles • Errors • Execution time (s)	• Number of holes • Velocity of mole	Inhibitory control; Time of responses; Plyometrics; Aerobic/anaerobic activities; Attention
• Number hit objects • Number missed objects • Execution time (s)	• Number of trumpets	Attention; Spatial exploration (right; left; up; down); Verbal fluency; Ideo-motor sequential; Balance/muscular tone/isometry
• Number hit strings • Number missed strings • Execution time (s)	• Number of strings • Length of the strings • Vibration time of strings	Procedural sequence; Ideo-motor praxis; Gnosis abilities; Neuromuscular lengthening
• Number hit objects • Number missed objects • Execution time (S)	• Number of objects • Layout of objects • Time in state 2	Procedural sequence; Selective attention; Introspective training/emotion; Aerobic and anaerobic activities; Fine motricity; Moving load
• Number picked clothes • Errors • Execution time (s)	• Number of clothes	Oculo-motor coordination; Creative think; Motor Strategies; Problem Solving; Denomination; Verbal; visuo-spatial memory; working memory; Motor strategies
• Number discovered couples • Errors • Execution time (s)	• Number of couple of cards	Visual-spatial memory; Divide Attention; Near-distal movement programming
• Number discovered scenarios • Execution time (s)	• Percentage of wall to clean • Discover radius	Sensory-motor integration; Balance; Attention Process
• Number picked ingredients • Errors • Execution time (s)	• Number of ingredients	Oculomotor coordination; Creative think; Motor strategies; Problem Solving; Denomination; Verbal; visuo-spatial memory; working memory; Motor strategies
• Number discovered scenarios • Execution time (s)	• Percentage of wall to clean • Discover radius	Spatial cognition;Visual-spatial abilities; Creative think; Coordination; Balance; Fine Motility
• Number picked objects • Errors	• Number of objects	Verbal memory; Procedural memory; Visuo-spatial memory; Attention process; Coordination superior art/motility

2.2 Instrumental and equipment

During the clinical trial were used different tools for both assessment and treatment. These tools included self-administrated questionnaires and different scales, regarding some physical and cognitive conditions, functional tests, already validated for pwMS, and specialized equipment for different quantitative parameters. Last two were administered, processed and interpreted by a physiotherapist, who could count with the help of an engineer, if required.

2.2.1 Registration form (Appendix 1)

In the registration form were written all personal data important to consider, both for the validation of inclusion criteria and for participant's anamnesis. It includes the following items:

- Code of patient
- Birth date
- Sex
- Weight
- Height
- EDSS

Moreover, to facilitate assessment routine and avoid mistakes, a simple list of tests, to check what have already been done during the assessment session, was included.

2.2.2 Clinical outcome measures

2.2.2.1 Clinical upper-limb tests

2.2.2.1.1 Box and Blocks Test (Appendix 6)

Box and Blocks Test (BBT) measures unilateral gross manual dexterity and is also included in the recommendations from the American Physical Therapy Association (APTA) Neurology section of task force and is validated for the assessment of coordination (non-equilibrium), muscle performance, reach and grasp in MS[130] and in this test all EDSS are included to be tested.

The equipment required consists in a wooden box divided in two equally-sized compartments that are separated by a 15.2 cm high divider and 150 wooden blocks (2.5 cm^2)[131] and a timer or stopwatch **(Figure 39)**.

Figure 39. Box and Blocks Set.
Source:https://www.performancehealth.com/media/catalog/product/cache/933c72112d518ec06f8b7477609fd2b9/8/1/81p-gdyfj1l._sl1500_.jpg

The BBT administration consists of asking the participant to move, one by one the maximum number of blocks from one compartment of a box to another of equal size, within 60 seconds. The box should be oriented lengthwise and placed at the participant's midline, with the compartment holding the blocks oriented towards the hands being tested. In order to practice and register baseline scores, the test should begin with the unaffected upper limb. Additionally, a 15 second trial period is permitted at the beginning of each side. Before the trial, after the standardized instructions are given to participants, they should be advised that their fingertips must cross the partition when transferring the blocks, and that they do not need to pick up the blocks that might fall outside of the box[131]. A score is recorded separately for each hand.

2.2.2.1.2 9 Hole Peg Test (Appendix 7)

9 Hole Peg Test (9HPT) measures finger dexterity in patients with various neurological diagnoses included MS from the APTA Neurology section of task force and is validated for the assessment of coordination (non-equilibrium), muscle performance, reach and grasp in MS[130] and in this test all EDSS are included to be tested. However, 9HPT should be used with caution in patients with low or high disability levels[132].

It is required the 9HPT apparatus, which consists in a board (wood or plastic): with 9 holes (10 mm diameter, 15 mm depth), placed apart by 32 mm[133-134] or 50 mm[135]; a container for the pegs: square box (100 x 100 x 10mm) apart from the board or a shallow round dish at the end of the board[136]; 9 pegs (7 mm diameter, 32 mm length)[133] and a stop watch **(Figure 40)**.

The 9HPT is a timed test in which the individual retrieves each peg from the well and places it in the pegboard. Once all 9 pegs are in the pegboard, the individual returns the pegs to the well, one at a time. The test is conducted on both the dominant and non-dominant hands and is measured in seconds.

Figure 40. 9 Hole Peeg Test Set.
Source:https://www.performancehealth.co.uk/media/catalog/product/cache/933c72112d518ec06f8b7477609fd2b9/0/8/081296599-jamar-9-hole-peg-test-kit-0_1_1.jpeg

2.2.2.2 Clinical gait tests

*2.2.2.2.1 Two Minute Walk Test (**Appendix 3**)*

The Six-minute walk test (6MWT) is often used to assess walking distance in MS, but can be both time consuming for the investigator and exhausting for pwMS That is why the shorter 2-minute Walk Test (2MWT) is considered as a practical replacement for the 6MWT in routine clinical assessment[137] and in research[130]. As the BBS, 2MWT is recommended for pwMS with EDSS under 6.5[130].

The International Classification of Functioning, Disability and Health (ICF) domain is activity and, the constructs measured are aerobic capacity or endurance as well as gait. The equipment required comprises a stopwatch. two small cones to mark the turnaround point, a chair that can be easily moved along the walking course, worksheets on a clipboard, sphygmomanometer. The test has been recommended in two practice walks prior to measurements secondary to initial training effects[138-139], 5 8 otherwise, who people who can resist, two minutes, plus additional time needed for instructions and practice trial[130].

The 2MWT measured the distance walked, and the number and duration of rests during the two minutes should be measured.

*2.2.2.2.2 Timed 25-Foot Walk (**Appendix 4**)*

The Timed 25-Foot Walk (T25FW), a component of Multiple Sclerosis Functional Composite (MSFC) [140-141], assess a patient's ability to walk 25 feet "as quickly as possible, but safely"[142] Due to its psychometric quality and ease of administration, the T25WT is the most commonly used standardized test of walking performance in MS patients, both in clinic and in clinical research[143]. As the previous tests is recommended until EDSS under 7.5[130].

The ICF domain is gait and it is also performance-based. The T25FW is one of several measures of gait velocity. Similar measures include timed walks of 10 meters[144] or 30 feet. The equipment required is the measured distance for a walking course and a stopwatch or other timing device. It is scored in second: higher numbers mean slower gait speed. When converted to velocity in metres/second or centimetres/second, higher numbers mean faster gait speed.

The instructions may be for self-selected walking speed or fastest safe walking speed. Time may be recorded manually with a stopwatch or via more mechanized equipment such as photocells. Frequently, the course is set so that the individual walks a total of 35 feet (14 metres[144]): 5 feet (or 2 metres) prior to the beginning of the timed course and 5 feet (or 2 metres) after the end of the timed course, to minimized the acceleration/deceleration period within the recorded time[130]. However, skewed scores (bunched at lower end with a long tail indicating that a few individuals might take a long time to walk 25 feet) so comparisons should be made using non-parametric statistics like Spearman's rho. In addition, it can be significant variability between trials for T25FW because this measure records both ambulatory impairment and effort[145].

2.2.2.3 Clinical balance tests

*2.2.2.3.1 Berg Balance Scale (**Appendix 2**)*

The Berg Balance Scale (BBS) is a 14-item, 56-point scale design to measure balance by the assessment of functional tasks[146] and fall risk in adults[147]. BBS is included in the recommendations from the APTA Neurology section of task force and is validated for the assessment of balance in MS[130]. BBS is suitable for the procedure in the research, being used in studies including people at EDSS 6.5 and lower, considering that higher EDSS rates reflects lack if clinical utility for patients with significant disability[130].

The ICF classifies BBS domains in evaluation of activity and it is performance-based. The equipment required consists in a chair with arm rests (plus one other chair o mat table for transfers), a 15 cm of height steps tool, yard stick, tape measure, paper, pencil, object to pick up (slipper) and a stopwatch. The test lasts around 20 minutes and is assessed by a physical therapist[46].

The evaluation consists in 14 items scored along a 5-point ordinal scale, with scores ranging from 0-4. Descriptive criteria are provided with 4 being able to perform independently and 0 unable to perform. Maximum score is 56, score of 45 or below is associated with high fall risk[130].

2.2.2.4 Four Square Step Test (Appendix 5)

The Four Square Step Test (FSST) is used to assess dynamic and the ability of the subject to step over low objects forwards, sideways and backward. It has been shown to have strong correlations with other measures of balance and mobility with good reliability shown in a number of populations[148] including MS[149-150].

The equipment needed consists in a stopwatch and 4 canes or rods (approximately 100 cm in length and 2.5 cm in diameter[151].

The participant is required to sequentially step over four canes set-up in a cross configuration on the ground. At the star of the test, the subject stands in square 1 facing square 2. The aim is to step as fast as possible into each square with both feet in the following sequence: Square 2, 3, 4, 1, 4, 3, 2, 1 (clockwise to counter clockwise) **(Figure 41)**. Test procedure may be demonstrated, one practice trial is allowed prior to administering the test. Two trials are then performed, and the better time (in seconds is taken as the score. Timing starts when the first foot contacts the floor in square 2 and finishes when the last foot comes back to touch the floor in square 1.

Figure 41. Display Four Square Step Test

The instructions are: "Try to complete the sequence as fast and safely as possible without touching the sticks. Both feet must make contact with the floor in each square. If possible, face forward during the entire sequence. The test must be repeated if the subject fails to complete the sequence successfully, loses balance or makes contact with the cane. Also, subjects who are unable to face forward during the entire sequence may turn before stepping into the next square and are timed accordingly. Any assistive device used during the test are noted down accordingly, in order to repeat the test in the same conditions

2.2.3 Instrumental outcome measures

The objective assessment of motor function for both upper and lower limb was performed using state-of-the art technology. In particular, gait and upper limb kinematics were assesses using an optical motion capture system, which represent the gold-standard for this kind of measurements. Inertial sensors and pressure platforms were also employed to perform functional mobility test and postural control assessment.

2.2.3.1 Kinematic analysis

Kinematic analysis was chosen for the quantifiable study of upper limb and lower limb.

Considering gait analysis (GA) for the kinematic study for the lower-limb. GA is the systematic study of human walking. Eventhough, there is no widely-accepted typical gait pattern in MS unlike in other neurological disorders[152], several studies assessing gait deviations described reduced gait speed and step length[153-158], reduced ROM of leg joints, increased double-limb support, and reduced dynamic stability. Regarding upper-limb functional analysis, Hand to Mouth Task (HTM) was performing as a goal-oriented task which has become a useful 3D kinematic analysis to asses performance of an everyday functional activity due to it resembles the act of eating and drinking[159]. The gold standard for both analyses consists of the kinematic analysis performed using a motion capture system based on optoelectronic stereophotogrammetry system. Such systems, are designed to satisfy all motion analysis requirements in clinical, sports and industrial fields[160].

Optical motion capture systems, considered the gold standard for human movement analysis, allow information to be obtained on the kinematics of the patient performing the study with an absolutely non-invasive method. Little elements of reflective material called markers **(Figure 42)**, are detected by a specific camera system which, by means of an infrared source, illuminates the markers at regular intervals while the reflection is captured by the coaxial camera. In this way the system reconstructs the three-dimensional coordinates of the markers from which, with special software, it is possible to obtain information on the kinematics of the movement of the body segment in which the markers are located.

The most commonly used protocol for GA is "Davis Protocol" **(Figure 35)** which first of all provides for the detection of the anthropometric measurements of the subject, then height, body weight and parameters relating to the bone segments necessary to estimate the joint centers (length of the tibia, distance between the femoral condyles, etc.).

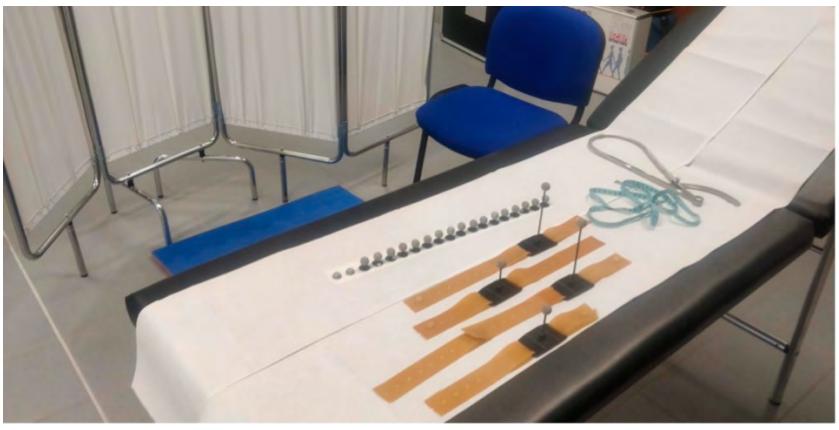


Figure 42. Markers and measuring instruments for gait analysis using the optoelectronic system.

The placement of the markers, 22 in total, in specified positions follows:

- On the trunk: two markers on the right and left sternoclavicular junctions and one at the level of the spinous process of C7.
- On the pelvis: at the level of the two anterior-superior iliac spines and at the level of the sacrum in such a way that the three points are on the same plane containing the anterior-superior and postero-superior iliac spines.
- On the thigh: greater trochanter, femoral epicondyle and a marker on a wand placed 1/3 of the length of the thigh.
- On the leg: lateral malleolus, fibula head and one on a rod similar to the thigh.
- In the foot: heel and head of the second metatarsal.

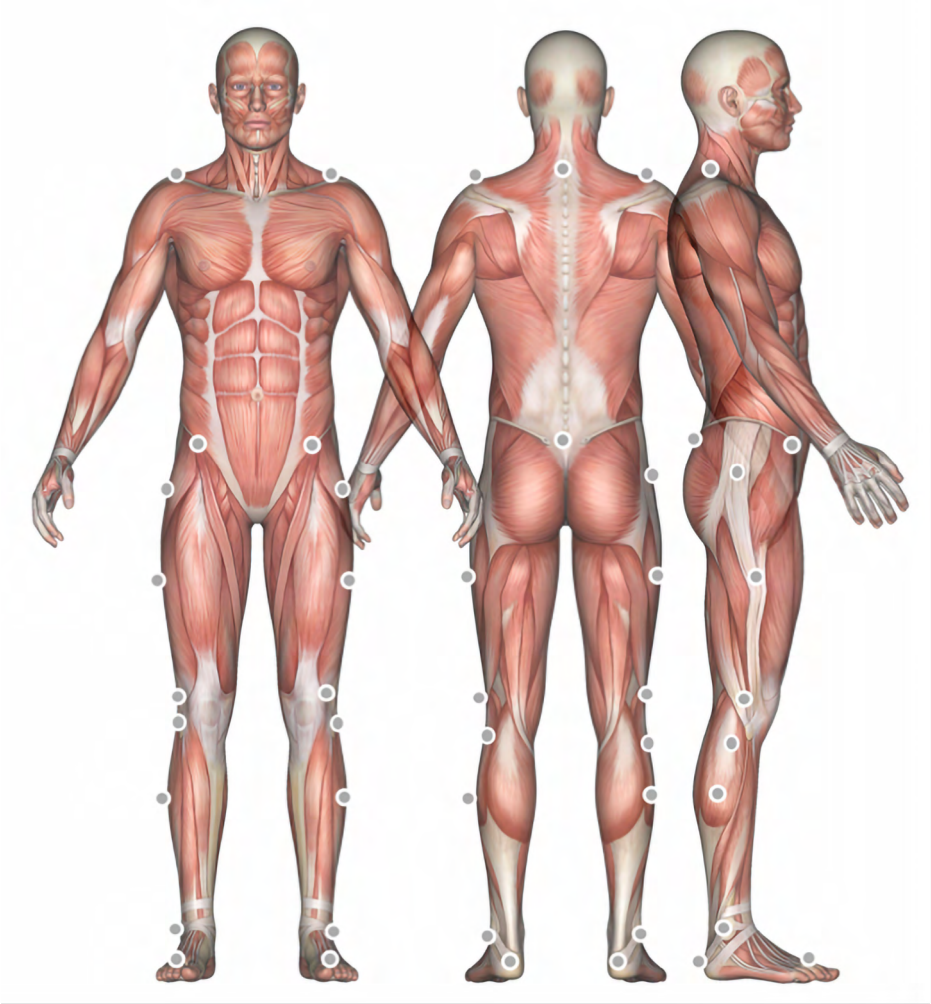


Figure 43. Markers setup in Davis Protocol

Source: researchgate.net/publication/341033046_Global_Muscle_Coactivation_of_the_Sound_Limb_in_Gait_of_People_with_Transfemoral_and_Transtibial_Amputation/figures?lo=1

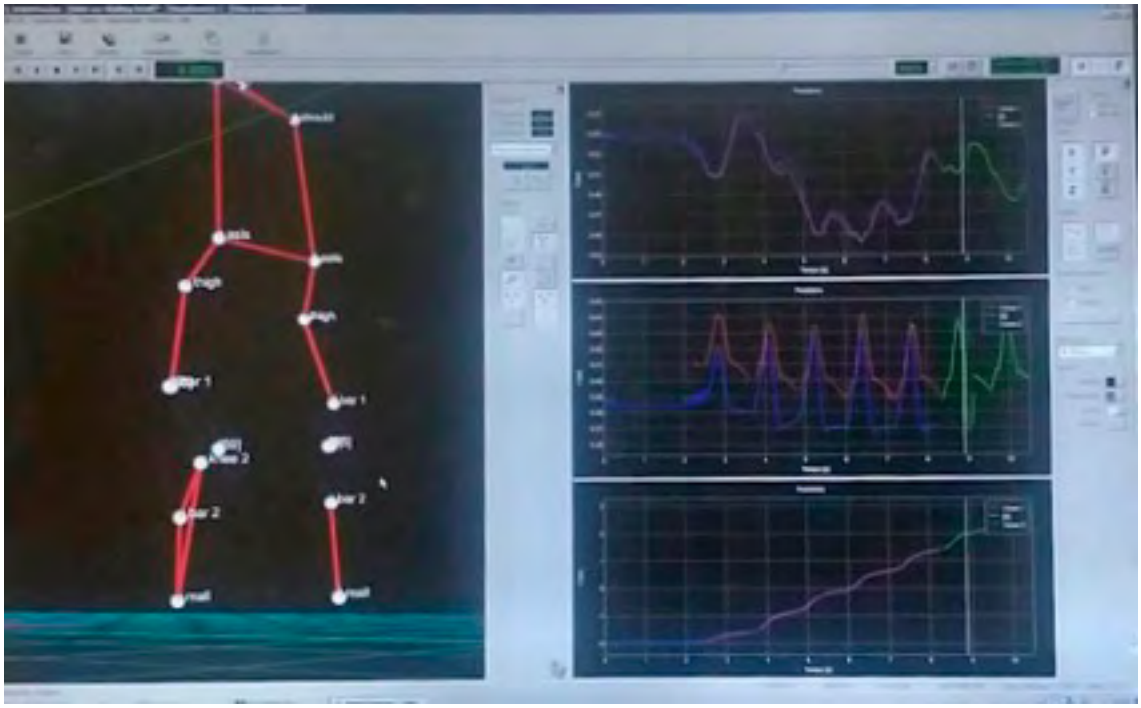


Figure 44. BTS Smart Clinic gait analysis.

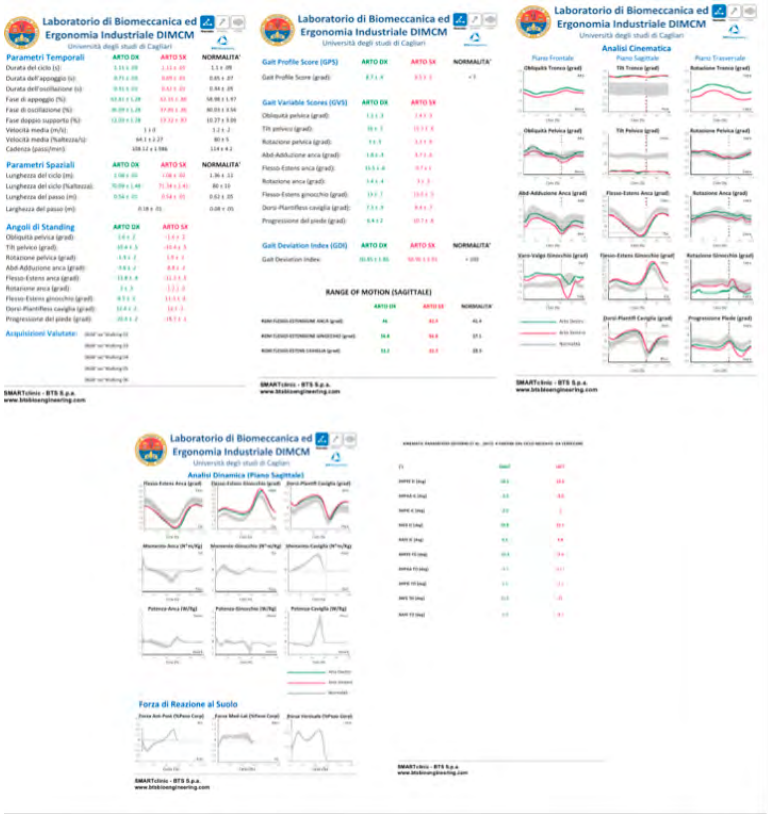


Figure 45. Gait Report from BTS Smart Clinic software.

The start of the acquisitions follows. A first static acquisition is carried out in which the subject remains in an upright position for a couple of seconds ("standing" phase) and at this time the software acquires the positions of the markers which, integrated with the anthropometric measurements, allow to outline the position of the centers joints of the lower limbs and the reference systems associated with the bone segments. At the end of this phase, the subject is asked to walk at normal speed and thus begins the dynamic acquisition which is repeated for a minimum of six times.

Regarding HTM protocol, the starting position of the task sees the patient sitting comfortably on a chair in front of a table, adjusted in height so that he can rest his palms on the table, facing down, shoulders relaxed, and elbows bent approximately 90°.

Three-dimensional UL model **(Figure 46)** consisted on eight segments (head, trunk with the shoulder girdle, right and left upper arm, right and left forearm, right and left hand). Markers were placed bilaterally on the acromion, lateral epicondyle, ulnar and radial styloid processes, on third metacarpal head in order to identify the position and orientation of the arm, forearm and hand segments. The head and trunk positions were estimated by placing markers respectively on the zygomatic and nasion processes and mouth (head), right and left acromion clavicular notch and spinous processes of the C7 and T8 vertebrae.

The marker on the chin was then removed after the acquisition of a rest trial in order to avoid interference with the fingernail marker during the acquisition of the HTM movement.

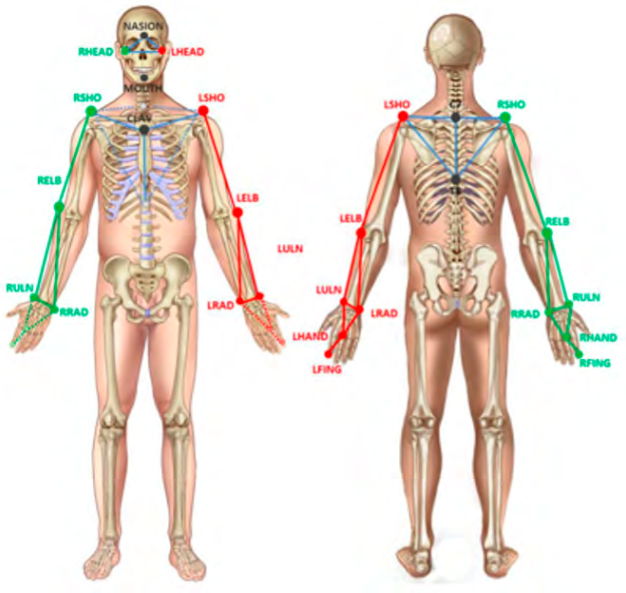


Figure 46. Frontal and posterior view of the marker setup and relative stick diagram for kinematic analysis of upper limbs. Markers of the left side are reported in red, markers of the right side in green, while the others are represented in black.

The patient is given the following instructions: from the initial position, following a verbal command, he must raise his hand and touch his lips with his fingers and then return to the starting position. The movement is repeated five times.

The HTM can ideally be broken down into three distinct phases:

- Going phase (GP) (s): The patient lifts his hand from the table to bring it to his mouth.
- Adjustment phase (AP) (s): The patient improves the trajectory of the hand approaching the mouth.
- Returning phase (RP) (s): The patient returns the hand to the starting position completing the movement.

With the appropriate measurement techniques it is possible to extrapolate, from this task, all the kinematic parameters necessary for the quantitative assessment of the mobility of the upper limb:

- The duration (s) of the entire movement and of each single phase is measured both as a percentage (i.e. what percentage of the total movement the measured phase occupies).
- The average of the hand speed (m/s) during the phases is also calculated.
- The peak velocity (m/s).
- The stability of the movement is instead estimated in terms of adjusting sway area (SA) (mm), which represents the total length traveled by the fingertips during the AP phase.

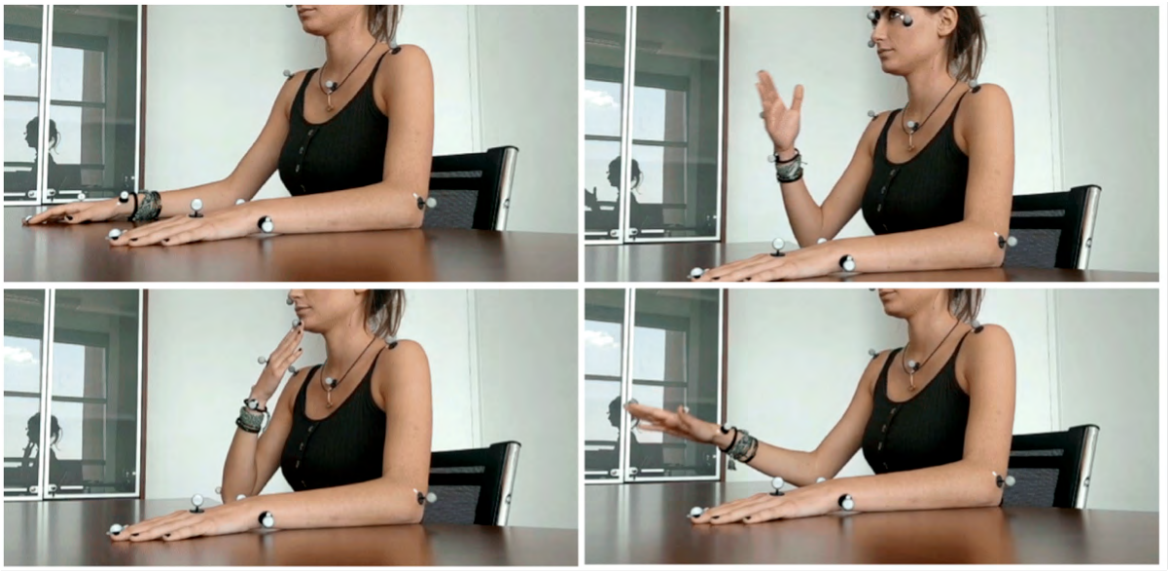


Figure 47. Hand to Mouth Performance.

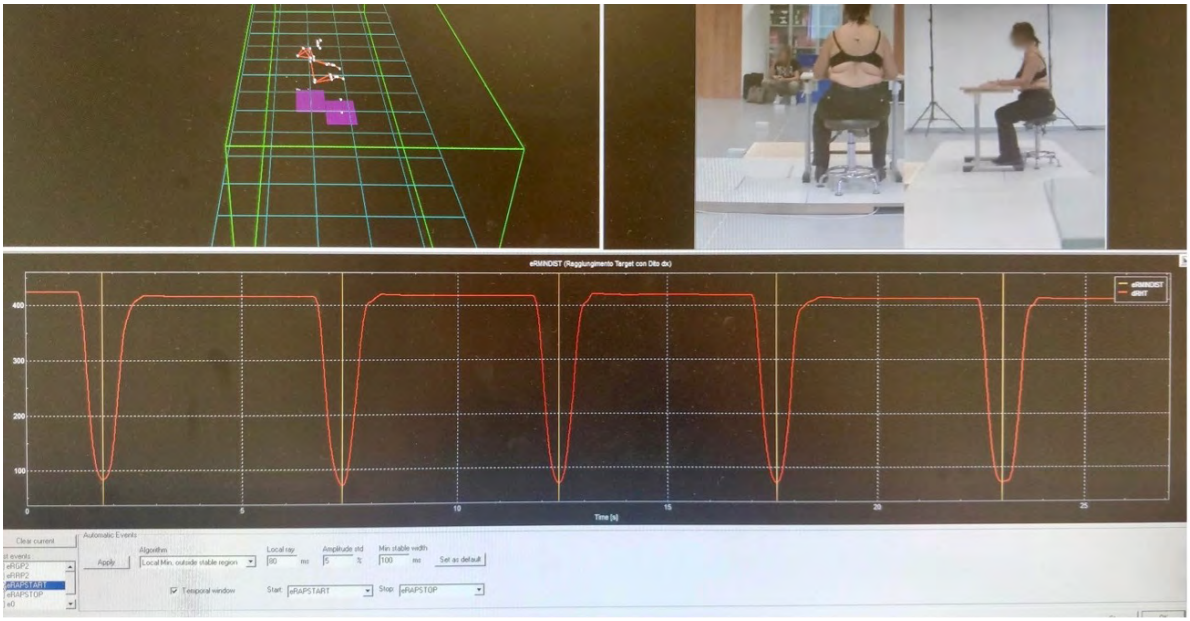


Figure 48. BTS Smart clinic Hand to Mouth analysis

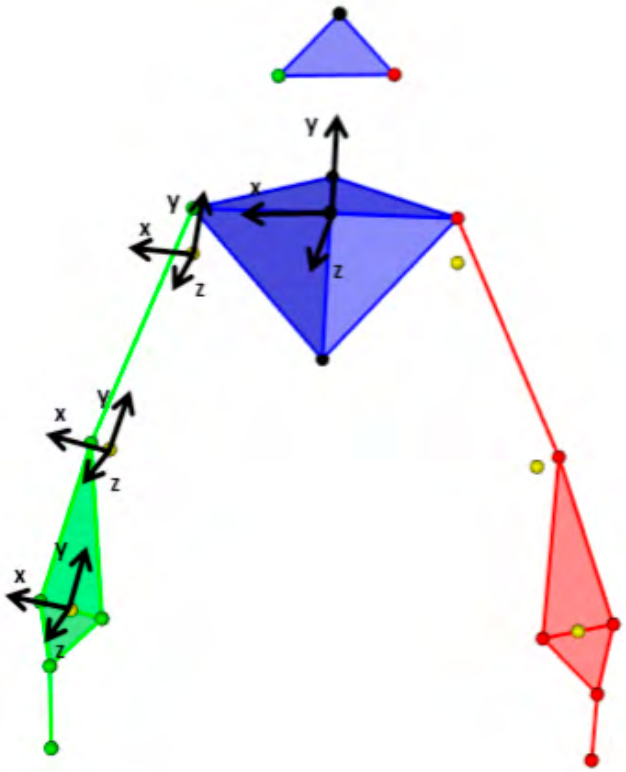


Figure 49. Upper limb model used to compute kinematics; segmental coordinate systems are displayed for the trunk and right upper limb. Joint centers are displayed with yellow circle/cross.

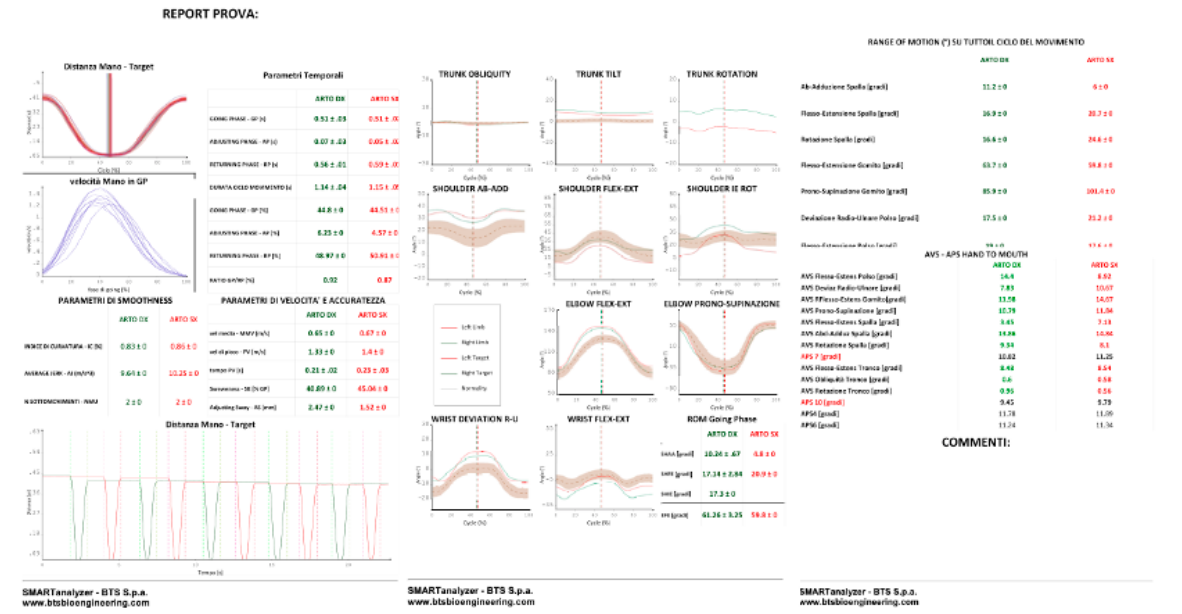


Figure 50. Hand to Mouth report from BTS Smart Clinic Software.

2.2.3.2 Stabilometric analysis

Stabilometry, or posturographic analysis, is an exam that allows to evaluate and measure the fine control of posture. The examined subject gets on a computerized platform, remains there motionless, in an upright position, for a predefined time; he is apparently stationary, but in reality, he makes small oscillations, not very perceptible visually, which a platform can record in the smallest details. These small oscillations are indispensable: they are the continuous fine adjustments that the brain makes to keep the body balance. Therefore, the maintenance of the upright position is not a static phenomenon, but a dynamic one.

The body in an orthostatic position swings to maintain balance and the performance of the control system can be evaluated by measuring these postural sways.

Stabilometry therefore, deals with the characterization of the oscillations in the upright posture in conditions of rest and in the absence of perturbations.

The examination is carried out with reference to standardized protocols:

1. Remove footwear
2. Place the feet on the platform: oriented at 30 °, intermalleolar distance 8-10 cm
3. Arms relaxed and placed along the hips, without contact between upper and lower limbs
4. Normal breathing
5. Avoid voluntary gestures
6. Fix a target placed 2-3 meters from the patient at eye level

Thus, participants were asked to position themselves on the platform with both feet and to stand still above it for a duration of 30 seconds **(Figure 52)**.

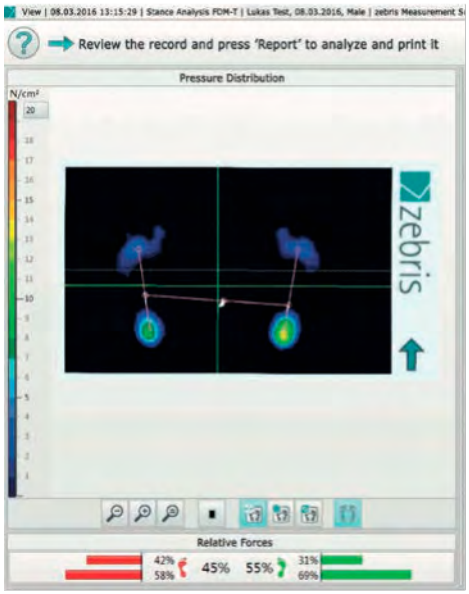


Figure 51. The zebris FDM Software
Source: https://www.zebris.de/fileadmin/Editoren/zebris-PDF/zebris-Prospekte-EN/27_9_FDM_EN_150.pdf

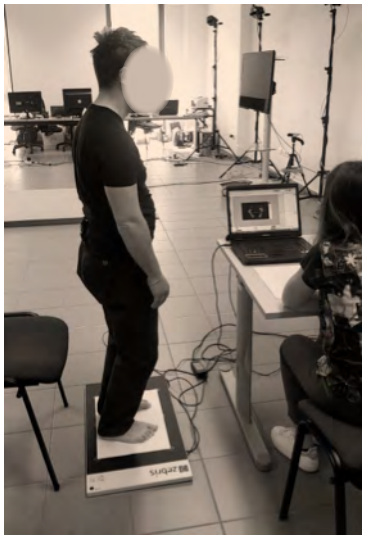


Figure 52. Patient performing the posturographic test on Zebris platform.

Two different types of tests were conducted three times:

- Bipodalic static analysis with eyes open.
- Bipodalic static analysis with closed eyes.

The static posturographic examination allows to verify the performance of the postural control system and to establish the level of motor coordination and the ability to maintain balance. In the interpretation of this phenomenon, two key variables are considered:

- COM intended as a centre of gravity indicating the geometric point where the point of application of the resultant of the mass actions of the entire system can be ideally located.
- It is vertical projection on the ground is called the COP.

The Statokinesiogram (Sway ball) is a planar representation of the evolution of the COP over time, obtained by recording the subsequent sampled positions of this parameter.

The median-lateral coordinate of the COP is represented on the axis X, while the antero-posterior coordinate is represented on the axis Y. It is a qualitative graph that immediately expresses the trend of the COP trajectory.

It is difficult to extract qualitative information from the ball, so we resort to the use of a series of standardized parameters:

- The confidence ellipse (sway area) represents a measure of the width of the surface described by the envelope of the COP positions and is defined as the surface that contains with 95% probability the single points that make up the ball.
- The length of the ball (COP Path Length) is the total length of the trajectory covered by the COP.
- The average speed (COP velocity) can be calculated with reference to the single test or as the average of the instantaneous speeds of the COP.

2.2.3.3 Hand Grip Test

A number of handgrip dynamometers (HGD) review articles have been published addressing the reliability, validity and standardization of HGD testing protocols across a range of populations[164-166]. The hand is a complex anatomical system comprising 27 bones and 15 joints with approximately 30° of rotational and translational freedom designed to grasp and apply fore to objects of all shapes and sizes and to perform a combination of intricate finely controlled movements[167] essential for the autonomy of many ADL. Therefore, the test aims to measure the maximum isometric force (MIF) exerted by the forearm muscles in particular:

- The forearm extensors muscles.
- The thumb adduction muscle.
- The metatarsals, phalanges and wrist flexors muscles.

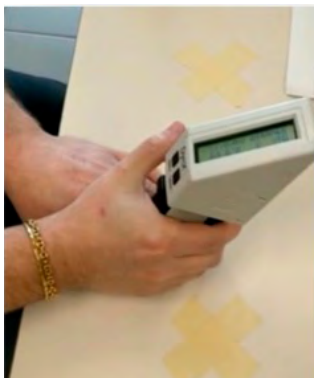


Figure 53. Handgrip test's execution.

For the test the patient is seated with shoulder adducted, elbow flexed to 90 degrees, and forearm and wrist neutral. The therapist places the dynamometer in the client's hand while gently supporting the base of the dynamometer, and he/she instructs the client to squeeze as hard as possible. Grip force should be applied smoothly, with rapid jerking motion. Allow the wrist to extend during the grip[168]. The test consists in the average of the three trials in each hand **(Figure 53)**.

2.2.4 Questionnaires

Although clinical tests show an improvement or not in different motor parameters, it is also important to consider the improvements in the quality of life felt by participants. This is the reason why different self-administrated questionnaires were chosen to report any benefit from the therapy in the ADL's participants and life balance[169].

2.2.4.1 Questionnaires for the Upperlimb

*2.2.4.1.1 The Disabilities of the arm, Shoulder and Hand (**Appendix 9**)*

The Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire is a 30-item questionnaire that looks at the ability of a patient to perform certain upper extremity activities[170-171]. Patients can rate difficulty and interference with daily life on a 5 point Likert scale[170-171].

Even the use of DASH in research in MS must still be developed is suitable for use in daily MC clinical practice[172].

*2.2.4.1.2 Manual Ability Measurement (**Appendix 11**)*

The Manual Ability Measurement (MAM-36) is a questionnaire on perceived ease or difficulty that a patient may experience when performing unilateral and bilateral ADL tasks. During a semi-structured interview, the persons are asked to rate 36 unilateral and bilateral ADL tasks using a 4-point scale[173].

The score of the different tasks are summed up and transformed using a Rasch-derived conversion table (annex 11).

2.2.4.2 Questionnaires for gait

*2.2.4.2.1 Twelve Item MS Walking Scale (**Appendix 10**)*

Twelve Item MS walking scale (MSWS-12) is a self-reported measure of the impact of MS on the individual's walking ability [174]. The original scoring provides options 1-5 for each item, with 1 meaning no limitation and 5 meaning extreme limitation to the gait-related item.

This questionnaire has been included in the gait outcome measures recommended by the consensus conference of the Consortium of Multiple Sclerosis Centres[175] and is also included in APTA. MSWS-12 is recommended as a good indicator of actual walking behaviour in people with EDSS between 3.5-7.5[176].

Cronbach alpha is 0.97 to 0.97 in patients with MS[174]. In the first version, which was selected, scores on the 12 items are summed. To transform to a 0-100 scale[177], the minimum score of 12 is subtracted from the sum; the result is divided by 48 and then multiplied by 100.

*2.2.4.2.2 Short Form Health Survey of the Medical Outcomes Study (**Appendix 8**)*

The Short Form Health Survey of the Medical Outcomes Study (SF-36) covers a broad range of domains of health-related QOL[178]. It stems from a study called the Medical Outcomes Study[179]. It comprises 36 questions which cover eight domains of health[180]: Limitations in physical activities because of health problems, limitations in social activities because physical or emotional problems, limitations in usual role activities because of physical health problems, bodily pain, general mental health (psychological distress and wellbeing), limitations in usual role activities because of emotional problems, vitality (energy and fatigue) and general health perceptions. The SF-36 was originally designed as a generic health measure but has also been applied to specific disease populations including MS.

In a MS population, the Cronbach's alpha for the various subscales of the SF-36 range from 0.67 to 0.94. There is considerable evidence for the validity of the SF-36 in a variety of populations including MS[181]. Moreover, the physical functioning and role limitations due to the physical problem's subscales were the ones that best discriminated between MS patients. In the field testing of the MSQLI, the physical functioning subscale of the SF-36 correlates very highly with the EDSS and the Ambulation Index.

2.2.4.3 The Stroop Colour Word Test

The Stroop Color Word Test (SCWT) is the interaction dual task excellence. It assesses the ability to inhibit cognitive interference due to the simultaneous processing of two features of the same stimulus[182]. The SCWT relates to decision-making tasks, and is able to evaluate attention, processing speed, cognitive flexibility and working memory [183-184]. Accordingly, the SCWT appears to be the most useful cognitive task during dual task (DT) for walking in pwMS for the following reasons:

- It is related to processing speed, which is the most relevant cognitive deficit in pwMS.
- It is an interference task.
- It can quantify executive functions[185].

Moreover a recent meta-analysis suggest that the SCWT is a good candidate for cognitive-motor interference[186].

In this study, the SCWT was administrated via a 48" LCD TV screen located perpendicularly to the gait direction. Participants had to name only the word's font colour and not to read the word. The time interval between two consecutive word occurances was varied to avoid a rhythm developing. The words (46-96 cm in width and 15-19 cm in height) were displayed at a distance in the range of 200-750 cm between the participant and the screen. For each condition, at least six trials were performed to obtain sufficient spatiotemporal and kinematic data[187].

2.2.4.4 System Usability Scale (Appendix 12)

The system Usability Scale (SUS) provides a "quick and dirty", reliable tool for measuring the usability. It consists of a 10 item questionnaire with five response options for respondents; from strongly agree to strongly disagree[188]. It was originally created for administering after usability tests on system like VT100 Terminal ("Green-Screen) applications. However, it has become an industry standard with references in over 6000 publications[189], including for valued virtual reality in rehabilitation.

It has a coefficient alpha of 0.91 and 0.70. For interpreting scoring the participant's scores for each question are converted to a new number, added together and then multiplied by 2.5 to convert the original scores of 0-40 to 0-100. Though the scores are 0-100, these are not percentages and should be considered only in terms of their percentile ranking.

2.3 Material/equipment required

2.3.1 Treatment equipment

2.3.1.1 Conventional therapy training

Figure 54. Bobath Ball (Brand: Galiastursalud, Model: Balon Bobath 65 cm)

Source: https://galiastursalud.com/1587/balon-bobath-65-cm.jpg

Figure 55. Espalier (Brand: Salter; Model: N370)

Source:https://www.fitnessdigital.com/images/productos/XL/2/Salter-N-370-1.jpg

Figure 56. Mat. (Brand: Tamdem; Model: 200 x 100 x 5 cm, 100Kg/m3)

Source: https://www.tamdem.net/wp-content/uploads/2015/04/colchoneta-suelo.jpg

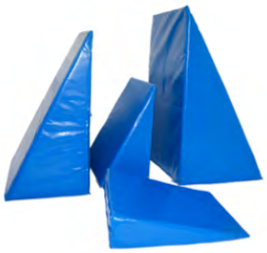


Figure 57. Wedges (Brand: Fisiolab; Dimensions:10x40x40, 20x50x50, 25x60x60, 15x50x50)

Source:https://cdn.shopify.com/s/files/1/2590/6974/products/Cunas_terapeuticas.png?v=1549494816

Figure 58. Foam Balls (Brand: Protone, 6 cm)

Source:https://almecatalogo.com/wp-content/uploads/2019/07/pelota-masaje-miofascial-2.jpg

Figure 59. Weighs (Brand: Mambo, 0,5, 1 and 2 Kg)

Source:https://www.institutoeuroproject.com/6263-large_default/pesas-neopreno-1-kg-amarilla.jpg

Figure 60. Weigths (Brand: Kallango Fit, 0,5, 1 and 2 Kg)

Source: https://a0.vnda.com.br/ortopon to/2019/07/19/0000789855971-caneleira-de-peso-0-5kg-kallango-para-fitness-e-fisioterapia-7372.jpg?1594906099

Figure 61. Elastic bands with different resistance (Brand: Theraband, different resistence bands).

Source:https://www.theraband.com/media/catalog/product/cache/18/image/9df78eab33525d08d6e5fb8d27136e95/2/0/20403-theraband-professional-latex-resistance-bands-yellow-red-green-beginner-0.jpg

Figure 62. Rocker board (Brand: Theraband)

Source: https://images-na.ssl-images-amazon.com/images/I/51D01XMkQNL._SX679_.jpg

Figure 63. Unstable disk (Brand: Theraband)

Source: https://cdn.shopify.com/s/files/1/2285/0379/products/Estabilizadores_Family_Shot_2_w_grande.jpg?v=1599261489

Figure 64. Small bricks (Brand: JKFitness; Model: MY)

Source: https://www.jkfitness.com/wp-content/uploads/2019/09/MY-MATTONCINI-YOGA-S-1024x711.jpg

Figure 65. Nordic sticks (Brand: Forclaz; Model: Arpenaz 100)

Source: https://contents.mediadecathlon.com/p1154687/k992e02a5e27160c62c38d98696540b84/1-bastoncino-a100-azzurro.jpg?format=auto&quality=60&f=650x0

Figure 66. Parallel Bars (Brand:Access Health; Model: Walking Rails Folding 4 metre Wooden Handrail)

Source:https://accesshealth.com.au/wp-content/uploads/2018/09/access-folding-walking-rails-2.jpg

Figure 67. Chair (Brand: Parrs; Model: F668)

Source: https://www.parrs.co.uk/images/basic-polypropylene-chair-p9527-13588_image.jpg

Figure 68. Steps (Brand: Moretti Spa; Modell: MI482)

Source: https://www.i-wellness.org/images/mo482.jpg

Figure 69. Bosu (Brand: Bosu; 65 cm)

Source: https://images-na.ssl-images-amazon.com/images/I/41MZAXleHIL._AC_SX425_.jpg

2.3.1.2 Augmented reality training

In ARG sessions, patients performed their training interacting with different scenarios provided by BTS NIRVANA®. BTS NIRVANA® is a medical system which helps neuromotor and cognitive rehabilitation in patients with neurological disorders by using VR. It creates a "sensory room" in which the patient is immersed in different interactive scenarios **(Figure 70)**. BTS NIRVANA® offers a wide range of different exergames which allows to modify the parameters of each game, such as velocity, number of objects, execution time, repetitions and side and height of working area. Moreover, the physiotherapist added some physical objects already used in CT **(Figure 54)(Figure 56)(Figure 59)(Figure 65)(Figure 67)(Figure 69)** in order to favour the principles of motor learning and it allows to program the execution of plays and pauses of the whole session.

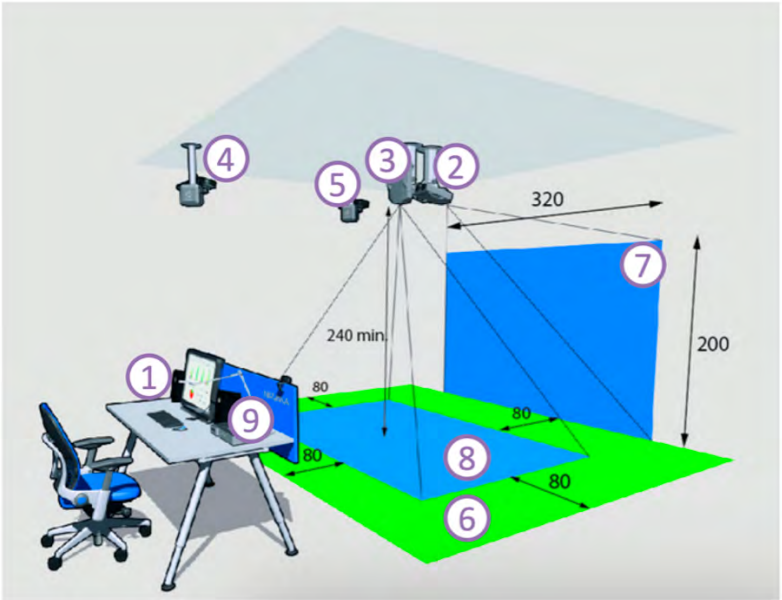


Figure 70. Nirvana Set.

1:PC 2:Wall mounted video projector. 3:Floor mounted video projector. 4:Kinect on the wall, 5:Floor Kinect. 6:Working area. 7:Virtual wall scenario. 8:Virtual floor scenario. 9:Nirvana Net.

Source: btsbioengineering.com/nirvana/it/sCOPri-nirvana/

Nirvana is the first device based on optoelectronic infrared sensors, through which the patient can simply interact through his movements. The rehabilitation exercises with audio-visual stimuli and feedback involve the perceptual-cognitive skills of patients, resulting in a motivational training, several modes and increasing levels of difficulty characterize each exercise, so the therapist can use a pre-defined rehabilitative solution or new ones, according to patient's needs. The results achieved during rehabilitation program. The system is connected to a projector or a big screen (put in front of the patient), reproducing an interactive series of exercises (for trunk, upper and lower limbs, and cognition), and thanks to an infrared video camera analyzing the patient's movements, it created interactivity. Notably BTS device the projector is located behind the patient, thus the shadow of the patient is projected on the screen. At the end of each session, it is possible to export the full list of all exercises performed and the score obtained for each of them. Concerning cognitive training, we included a series of exercises involving attention, memory (verbal and visuospatial), spatial cognition, ocular-manual coordination, gnosis abilities, problem solving, executive function and constructive praxis.

2.3.2 Assessment equipment

2.3.2.1 Optoelectronic system

Motion Capture System based on passive markers equipped with 8 infrared cameras set at a sampling rate of 120 Hz (SMART-D, BTS Bioengineering, Italy). Two digital video cameras (BTS Vixta, Bioengineering, Italy), integrated with the motion capture system, recorded the movement in frontal and sagittal planes for documentation purposes. Prior to data collection, the cameras were calibrated to a measurement volume of almost 75x75x65 cm and the markers visibility throughout the task was verified with a person sitting in the measurement area. The global coordinate system was defined with X-axis directed laterally to the right, Y-axis directed forward (anteriorly) and Z-axis directed upward (superiorly).

After kinematic data collection, each trial was checked in the Smart Tracker environment (BTS Bioengineering, Italy), where markers were labelled in according with the biomechanical model, and their entire 3D trajectory was reconstructed as a function of time.

Then, the raw data was processed by means of a custom code implemented in the Smart Analyzer environment (BTS Bioengineering, Italy). The 3D trajectories data was filled using a cubic-spline and low-pass filtered before further calculations (4th order zero-lag Butterworth filter, cut-off frequency of 6 Hz). Then velocity and acceleration of each marker were computed through numerical differentiation.

Figure 71. Cameras Smart DX used with the Smart Clinic Software.

In particular, information such as the trajectory, the angular quantities and therefore the relative angles of flexion / extension, ab / adduction and extra / intra-rotation of the main joints are derived. The system, consisting of at eight cameras, combines the two-dimensional images from each of these and processes a three-dimensional image. To do this, it is therefore necessary to know the position and orientation of each camera.

2.3.2.2 Zebris Platform

Data acquisition for laboratory tests was made possible thanks to the use of the pressure platform Zebris FDM-S.

The platform carries out, through a capacitive system equipped with 2560 pressure sensors organized in a matrix of 64 by 40 cm, the static analysis and the analysis of the pressure distribution, the load exerted by the left and right side of the body and in the anterior-posterior part of the foot.

The system is connected via USB interface to a PC and records the line that connects the main points of the COP providing immediate information regarding asymmetry and load sharing. The data measurement is recorded over a certain period (adjustable and modifiable according to the protocol) and the results are processed on the computer through the use of the WinFDM-S program.

The COP data was post-processed with a custom Matlab routine to calculate the following oscillation parameters:

- Sway area (95% confidence ellipse);
- Length of the COP path, i.e., the overall distance covered by the COP during the study;
- Maximum displacement of the COP, i.e., the difference between the maximum and minimum value of the selected coordinate recorded during the test, in the mid-lateral (ML) and antero-posterior (AP) direction;
- Average speed of the COP, or the average speed value calculated for each of the temporal events into which the trial was divided.

Figure 72. The Zebris platform

Source: https://www.zebris.de/fileadmin/Editoren/zebris-PDF/zebris-Prospekte-EN/27_9_FDM_EN_150.pdf

2.3.2.3 G-Sensor

This G-Sensor, which is attached to the patient's waist using a semi-elastic belt at the anatomical reference of L2, provides acceleration values along three orthogonal axes and transmits them via Bluetooth to a PC. At the end of the acquisition procedure, the software will automatically show the examination report window with all the space-time parameters relating to each phase of interest and allow the creation of an overall graph in which the vertical acceleration trend is highlighted, rotation and tilt.

The G-walk is the software piece which allows to calculate spatio-temporal parameters of gait from the accelerations recorded by the G-Sensor. G-Sensor is a wireless inertial platform which, among other things, provides linear acceleration values along three orthogonal axes: antero-posterior, mid-lateral and super-inferior. The acceleration data is transmitted vis Bluetooth to a PC and processed using dedicated software (BTS G-Studio).

Each sensor measures 70 mm x 40 mm x 18 mm, has weight of 37 g and is composed of:

- a 3-axis accelerometer
- a 3-axis gyrosCOPe
- a 3-axis magnetometer

Figure 73. G-Sensor BTS.

Source: https://tlmandina.com.co/analisis-de-movimiento/sensor-inercial/

2.3.2.4 Dnyx Dynamometer

The HGD used for the assessments was DynX which at the end of the force executed by the patient, provides the grip force expressed in kilograms (kg). Moreover, the handle is adjustable from 4.6 to 7cm and must be properly assessed by the operator based on the comfort and mobility of the user.

2.4 Statistical analysis

In this thesis primary and secondary outcomes have been established for UL, gait, DT and Balance analysis (Table 6).

Table 6. Primary and secondary outcomes in upperlimb, gait, dual task and balance

	UP	Gait	DT	Balance
Primary outcomes	9HPT BBT	T25FW 2MWT	Gait speed	BBS
Secondary outcomes	HGT HTM kinematics parameters (Complete Movement, Going Phase, Adjusting Phase, Returning Phase, Adjustemnt Sway, Curvature Index) DASH MAM36	Gait kinematic parameters (GCD, Stance phase, Swing phase, Double Support, Gait Speed, Cadence, Stride length, Step length, Step length, Step width, GPS, Hip FE, Knee FE, Ankle FE) MSWS-12	Gait kinematic parameters (GCD, Stance phase, Swing phase, Double Support, Cadence, Stride length, Step length, Step length, Step width, GPS, Hip FE, Knee FE, Ankle FE)	FSST Stabilometry parameters (ML and AP COP displacement, Sway area, COP path, COP speed)

9HPT: Nine Hole Peg Test; Box and Block test; HGT: Hand Grip Test; T25FW: Timed 25-foot walk test; GCD: Gait Cycle Duration; FE: Flexo-extension; MSWS-12: Twelve Item Multiple Sclerosis walking Scale; BBS: Berg Balance Scale; FSST: Four Square Step Test; ML: Mediolateral; AP: Anteroposterior; COP: Centre of Pressure.

In order to verify the effect of the rehabilitation intervention and to compare any difference between the two types of rehabilitation, a statistical analysis was carried out. In particular, to verify the possible presence of improvements in motor parameters before and after therapy and between the two groups, a two-way analysis of variance for repeated measures ANOVA was performed, whereas variables “time” (pre-post rehabilitation) and “group” (experimental CTG vs ARG) were set, as dependent variables all the kinematic parameters of interest and the score of the questionnaires were gradually chosen. The significance level of the analysis was set at p=0.05. Statistical analyses were performed using SPSS software version 26 (IBM, Armonk, NY, USA).

Chapter 3

Outcomes

3 OUTCOMES

3.1 Participants

At Binaghi Hospital in Sardinia, 30 patients who satisfied all the inclusion criteria were selected by neurologists to participate in the study as it shows in the flow diagram (Figure 74). Two of the thirty were excluded before randomized the sample and other 2 afterwards. During the follow-up 3 participants were lost, having a final sample of 23 participants, 11 in VTG and 12 in CTG.

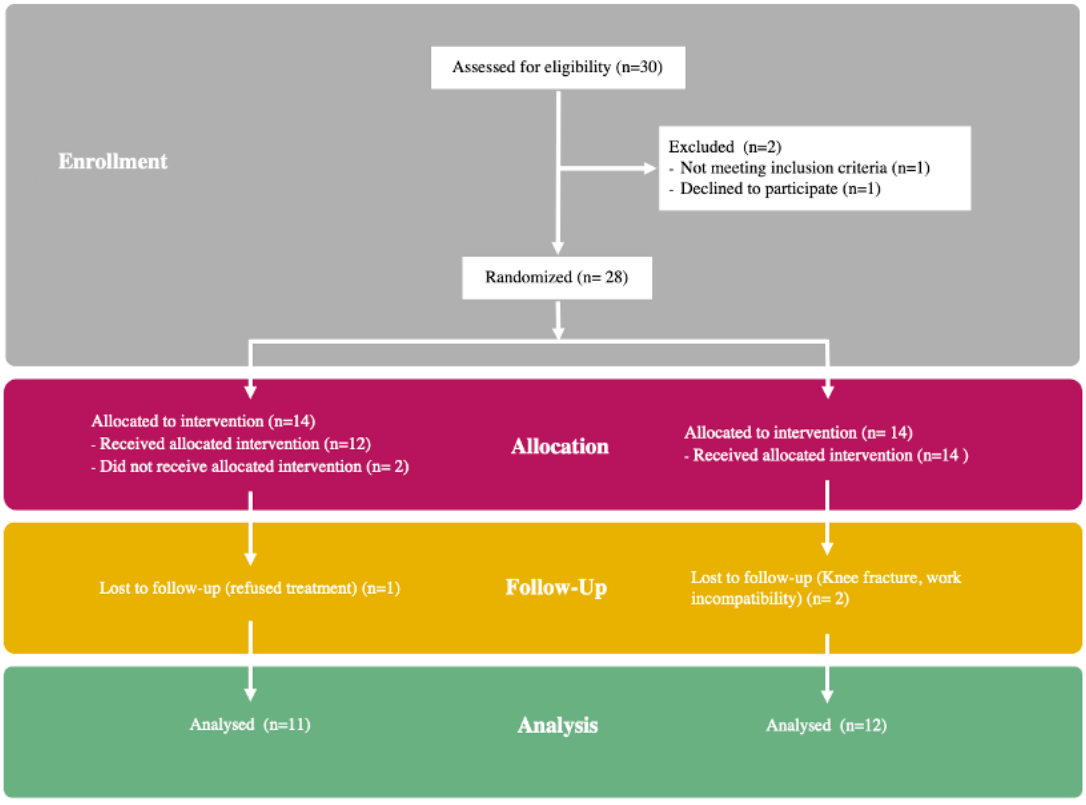


Figure 74. Flow diagram based on CONSORT.

The sample consisted of 30 subjects, 16 women and 14 men, all of them with diagnostic of MS. The mean age for both groups was 49.6 years old, being 54 in CTG and 45.67 in ARG. The anthropometric data of the subjects presents very similar values in the various variables, being shown in Table 7. The medium EDSS score sample was 4.65; 4.71 in CTG and 4.59 in ARG. Both groups recorded similar values for weight, height and at baseline measurement.

Table 7. Sample descriptive analyses

	CTG		ARG		X^2 (p)
	N (12)	%	N (11)	%	
Sex					**2.1;0.14**
Female	8	66.67	4	63.64	
Male	4	33.33	7	58.33	
	Mean	**SD**	**Mean**	**SD**	**t-test (p)***
Age (years)	45.67	11.38	54.00	10.27	-1.83(0.81)
Height (m)	162.00	8.43	168.18	8.20	-1.78(0.09)
Weight (kg)	64.58	19.57	70.82	11.54	-0.92(0.37)
EDSS (score)	4.70	1.19	4.60	1.11	0.24(0.81)

*Normal distribution of the sample by KS test with the Lilliefors correction. All values are $p < 0.05$, no differences between groups.
* *Differences between groups

3.2 Upper-limb

As it is shown in Table 8 both groups show a normal distribution of the sample in the UL parameters except in HGT and in two parameters of kinematic analysis in HTM: complete movement and adjusting sway.

Table 8. Descriptive upper-limb variables before the treatment

	CTG		ARG		T-TEST (p)*
	Mean	SD	Mean	SD	
9HPT (s)	29.32	4.87	32.76	8.37	-1.16(0.25)
BBT (score)	50.04	8.93	50.85	14.06	-0.16(0.87)
HGT (Kg)	14.77	6.41	24.84	11.97	-2.51(0.02)**
CM (s)	1.63	0.25	1.94	0.36	-2.32(0.03)**
GP (s)	0.72	0.12	0.81	0.12	-1.61(0.12)
AP (s)	0.15	0.08	0.29	0.21	-1.97(0.62)
RP (s)	0.75	0.08	0.85	0.13	-1.92(0.69)

	CTG		ARG		T-TEST (p)*
	Mean	SD	Mean	SD	
AS (mm)	4.06	1.62	6.88	3.71	-2.39(0.02)**
CI (%)	0.92	0.10	0.92	0.06	-0.07(0.94)
DASH (score)	28.69	16.22	29.09	22.89	-0.48(0.96)
MAM 36 (score)	71.50	14.45	75.70	21.63	-0.54(0.59)

*Normal distribution of the sample by KS test with the Lilliefors correction. All values are $p < 0.05$, no differences between groups.

* *Differences between groups

9HPT: Nine Hole Peg Test; BBT: Box and Block Tests; HGT: Handgrip test; MC: Complete Movement; GP: Going Phase; AP: Adjusting Phase; RP: Returning Phase; AS: Adjusting Sway; CI: Curvature Index; DASH: The disabilities of the Arm, Shoulder and Hand Questionnaire; MAM 36: Manual ability Measure.

The primary outcomes in UL, 9HPT and BBT, showed that both groups revealed significant changes in time but not, between groups. Thus, translating into an effectiveness of both treatments equally.

The secondary outcomes in UL, showed also that both groups revealed significant changes in time but not, in the between groups. However, in Curvature index of the HTM Kinematic analysis and in que Self-reported questionnaire MAM-36 there were not differences neither in time.

Figure 75 shows an overview of the all upper limb measurements while Table 9 shows the comparison of T0 (assessment before treatment) and T1 (assessment after treatment) for each variable in both groups.

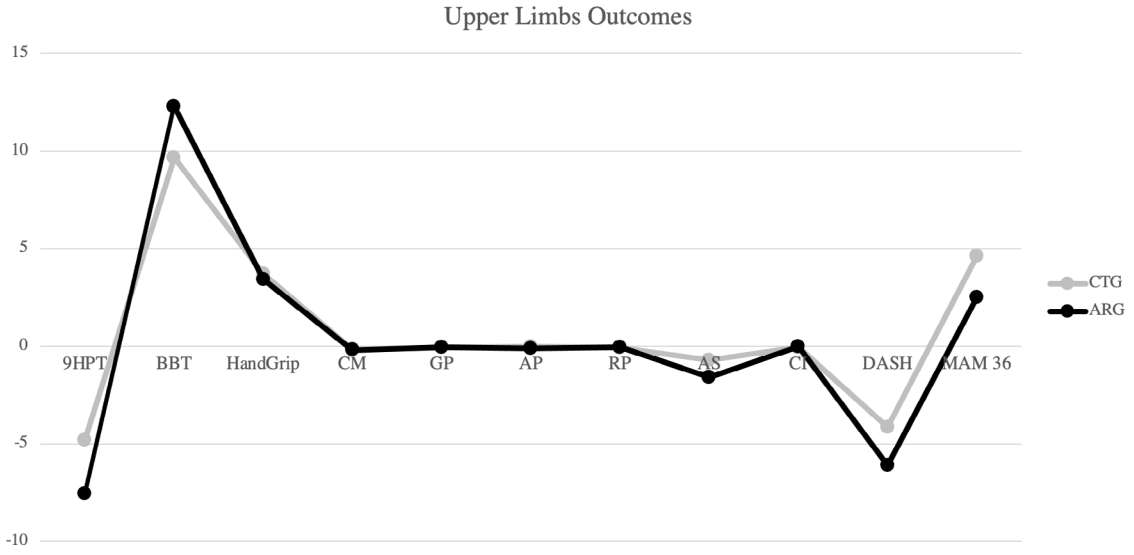


Figure 75. Upper limb outcomes

Table 9. Comparison of means (T0-T1) within group in Upper-Limb

	Group	Mean T0	Mean T1	Mean difference between T0-T1	Standard error	Sig.	95% Confidence interval	
							Inferior limit	Superior limit
Clinical outcomes								
9HPT (s)	CTG	29.32(4.87)	24.5(4.3)	4.88	0.99	<0.001	2.80	6.96
	ARG	32.76(8.93)	25.2(5.8)	7.49	1.10	<0.005	5.21	9.58
BBT (pieces)	CTG	50.04(8.93)	59.71(7.84)	-9.67	1.43	<0.001	-12.65	-6.68
	ARG	50.85(14.06)	60.41(11.77)	-11.05	1.57	<0.001	-14.32	-7.78
HandGrip (kg)	CTG	14.77(6.41)	18.48(8.31)	-3.71	1.17	0.005	-6.14	-1.27
	ARG	24.84(11.97)	28.27(12.42)	-3.42	1.28	0.015	-6.10	-0.71
Kinematic Hand to Mouth outcomes								
CM (s)	CTG	1.63(0.25)	1.46(0.21)	0.17	0.07	0.04	0.01	0.34
	ARG	1.94(0.36)	1.75(0.40)	0.19	0.08	0.03	0.01	0.37
GP (s)	CTG	0.72(0.12)	0.65(0.09)	0.06	0.03	0.04	0.002	0.13
	ARG	0.81(0.12)	0.76(0.15)	0.05	0.03	0.19	-0.02	0.11
AP (s)	CTG	0.15(0.08)	0.12(0.06)	0.03	0.03	0.34	-0.04	0.11
	ARG	0.29(0.21)	0.19(0.13)	0.09	0.04	0.02	0.01	0.17
RP (s)	CTG	0.75(0.08)	0.68(0.07)	0.07	0.03	0.02	0.01	0.13
	ARG	0.85(0.13)	0.79(0.16)	0.05	0.03	0.11	-0.01	0.12
AS (mm)	CTG	4.06(1.62)	3.35(1.43)	-2.82	1.18	0.02	-5.29	-0.35
	ARG	6.88(3.71)	5.30(3.64)	-1.95	1.14	0.10	-4.33	0.43
CI (%)	CTG	0.92(0.10)	0.87(0.05)	-	-	-	-	-
	ARG	0.92(0.06)	0.91(0.07)	-	-	-	-	-
Questionnaires								
DASH (Score)	CTG	28.69(16.22)	24.55(10.57)	4.13	3.21	0.21	-2.57	10.83
	ARG	29.09(22.89)	22.99(18.32)	6.08	3.51	0.10	-1.25	13.42
MAM 36 (Score)	CTG	71.50(14.45)	76.12(13.38)	-	-	-	-	-
	ARG	75.70(21.63)	78.20(20.42)	-	-	-	-	-

9HPT: Nine Hole Peg Test; BBT: Box and Block Tests; Handgrip: Handgrip test; MC: Complete Movement; GP: Going Phase; AP: Adjusting Phase; RP: Returning Phase; AS: Adjusting Sway; CI: Curvature Index; DASH: The disabilities of the Arm, Shoulder and Hand Questionnaire; MAM 36: Manual ability Measure.

For a more detailed statistical analysis, the outcomes of each test, HTM kinematic parameters and questionnaires are shown below.

9HPT: The ANOVA revealed significant changes in time (F=69.81; p<0.001; etap=0.777) but not, in the time*group interaction (F=3.12; p=0.092; etap=0.135). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in both groups CTG (p<0.001; d=1.05 r= 0.46) and ARG (p=0.005; d=1.00 r= 0.45). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

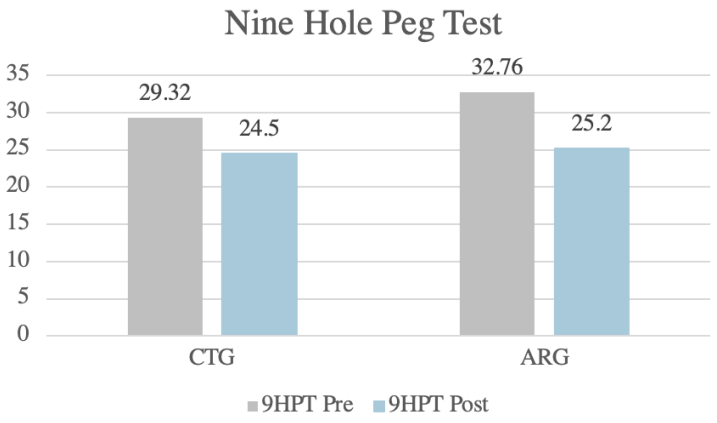


Figure 76. Nine Hole Peg Test outcomes

BBT: The ANOVA revealed significant changes in time (F=95.18; p<0.001; etap=0.826) but not, in the time*group interaction (F=0.42; p=0.522; etap=0.021). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a large/moderate/small effect size in both groups/one group (p=x; d=y). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

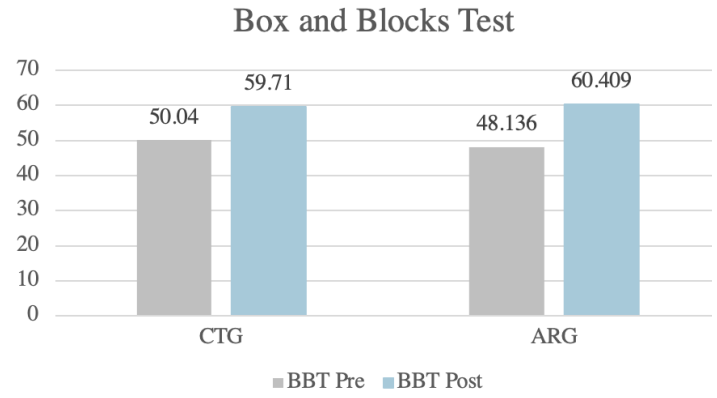


Figure 77. Box and Blocks Test outcomes

Handgrip: The ANOVA revealed significant changes in time (F=16.93; p=0.01; etap=0.458) but not, in the time*group interaction (F=0.026; p=0.873; etap=0.001). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in both groups/ CTG (p=0.005; d=-0.50 r= -0.24) and ARG (p=0.015; d=0.05 r= 0.02). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

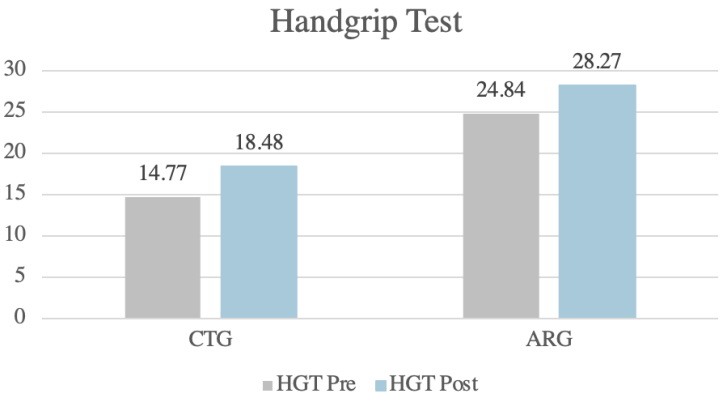


Figure 78. Hand Grip Test outcomes

CM: The ANOVA revealed significant changes in time (F=9.857; p=0.005; etap=0.330) but not, in the time*group interaction (F=0.30; p=0.864; etap=0.001). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in both groups/ CTG (p=0.04; d=0.74 r= 0.35) and ARG (p=0.03; d=0.50 r= 0.24). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

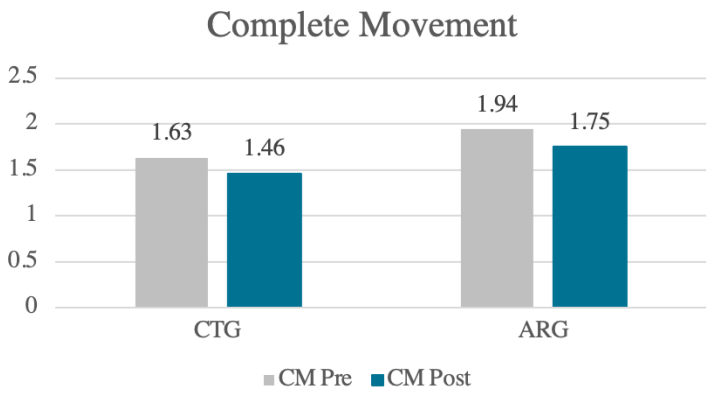


Figure 79. Hand to Mouth Complete movement outcomes

GP: The ANOVA revealed significant changes in time (F=5.937; p=0.02; etap=0.23) but not, in the time*group interaction (F=0.211; p=0.65; etap=0.01). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG group (p=0.04; d=0.66 r=0.31). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

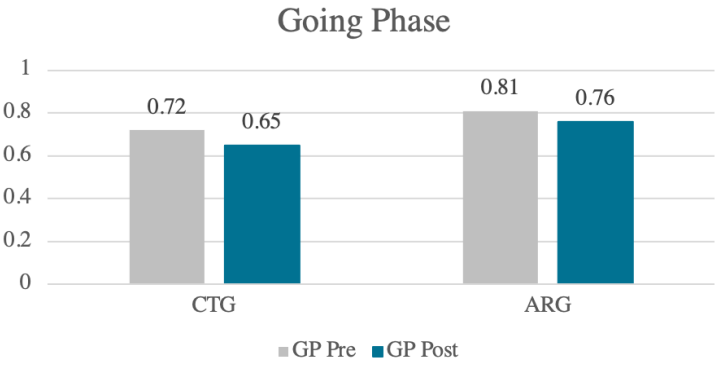


Figure 80. Hand to Mouth Going Phase outcomes

AP: The ANOVA revealed significant changes in time (F=5.717; p=0.027; etap=0.222) but not, in the time*group interaction (F=1.169; p=0.292; etap=0.055). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in ARG group (p=0.02; d=0.57 r=0.28). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

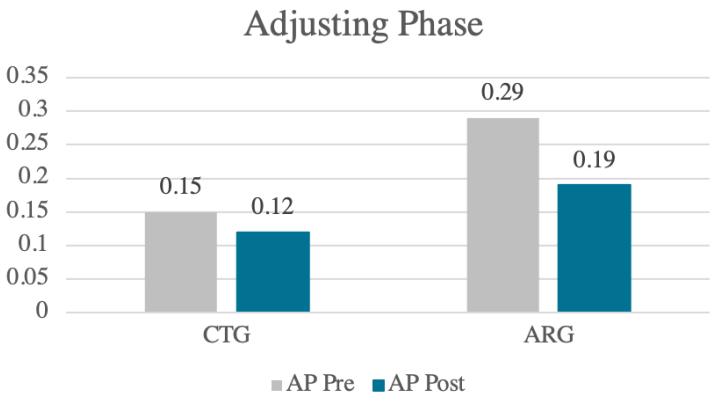


Figure 81. Hand to Mouth Adjusting phase outcomes

RP: The ANOVA revealed significant changes in time (F=8.219; p=0.01; etap=0.291) but not, in the time*group interaction (F=0.160; p=0.694; etap=0.08). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG group (p=0.02; d=0.93 r= 0.42). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

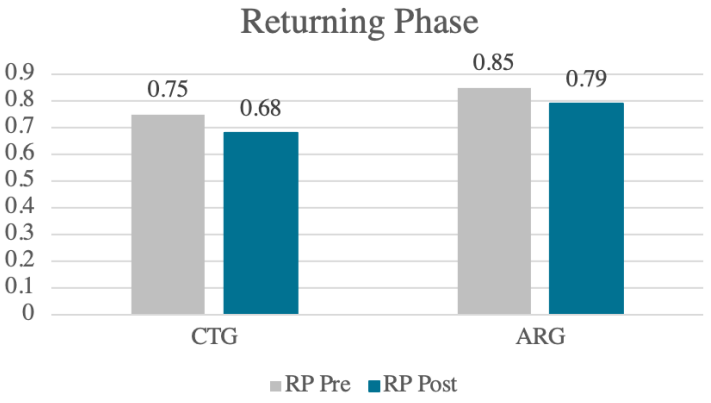


Figure 82. Hand to Mouth Returning phase outcomes

AS: The ANOVA revealed significant changes in time (F=9.692; p=0.005; etap=0.326) but not, in the time*group interaction (F=1.426; p=0.246; etap=0.067). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a large/moderate/small effect size in both groups/one group (p=x; d=y). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

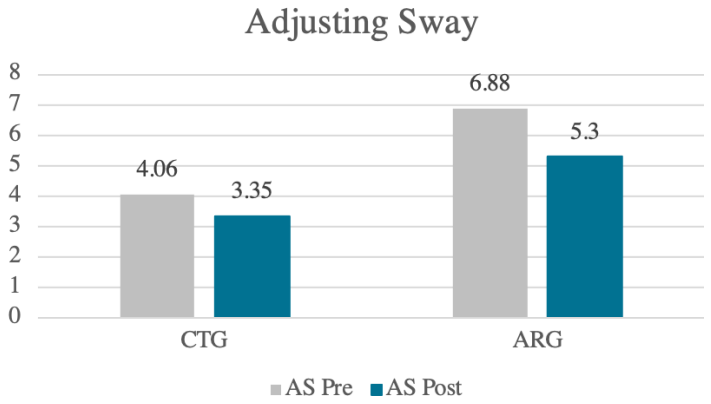


Figure 83. Hand to Mouth Adjusting sway outcomes

IC: The ANOVA revealed no significant changes in time (F=1.909; p=0.182; etap=0.087) nor in the time*group interaction (F=0.518; p=0.480; etap=0.025).

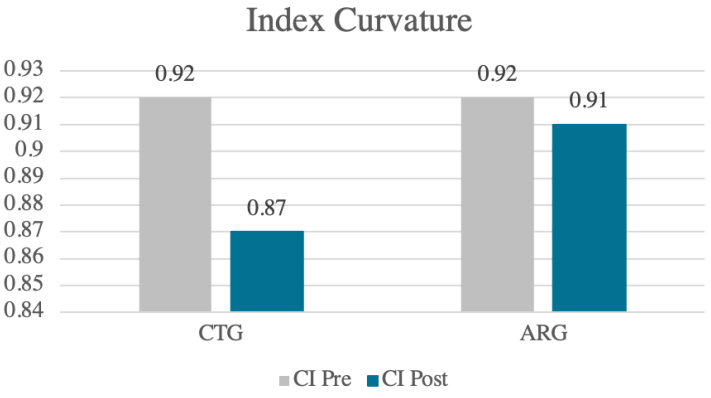


Figure 84. Hand to Mouth Index curvature outcomes

DASH: The ANOVA revealed no significant changes in time (F=4.598; p=0.044; etap=0.187) nor in the time*group interaction (F=0.169; p=0.686; etap=0.08). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a large/moderate/small effect size in both groups/one group (p=x; d=y). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

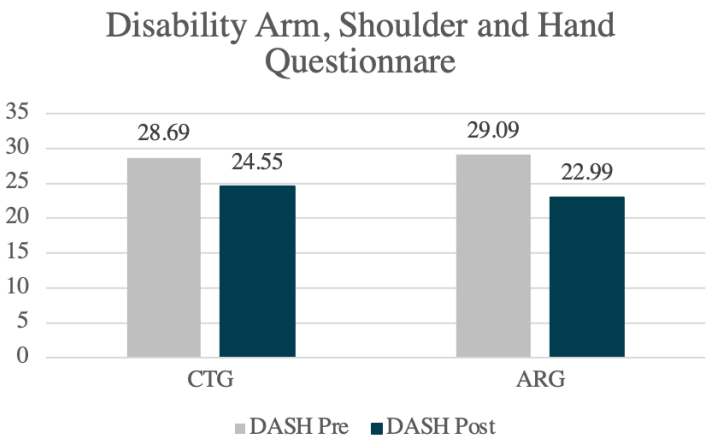


Figure 85. Disability arm, shoulder and Hand Questionnare outcomes.

MAM36: The ANOVA revealed no significant changes in time (F=2.459; p=0.133; etap=0.109) nor in the time*group interaction (F=0.219; p=0.645; etap=0.011).

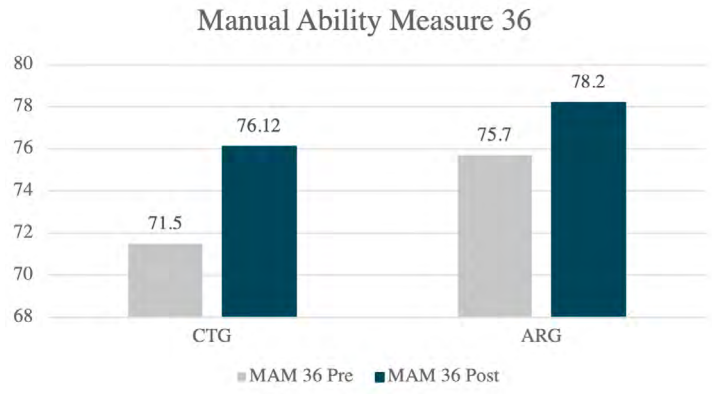


Figure 86. Manual Ability Measure outcomes

3.3 Gait

As it is shown in **Table 10** both groups show a normal distribution of the sample in the all the gait clinical tests, kinematic parameters and questionnaire.

Table 10. Descriptive gait variables before the treatment

	CTG		ARG		T-TEST (p)*
	Mean	SD	Mean	SD	
T25FW (s)	10.44	2.95	11.12	3.43	-0.50(0.62)
2MWT (m)	125.55	29.15	115.45	39.36	0.68(0.50)
GCD (s)	1.27	0.25	1.33	0.20	-0.61(0.54)
Stance phase (%)	64.83	3.50	65.65	3.21	-0.57(0.57)
Swing phase (%)	35.31	3.18	34.41	3.27	0.65(0.52)
Double support (%)	14.78	3.36	15.58	3.14	-0.57(0.57)
Gait speed (m/s)	0.77	0.22	0.72	0.25	0.48(0.63)
Cadence (steps/min)	97.39	15.11	92.10	13.05	0.87(0.39)
Stride length (m)	0.93	0.17	0.91	0.24	0.21(0.83)
Step length (m)	0.46	0.08	0.45	0.12	0.10(0.91)
Step width (m)	0.23	0.04	0.24	0.03	-0.14(0.88)
GPS	11.44	8.21	8.58	1.42	1.13(0.26)
Hip FE (º)	37.10	12.21	40.17	9.61	-0.65(0.52)
Knee FE (º)	47.48	8.92	51.00	10.34	-0.85(0.40)
Ankle FE (ª)	23.57	5.53	20.59	4.68	1.33(0.19)
MSWS-12 (score)	78.78	21.44	64.96	21.94	1.49(0.15)

*Normal distribution of the sample by KS test with the Lilliefors correction. All values are $p < 0.05$, no differences between groups.

* *Differences between groups

T25FW: Timed 25-Foot Walk; 2MWT: Two Minutes Walking Test; GCD: Gait Cycle Duration; GPS: Gait Profile Score; FE: Flexo-extension; MSWS-12: Twelve Item Multiple Sclerosis Walking Scale

The primary outcomes in gait analysis, T25FW and 2MWT, showed that both groups revealed significant changes in time but did not between groups. Thus, translating into an effectiveness of both treatments equally.

The secondary outcomes in gait, showed also that both groups revealed significant changes in time in all the clinical tests and questionnaire and also in the majority of kinematic parameters in time but not between groups. However, in step width, GPS and ankle's ROM, no differences between time neither group were found.

Figure 87 shows an overview of the all upper limb measurements while Table 11shows the comparison of T0 and T1 for each variable in both groups.

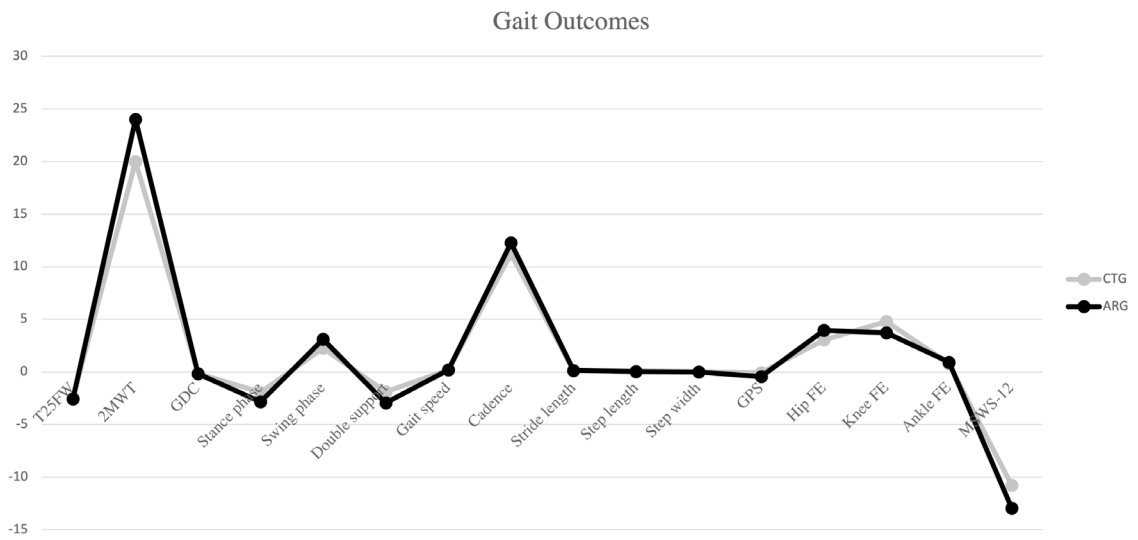


Figure 87. Gait outcomes

Table 11. Comparison of means (T0-T1) within group in gait analysis

	Group	Mean T0	Mean T1	Mean difference between T0-T1	Standard error	Sig.	95% Confidence interval	
							Inferior limit	Superior limit
Clinical outcomes								
T25FW (s)	CTG	10.44(2.95)	7.96(1.50)	2.498	0.571	<0.001	1.307	3.689
	ARG	11.12(3.43)	8.55(2.31)	2.569	0.571	<0.001	1.378	3.760
2MWT (m)	CTG	125.55(29.15)	145.55(24.83)	-20.000	3.898	<0.001	-28.13	-11.87
	ARG	115.45(39.36)	139.45(37.48)	-24.000	3.898	<0.001	-32.13	-15.87
Kinematics gait outcomes								
CTG (s)	CTG	1.27(0.25)	1.13(0.19)	0.136	0.061	0.039	0.008	0.264
	ARG	1.33(0.20)	1.16(0.10)	0.170	0.061	0.012	0.042	0.298
Stance phase (%)	CTG	64.83(3.50)	62.88(1.68)	1.949	0.858	0.034	0.160	3.739
	ARG	65.65(3.12)	62.81(3.17)	2.835	0.858	0.004	1.046	4.625
Swing phase (%)	CTG	35.31(3.18)	37.58(1.53)	0.03	0.03	0.34	-0.04	0.11
	ARG	34.41(3.27)	37.52(3.11)	0.09	0.04	0.02	0.01	0.17

	Group	Mean T0	Mean T1	Mean difference between T0-T1	Standard error	Sig.	95% Confidence interval	
							Inferior limit	Superior limit
Double Support (%)	CTG	14.78(3.36)	12.89(1.56)	1.88	0.882	0.045	0.044	3.726
	ARG	15.58(3.15)	12.64(3.21)	2.936	0.882	0.003	1.096	4.777
Gait speed (m/s)	CTG	0.77(0.22)	0.95(0.17)	-0.177	0.059	0.007	-0.300	-0.55
	ARG	0.72(0.25)	0.93(0.28)	-0.209	0.059	0.002	-0.331	-0.087
Cadence (steps/min)	CTG	97.39(15.11)	108.60(16.76)	-11.215	4.46	0.021	-20.51	-1.91
	ARG	92.10(13.05)	104.38(9.81)	-12.276	4.46	0.012	-21.57	-2.972
Stride length (m)	CTG	0.93(0.17)	1.05(0.11)	-0.114	0.04	0.01	-0.198	-0.03
	ARG	0.91(0.24)	1.06(0.25)	-0.146	0.04	0.002	-0.23	-0.062
Step length (m)	CTG	0.46(0.08)	0.54(0.07)	-0.079	0.031	0.021	-0.144	-0.013
	ARG	0.45(0.12)	0.49(0.07)	-0.037	0.031	0.255	-0.102	0.029
Step width (m)	CTG	0.23(0.04)	0.24(0.37)	-	-	-	-	-
	ARG	0.24(0.03)	0.24(0.03)	-	-	-	-	-
GPS	CTG	11.44(8.21)	11.37(8.46)	-	-	-	-	-
	ARG	8.58(1.42)	8.13(1.03)	-	-	-	-	-
Hip (°)	CTG	37.10(12.21)	40.14(12.79)	-3.032	1.499	0.057	-6.158	0.094
	ARG	40.17(9.61)	44.13(10.01)	-3.964	1.499	0.016	-7.090	-0.838
Knee (°)	CTG	47.48(8.92)	52.29(6.20)	-4.805	1.571	0.006	-8.082	-1.527
	ARG	51.00(10.34)	54.71(11.64)	-3.709	1.571	0.028	-6.986	-0.432
Ankle (°)	CTG	23.57(5.53)	24.34(5.33)	-	-	-	-	-
	ARG	20.59(4.68)	21.52(6.11)	-	-	-	-	-
Questionnaires								
MSWS-12 (score)	CTG	78.78(21.44)	67.99(12.98)	10.795	5.935	0.084	-1.58	23.17
	ARG	64.96(21.94)	57.00(20.44)	7.955	5.935	0.195	-4.42	20.33

T25FW: Timed 25-Foot Walk; 2MWT: Two Minutes Walking Test; CGT: Gait Cycle Duration; GPS: Gait Profile Score; FE: Flexo-extension; MSWS-12: Twelve Item Multiple Sclerosis Walking Scale

For a more detailed statistical analysis, the outcomes of each test, gai kinematic parameters and questionnare are shown below.

T25FW: The ANOVA revealed significant changes in time (F=39.363; p<0.001; etap=0.663) but not, in the time*group interaction (F=0.008; p=0.931; etap=0.000). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG group (p<0.001; d=1.06 r=0.47) and in ARG (p<0.001; d=0.88 r=0.40. In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

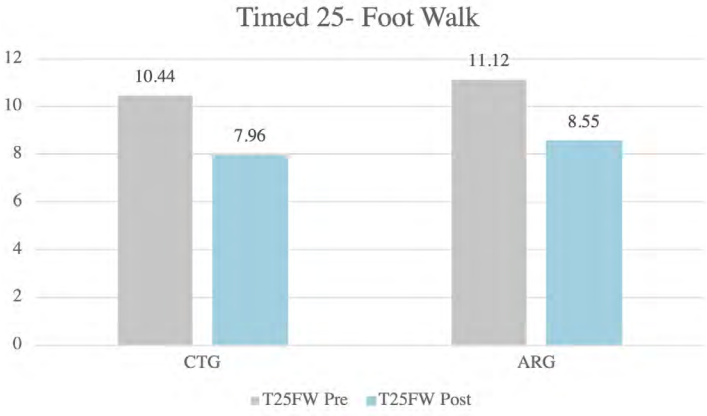


Figure 88. Timed 25-Foot walk outcomes

2MWT: The ANOVA revealed significant changes in time (F=63.722; p<0.001; etap=0.761) but not, in the time*group interaction (F=0.527; p=0.476; etap=0.026). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG group (p<0.001; d=-0.74 r=-0.35) and in ARG (p<0.001; d=-0.62 r=-0.30). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

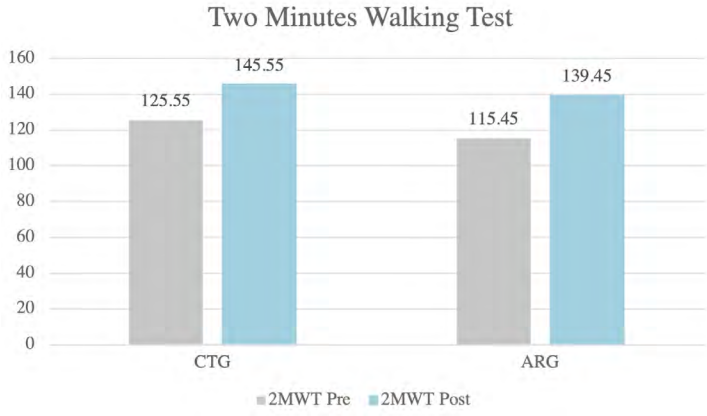


Figure 89. Two Minutes Walking Test outcomes

CTG: The ANOVA revealed significant changes in time (F=12.389; p=0.002; etap=0.383) but not, in the time*group interaction (F=0.150; p=0.702; etap=0.007). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG group (p<0.039; d=0.63 r=0.30) and in CTG (p=0.012; d=1.08 r=0.47) In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

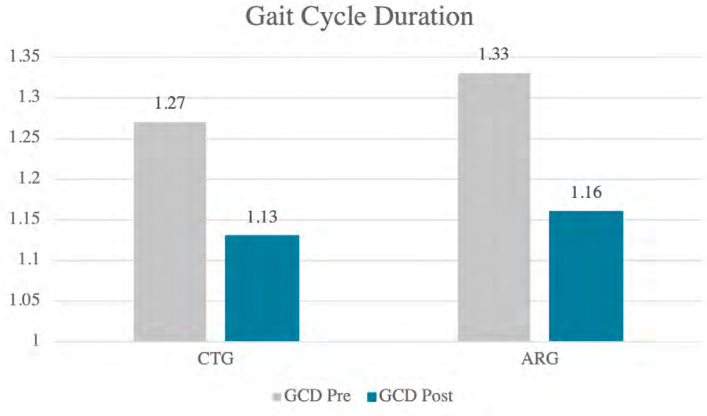


Figure 90. Gait Cycle Duration outcomes

Stance phase: The ANOVA revealed significant changes in time (F=15.549; p=0.001; etap=0.437) but not, in the time*group interaction (F=0.533; p=0.474; etap=0.026). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG (p=0.034; d=0.71 r=0.33) and in ARG (p=0.004; d=0.90 r=0.41. In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

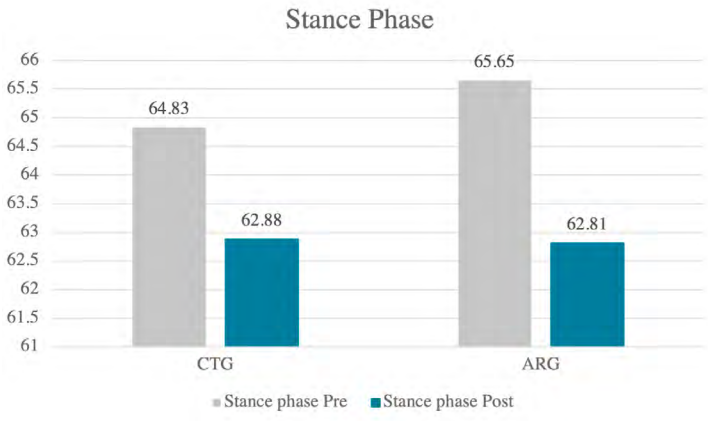


Figure 91. Stance phase outcomes

Swing phase: The ANOVA revealed significant changes in time (F=18.910; p<0.001; etap=0.486) but not, in the time*group interaction (F=0.459; p=0.506; etap=0.022). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in ARG (p=0.02; d=-0.97 r=-0.44). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

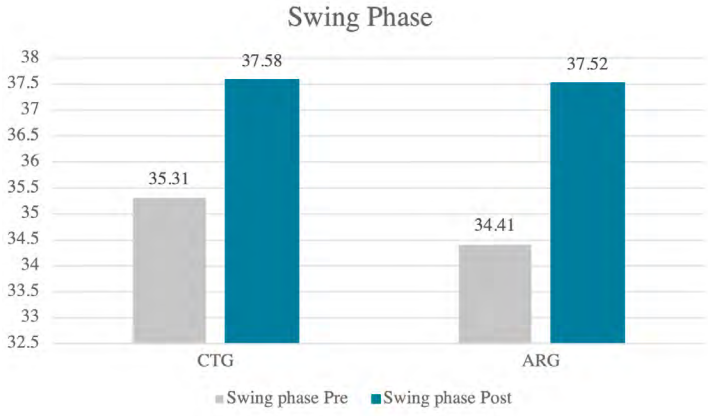


Figure 92. Swing phase outcomes

Double support: The ANOVA revealed significant changes in time (F=14.928; p=0.001; etap=0.427) but not, in the time*group interaction (F=0.710; p=0.409; etap=0.034). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect in CTG (p=0.045; d=0.72 r=0.34) size in ARG (p=0.003; d=0.92 r=0.42). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

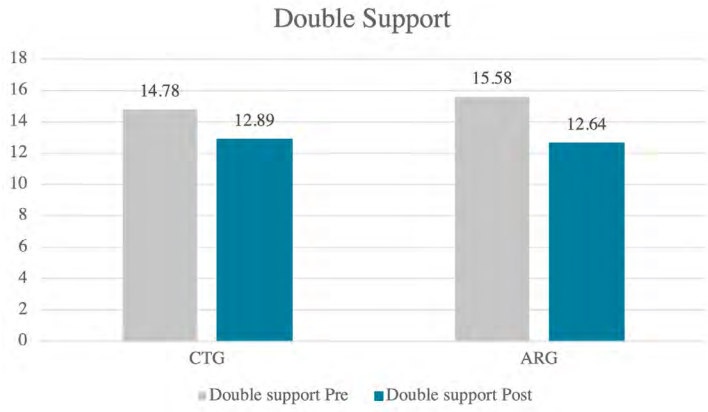


Figure 93. Double support outcomes

Gait speed: The ANOVA revealed significant changes in time (F=21.723; p<0.001; etap=0.521) but not, in the time*group interaction (F=0.147; p=0.705; etap=0.007). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG (p=0.007 d= -0.92 r=-0.42) and in ARG (p=0.002 d= -0.79 r= -0.37). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

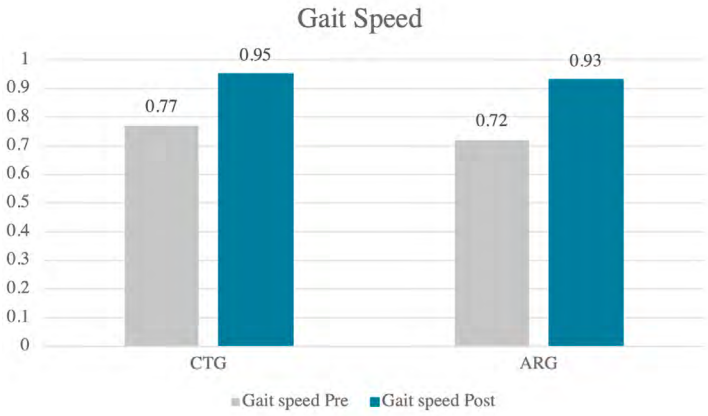


Figure 94. Gait speed outcomes

Cadence: The ANOVA revealed significant changes in time (F=13.869; p=0.001; etap=0.409) but not, in the time*group interaction (F=0.028; p=0.868; etap=0.001). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG (p=0.021; d=-0.95 r=-0.43) and in ARG (p=0.012 d=-1.06 r=-0.47). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

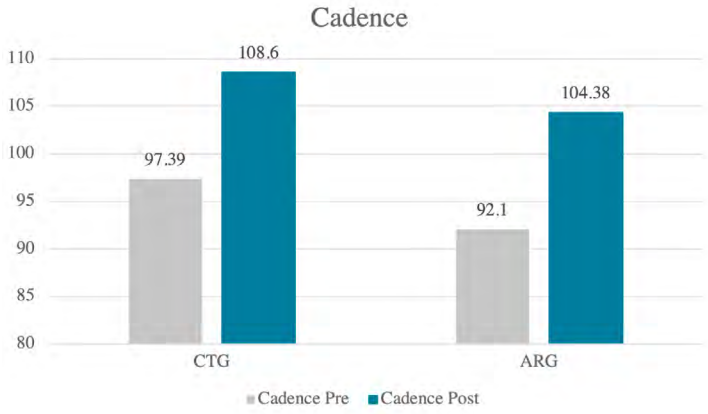


Figure 95. Cadence outcomes

Stride lenght: The ANOVA revealed significant changes in time (F=20.984; p<0.001; etap=0.512) but not, in the time*group interaction (F=0.317; p=0.580; etap=0.016). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG (p=0.01; d=-0.84 r=-0.39) and in ARG (p=0.002 d=-0.61 r=-0.29). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

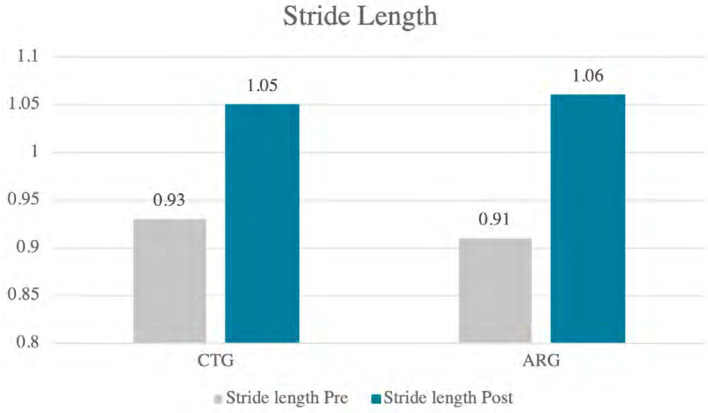


Figure 96. Stride length outcomes

Step length: The ANOVA revealed significant changes in time (F=6.770; p=0.017; etap=0.253) but not, in the time*group interaction (F=0.894; p=0.356; etap=0.043). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG (p=0.021; d=-1.06 r=-0.47). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

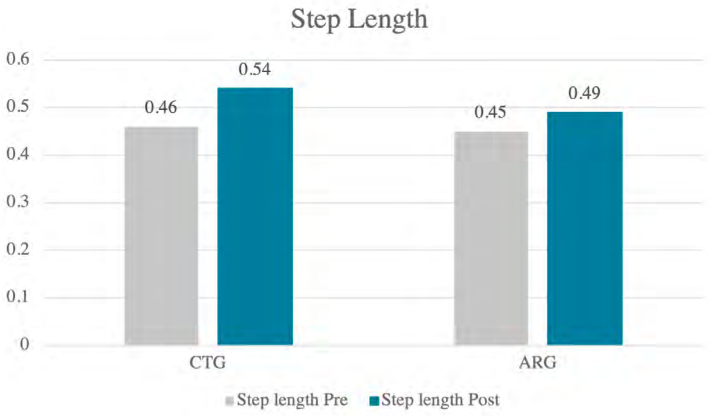


Figure 97. Step length outcomes

Step width: The ANOVA revealed no significant changes in time (F=0.036; p=0.851; etap=0.002) nor in the time*group interaction (F=0.145; p=0.708; etap=0.007).

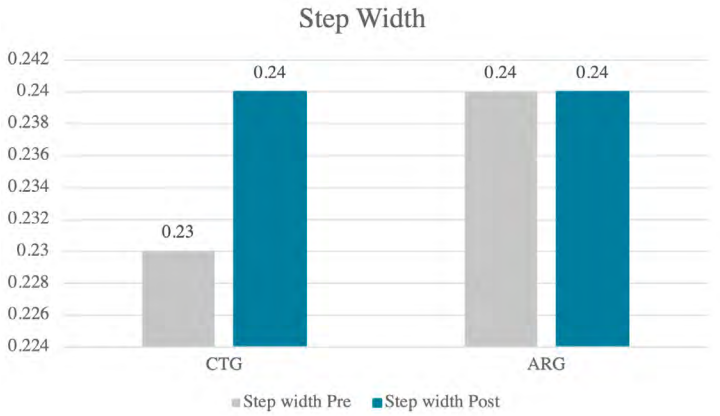


Figure 98. Step width outcomes

GPS: The ANOVA revealed no significant changes in time (F=0.652; p=0.429; etap=0.032) nor in the time*group interaction (F=0.344; p=0.564; etap=0.017).

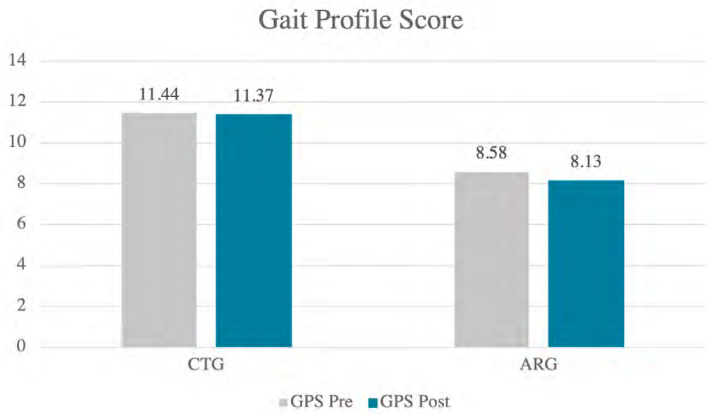


Figure 99. Gait profile score outcomes

HIP FE: The ANOVA revealed significant changes in time (F=10.894; p=0.004 etap=0.353) but not, in the time*group interaction (F=0.193; p=0.665; etap=0.010). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in ARG (p=0.016; d=-0.40 r=-0.20). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

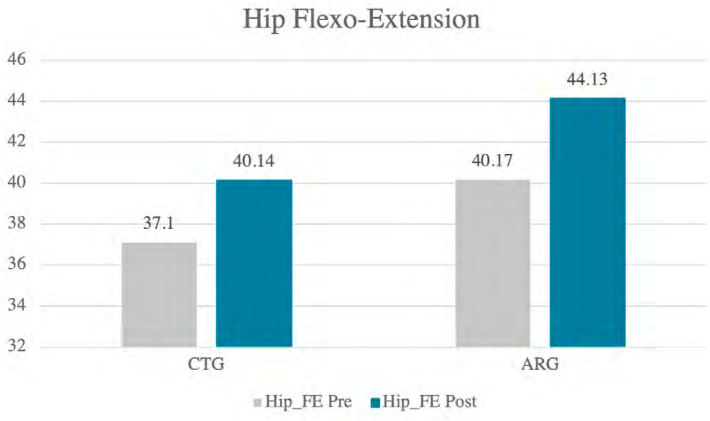


Figure 100. Hip Flexo-extension outcomes

KNEE FE: The ANOVA revealed significant changes in time (F=14.683; p=0.001 etap=0.423) but not, in the time*group interaction (F=0.243; p=0.627; etap=0.012). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG (p=0.006; d=-0.63 r=-0.30) and in ARG (p=0.028 d=-0.34 r=-0.17). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

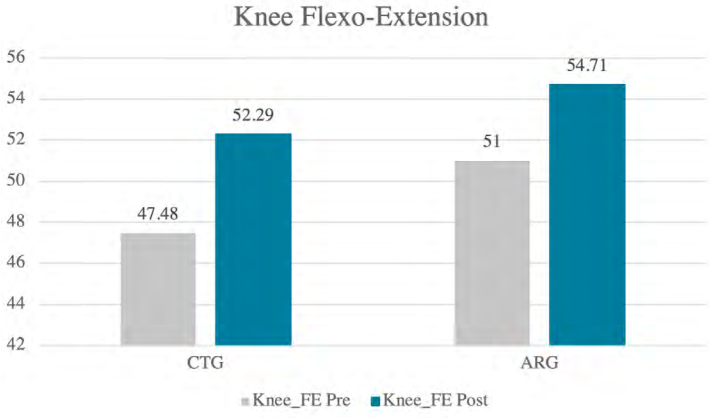


Figure 101. Knee Flexo-extension outcomes

ANKLE FE: The ANOVA revealed no significant changes in time (F= 0.979; p=0.335; etap=0.049) nor in the time*group interaction (F=0.009; p=0.927; etap=0.000).

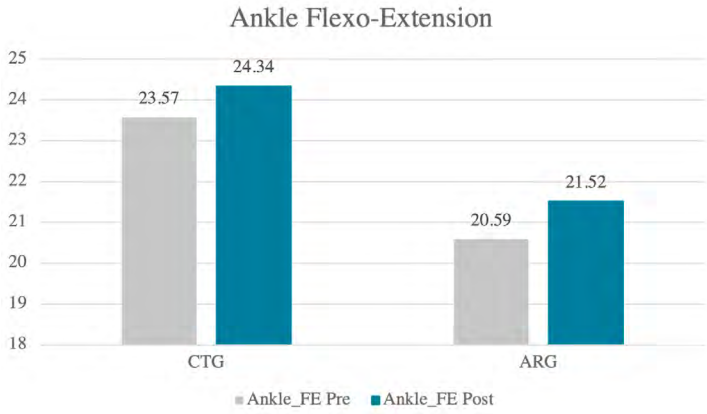


Figure 102. Ankle flexo-extension outcomes

MSWS-12: The ANOVA revealed significant changes in time (F=4.991; p=0.037; etap=0.200) but not, in the time*group interaction (F=0.115; p=0.739; etap=0.006). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG group (p=0.084; d=0.61 r=0.29). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

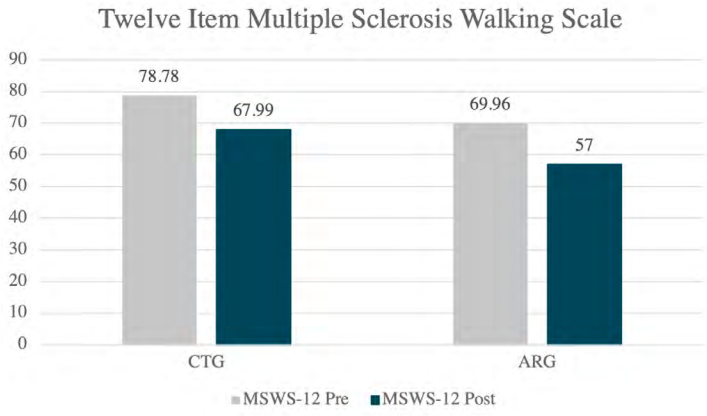


Figure 103. Twelve item multiple sclerosis walking scale outcomes

3.4 Dual task

As it is shown in **Table 12** both groups show a normal distribution of the sample in the all the gait kinematic parameters and questionnaire.

Table 12. Descriptive gait variables during dual task before the treatment

	CTG		ARG		T-TEST (p)*
	Mean	SD	Mean	SD	
GCD (s)	1.28	0.26	1.36	0.19	-0.621(0.545)
Stance phase (%)	65.26	3.37	65.42	1.82	-0.109(0.915)
Swing phase (%)	34.95	3.12	34.29	2.28	0.455(0.656)
Double support (%)	15.19	3.25	15.58	1.94	-0.267(0.793)
Gait speed (m/s)	0.75	0.20	0.65	0.12	1.029(0.321)
Cadence (steps/min)	96.79	15.79	89.88	11.41	0.930(0.368)
Stride length (m)	0.91	0.15	0.86	0.11	0.588(0.566)
Step length (m)	0.45	0.08	0.43	0.06	0.445(0.663)
Step width (m)	0.24	0.04	0.25	0.03	-0.355(0.728)
GPS	11.78	8.58	8.32	1.40	0.966(0.351)
Hip FE (º)	36.42	12.65	36.23	3.86	0.036(0.972)
Knee FE (º)	46.78	9.09	48.55	6.01	-0.423(0.679)
Ankle FE (º)	23.17	5.70	20.21	4.24	1.082(0.299)
SF 36					

*Normal distribution of the sample by KS test with the Lilliefors correction. All values are $p < 0.05$, no differences between groups.

* *Differences between groups

GCD: Gait Cycle Duration; SF-36: Short form Health Survey; FE: Flexo-extension.

The primary outcomes in gait analysis while performing the stroop test, gait speed and step length, showed that both groups revealed significant statically changes in time. but did not between groups. Thus, translating into an effectiveness of both treatments equally.

The secondary outcomes in gait kinematic parameters, showed also that both groups revealed significant changes in time in most kinematic parameters in time but neither between groups. However, in step width, GPS and ankle's FE, no differences between time neither group were found.

Figure 104 shows an overview of the all upper limb measurements while Table 13 shows the comparison of T0 and T1 for each variable in both groups.

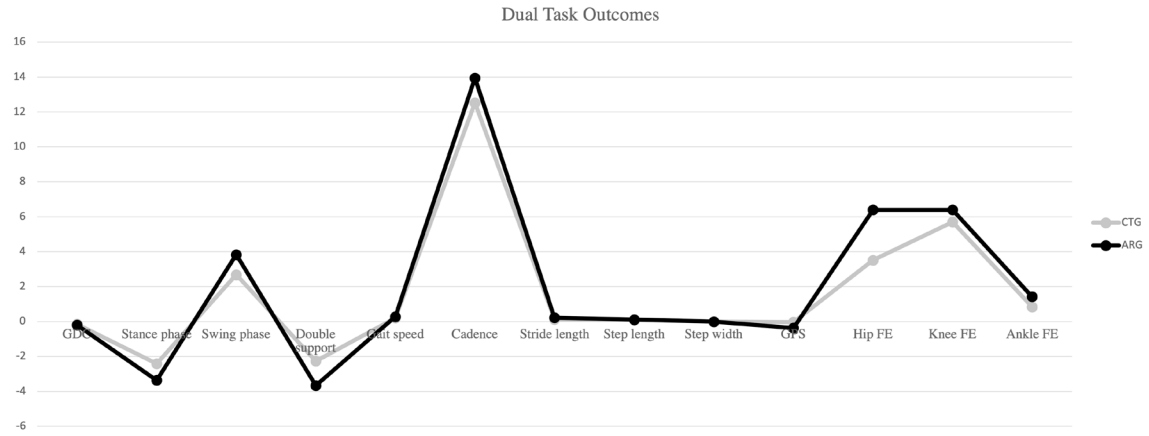


Figure 104. Gait kinematic parameters while dual task outcomes

Table 13. Comparison of means (T0-T1) within group in gait analysis during Stroop test

	Group	Mean T0	Mean T1	Mean difference between T0-T1	Standard error	Sig.	95% Confidence interval	
							Inferior limit	Superior limit
Kinematic gait outcomes								
GCD (s)	CTG	1.28(0.26)	1.13(0.20)	0.152	0.062	0.028	0.019	0.284
	ARG	1.36(0.20)	1.16(0.11)	0.193	0.080	0.030	0.022	0.365
Stance phase (%)	CTG	65.26(3.37)	62.85(1.77)	2.405	0.883	0.016	0.511	4.299
	ARG	65.42(1.82)	62.05(1.71)	3.372	1.140	0.010	0.926	5.817
Swing phase (%)	CTG	34.96(3.11)	37.64(1.60)	-2.677	0.921	0.012	-4.653	-0.701
	ARG	34.29(2.28)	38.12(2.06)	-3.833	1.189	0.006	-6.384	-1.282
Double support (%)	CTG	15.18(3.24)	12.91(1.64)	2.277	0.918	0.026	0.308	4.245
	ARG	15.58(1.94)	11.92(1.80)	3.660	1.185	0.008	1.118	6.202
Gait speed (m/s)	CTG	0.75(0.20)	0.95(0.18)	-0.205	0.051	0.001	-0.315	-0.095
	ARG	0.65(0.12)	0.93(0.16)	-0.383	0.066	0.001	-0.426	-0.141
Cadence (steps/min)	CTG	96.79(15.79)	109.31(17.50)	-12.520	4.505	0.015	-22.18	-2.857
	ARG	89.88(11.41)	103.83(9.77)	-13.947	5.816	0.031	-26.42	-1.472
Stride length (m)	CTG	0.91(0.15)	1.04(0.11)	-0.134	0.039	0.004	-0.218	-0.050
	ARG	0.86(0.11)	1.08(0.12)	-0.211	0.051	0.001	-0.319	-0.102
Step length (m)	CTG	0.45(0.08)	0.54(0.07)	-0.091	0.027	0.005	-0.150	-0.032
	ARG	0.43(0.06)	0.52(0.07)	-0.088	0.035	0.027	-0.163	-0.012
Step width (m)	CTG	0.24(0.04)	0.24(0.04)	-	-	-	-	-
	ARG	0.25(0.03)	0.24(0.01)	-	-	-	-	-
GPS	CTG	11.78(8.58)	11.75(8.82)	-	-	-	-	-
	ARG	8.32(1.40)	7.95(1.04)	-	-	-	-	-
Hip FE (°)	CTG	36.43(12.66)	39.94(13.47)	-3.515	1.636	0.050	-7.023	-0.007
	ARG	36.23(3.86)	42.63(6.63)	-6.400	2.112	0.009	-10.92	-1.871
Knee FE (°)	CTG	46.78(9.09)	52.48(6.50)	-5.695	1.474	0.002	-8.856	-2.534
	ARG	48.56(6.01)	54.96(9.26)	-6.400	1.902	0.005	-10.48	-2.320
Ankle FE (°)	CTG	23.17(5.71)	24.01(5.54)					
	ARG	20.21(4.24)	21.63(5.80)					

GCD: Gait Cycle Duration; FE: Flexo-extension

For a more detailed statistical analysis, the outcomes of each gait kinematic parameter while performing stroop test are shown below.

CTG: The ANOVA revealed significant changes in time (F= 11.603; p=0.004; etap=0.453) but not, in the time*group interaction (F=0.171; p=0.686; etap=0.012). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG (p=0.028; d=0.65 r=0.31) and in moderate effect size in ARG (P=0.030 d=1.24 r=0.53). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

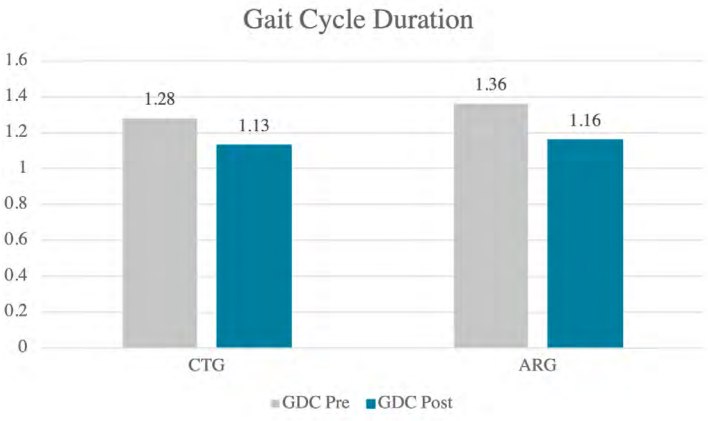


Figure 105. Gait cycle duration dual task outcomes

Stance phase: The ANOVA revealed significant changes in time (F=16.046; p=0.001; etap=0.534) but not, in the time*group interaction (F=0.449; p=0.514; etap=0.031). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG (p=0.016; d=0.90 r=0.41) and in moderate in ARG (p=0.010 d=1.91 r=0.69). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

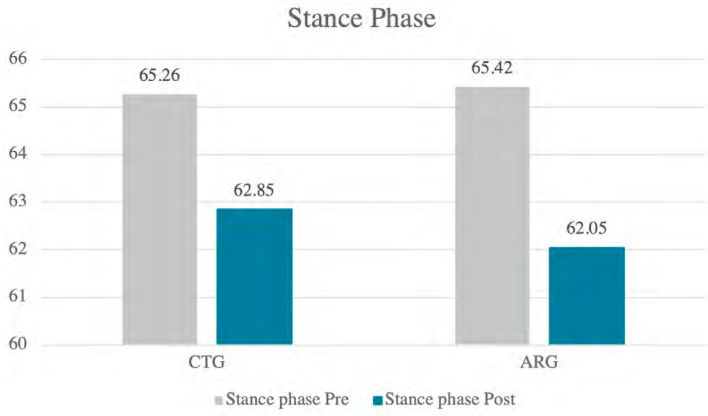


Figure 106. Stance phase dual task outcome

Swing phase: The ANOVA revealed significant changes in time (F=;18.72 p=0.001; etap=0.572) but not, in the time*group interaction (F=0.591; p=0.455; etap=0.541). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG (p=0.012; d=-1.08 r=-0.48) and moderate in ARG (P=0.006 d=-1.76 r=-0.66). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

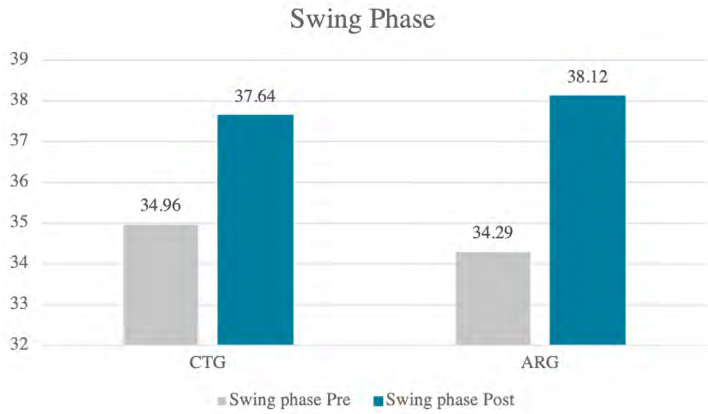


Figure 107. Swing phase dual task outcomes

Double support: The ANOVA revealed significant changes in time (F=15.682 p=0.001; etap=0.528) but not, in the time*group interaction (F=0.852; p=0.372.; etap=0.057). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG (p=0.026; d=0.88 r=0-40) and moderate in ARG (P=0.008 d=1.96 r=0.70). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

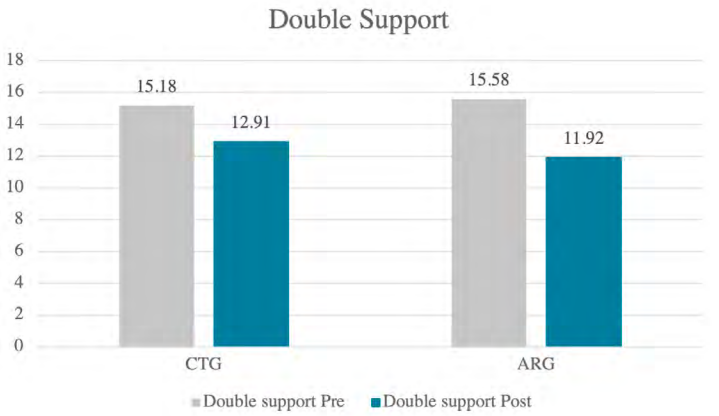


Figure 108. Double support dual task outcomes

Gait speed: The ANOVA revealed significant changes in time (F=33.784; p<0.001; etap=0.707) but not, in the time*group interaction (F0.869=; p=0.367; etap=0.058). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG (p=0.001; d=-1.05 r=-0.47) and moderate in ARG (P=0.001 d=-1.98 r=-0.70). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

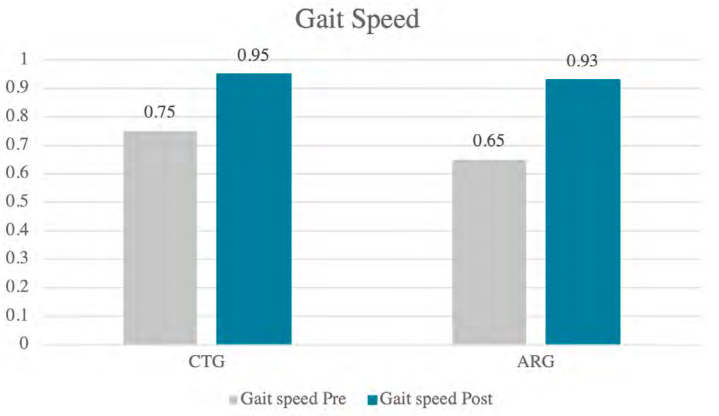


Figure 109. Gait speed dual task outcomes

Cadence: The ANOVA revealed significant changes in time (F=12.942; p=0.003; etap=)0.480 but not, in the time*group interaction (F=0.038; p=0.849; etap=0.003). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG (p=0.015; d=-0.75 r=-0.35) and moderate in ARG (P=0.031 d=-1.31 r=-0.55). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

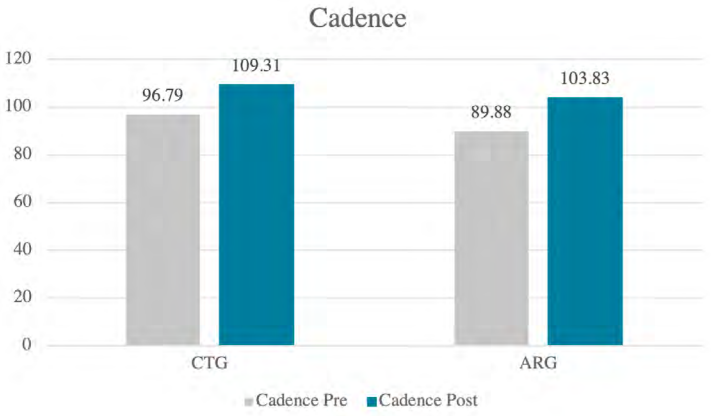


Figure 110. Cadence dual task outcomes

Stride length: The ANOVA revealed significant changes in time (F=29.033; p<0.001; etap=0.675) but not, in the time*group interaction (F=1.453; p=0.248; etap=0.094). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG (p=0.004; d=-0.99 r=-0.44) and moderate in ARG (P=0.001 d=-1.91 r=-0.69). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

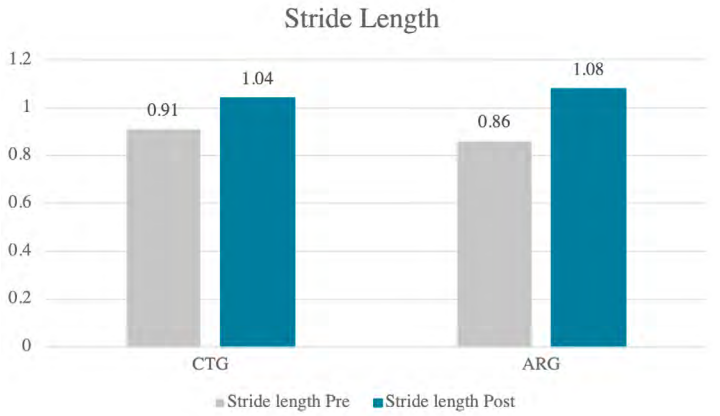


Figure 111. Stride length dual task outcomes

Step length: The ANOVA revealed significant changes in time (F=15.862; p=0.001; etap=0.531) but not, in the time*group interaction (F=0.005; p=0.943; etap=0.000). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a moderate effect size in CTG (p=0.005; d=-1.20 r=-0.51) and in ARG(P=0.027 d=-1.38 r=-0.57). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

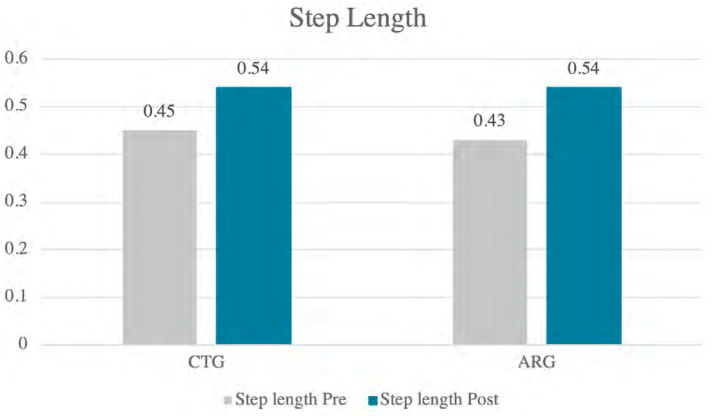


Figure 112. Step length dual task outcomes

Step width: The ANOVA revealed no significant changes in time (F0.738=; p=0.405; etap=0.050) nor in the time*group interaction (F=0.277; p=0.607; etap=0.019).

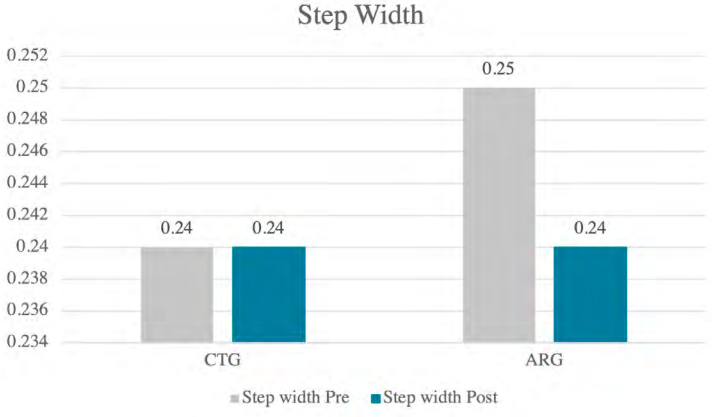


Figure 113. Step width dual task outcomes

GPS: The ANOVA revealed no significant changes in time (F=0.220; p=0.647; etap=0.015) nor in the time*group interaction (F=0.151; p=0.703; etap=0.011).

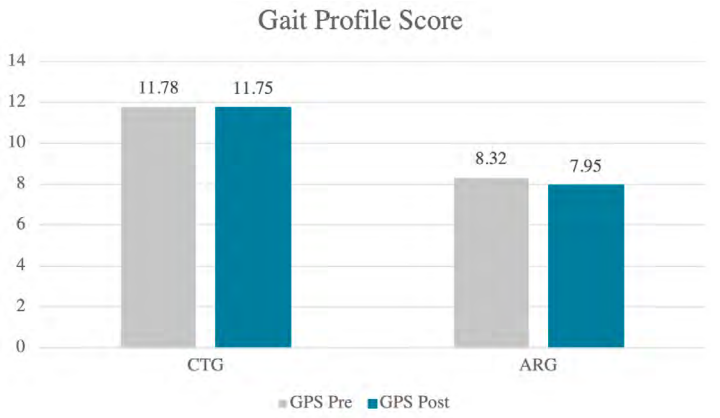


Figure 114. Gait profile score dual task outcomes

Hip FE: The ANOVA revealed significant changes in time (F=13.780; p=0.002 etap=0.496) but not, in the time*group interaction (F=1.167; p=0.298; etap=0.077). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG (p=0.050; d=-0.27 r=-0.13) and moderate in ARG (P=0.009 d=-1.18 r=-0.51). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

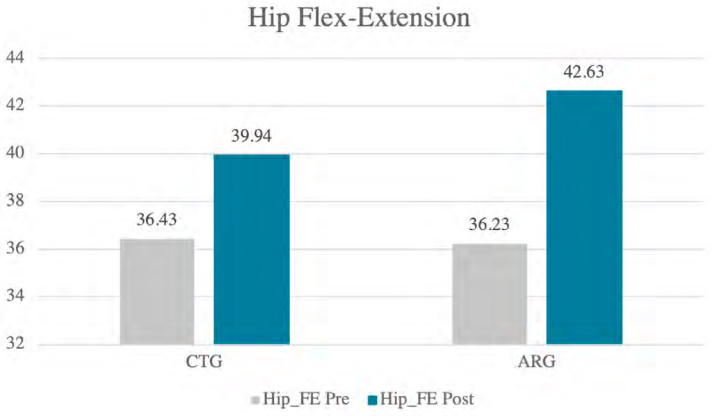


Figure 115. Hip flexo-extension dual task outcomes

Knee FE: The ANOVA revealed significant changes in time (F=25.262; p<0.001 etap=0.646) but not, in the time*group interaction (F=0.086; p=0.774; etap=0.006). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in CTG (p=0.002; d=-0.72 r=-0.34) and in ARG (P=0.005 d=-0.82 r=-0.38). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

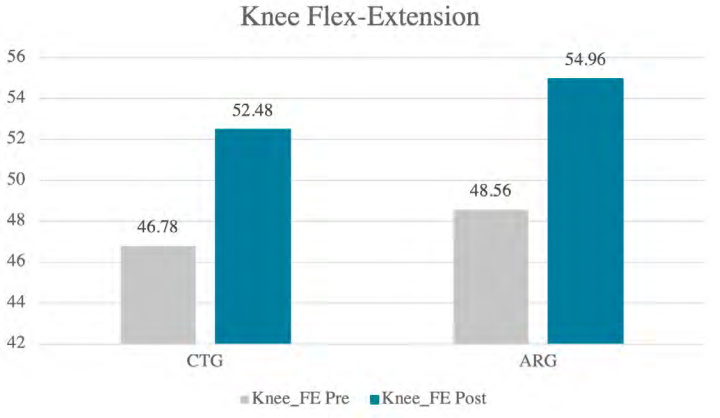


Figure 116. Knee flexo-extension dual task outcomes

Ankle FE: The ANOVA revealed no significant changes in time (F=0.872; p=0.367; etap=0.063) nor in the time*group interaction (F=0.058; p=0.814; etap=0.004).

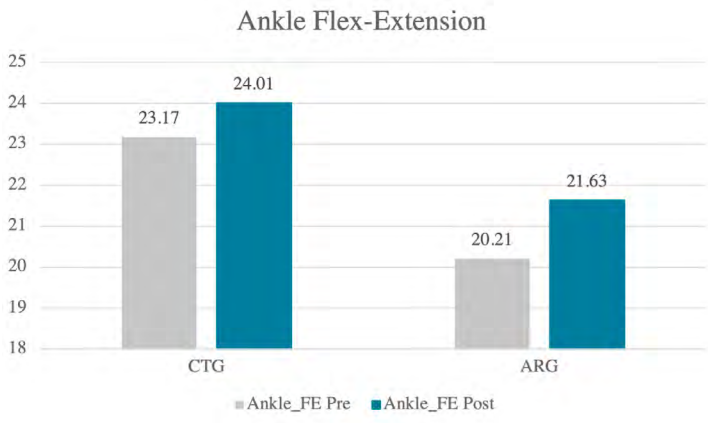


Figure 117. Ankle flexo-extension dual task outcome

3.5 Balance

As it is shown in (Table 14)both groups show a normal distribution of the sample in all clinical tests and balance parameters.

Table 14. Descriptive balance variables before the treatment

	CTG		ARG		T-TEST (p)*
	Mean	SD	Mean	SD	
BBS (score)	44.64	5.22	43.00	4.84	0.76(0.455)
FSST (s)	12.33	4.12	13.58	3.30	-0.951(0.437)
MLCOPD_OE (mm)	26.34	14.44	25.12	10.88	0.21(0.835)
MLCOPD_EC (mm)	44.03	32.28	40.44	18.64	0.297(0.770)
APCOPD_OE (mm)	32.30	14.61	31.39	10.00	0.161(0.874)
APCOPD_EC (mm)	53.12	25.63	49.76	14.21	0.353(0.728)
Sway Area_OE (mm)	329.75	212.73	313.47	143.60	0.185(0.856)
Sway Area_EC (mm)	356.16	215.17	668.51	538.44	-1.417(0.184)
COP_Path_OE	326.30	131.97	468.50	202.88	-1.892(0.075)
COP_Path_EC	705.38	466.37	966.32	464.71	-1.309(0.205)
COP_Speed_OE	12.30	5.98	19.01	11.75	-1.736(0.098)
COP_Speed_EC	23.98	15.85	32.87	15.82	-1.311(0.205)

*Normal distribution of the sample by KS test with the Lilliefors correction. All values are $p < 0.05$, no differences between groups.

* *Differences between groups

BBS: Berg Balance Scale; FSST: Four Square Step Test; MLCOPD: Medio-lateral Centre of Pressure Displacement; APCOPD: Antero-posterior Centre of Pressure Displacement ; OE: Open eyes; EC: Eyes closed; COP: Centre of Pressure.

The primary outcomes in balance analysis, BBS, showed that both groups revealed significant statically changes in time. but did not between groups. Thus, translating into an effectiveness of both treatments equally.

The secondary outcomes in balance variables, showed that only ARG group revealed statistical significant changes in time in COP speed performing with open eyes and mediolateral balance with open and closed eyes in time.

Figure 118 shows an overview of the all upper limb measurements while Table 15 shows the comparison of T0 and T1 for each variable in both groups.

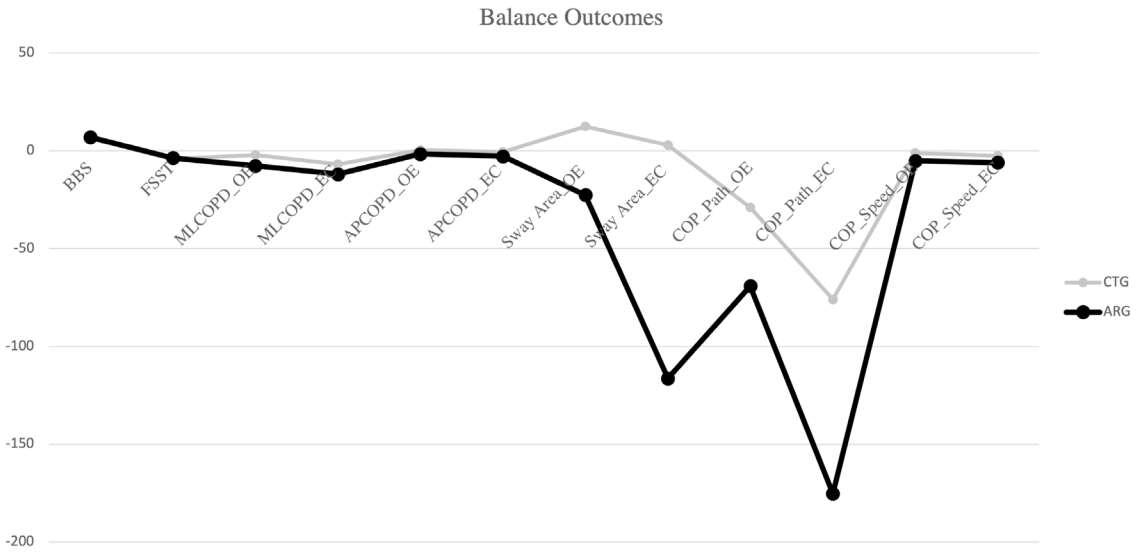


Figure 118. Balance outcomes

Table 15. Comparison of means (T0-T1) within group in balance variables

	Group	Mean T0	Mean T1	Mean difference between T0-T1	Standard error	Sig.	95% Confidence interval	
							Inferior limit	Superior limit
Clinical outcomes								
BBS (score)	CTG	44.64(5.22)	50.82(5.21)	-6.182	0.971	<0.001	-8.208	-4.155
	ARG	43.00(4.84)	50.00(3.46)	-7.000	0.971	<0.001	-9.027	-4.973
FSST (m)	CTG	12.33(4.12)	8.27(1.78)	4.051	0.848	<0.001	2.282	5.820
	ARG	13.59(3.29)	9.92(3.42)	3.669	0.848	<0.001	1.900	5.438
Stabilometric outcomes								
ML_OE (mm)	CTG	26.34(14.44)	24.14(14.06)	2.325	2.816	0.419	-3.568	8.218
	ARG	25.12(10.88)	17.46(5.18)	7.660	3.251	0.029*	0.855	14.465
ML_EC (mm)	CTG	44.03(32.28)	37.15(25.69)	6.878	4.601	0.151	-2.752	16.507
	ARG	40.44(18.64)	28.51(6.75)	11.929	5.312	0.037*	0.810	23.048
AP_OE (mm)	CTG	32.30(14.61)	32.66(16.97)	-	-	-	-	-
	ARG	31.39(10.00)	29.78(8.52)	-	-	-	-	-
AP_EC (mm)	CTG	53.12(25.63)	52.62(26.75)	-	-	-	-	-
	ARG	49.76(14.21)	46.97(11.76)	-	-	-	-	-
Sway area_ OE	CTG	329.75(212.73)	342.24(302.49)	-	-	-	-	-
	ARG	313.47(143.60)	290.84(159.45)	-	-	-	-	-
Sway area_ EC	CTG	356.16(215.17)	359.16(227.80)	-	-	-	-	-
	ARG	668.51(538.44)	552.17(249.13)	-	-	-	-	-
Path_OE	CTG	326.30(131.97)	297.31(117.48)	-	-	-	-	-
	ARG	468.50(202.88)	399.38(123.72)	-	-	-	-	-
Path_EC	CTG	705.38(466.37)	629.42(389.81)	75.962	84.460	0.379	-100.21	252.14
	ARG	966.32(464.71)	791.11(288.19)	175.213	92.521	0.073	-17.78	368.20
Speed_OE	CTG	12.30(5.99)	11.18(5.32)	1.121	2.040	0.589	-3.134	5.376
	ARG	19.02(11.75)	13.85(4.04)	5.170	2.234	0.031*	0.509	9.831
Speed_EC	CTG	23.98(15.85)	21.40(13.25)	2.577	2.875	0.381	-3.421	8.575
	ARG	32.87(15.82)	26.89(9.80)	5.976	3.150	0.072	-0.595	12.546

For a more detailed statistical analysis, the outcomes of each balance variable are shown below.

BBS: The ANOVA revealed significant changes in time (F=92.053; p>0.001; etap=0.822) but not, in the time*group interaction (F=0.355; p=0.558; etap=0.017). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a moderate effect size in CTG (p<0.001; d=-1.19 r=-0.51) and ARG (P<0.01 d=-1.66 r=-0.64). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

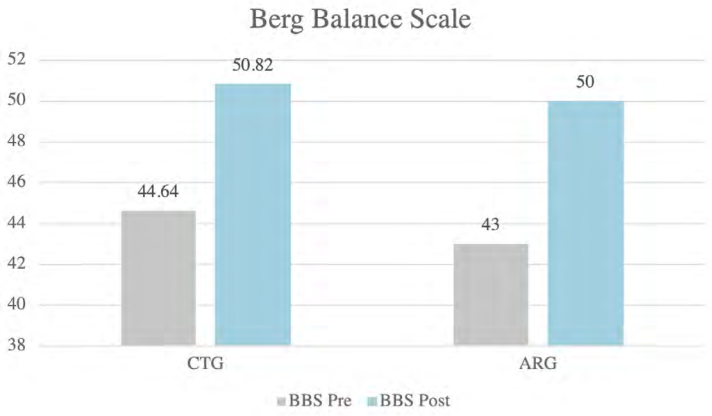


Figure 119. Berg Balance Scale outcomes

FSST: The ANOVA revealed significant changes in time (F=41.436; p>0.001; etap=0.674) but not, in the time*group interaction (F=0.101; p=0.754; etap=0.005). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a moderate effect size in CTG group (p<0.01; d=1.28 r=0.54) and in ARG (P<0.01 d=1.09 r=0.48). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

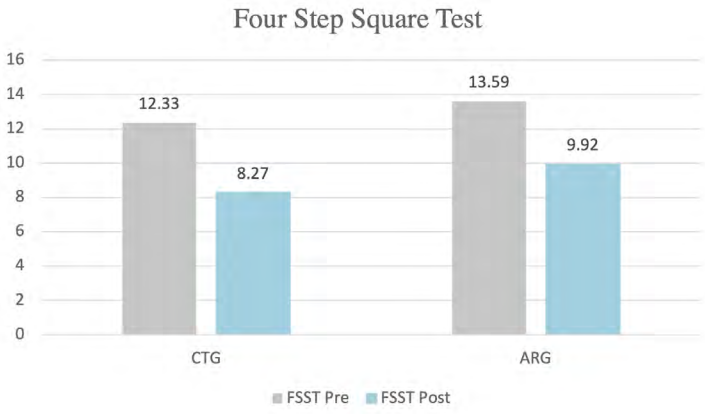


Figure 120. Four Step Sqaure Test Outcomes

ML_OE: The ANOVA revealed significant changes in time (F=5.390; p=0.032; etap=0.221) but not, in the time*group interaction (F=1.539; p=0.230; etap=0.075). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in ARG group (p=0.029; d=0.90 r=0.41). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

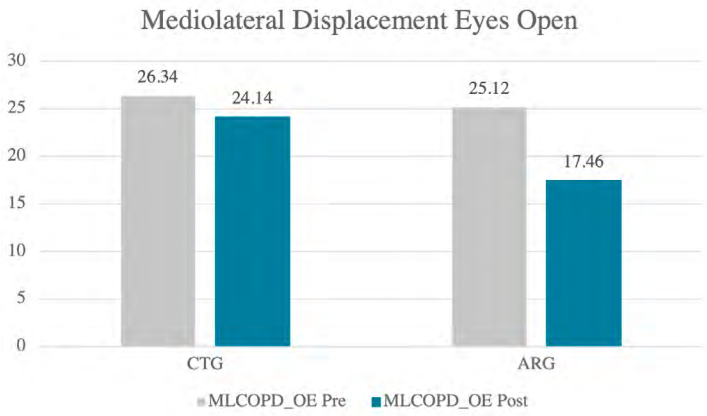


Figure 121. Medio-lateral Centre of Pressure Displacement open eyes outcomes

ML_EC: The ANOVA revealed significant changes in time (F=7.161; p=0.015; etap=0.274) but not, in the time*group interaction (F=0.017; p=0.481; etap=0.026). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in ARG group (p=0.037; d=0.85 r=0.39). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

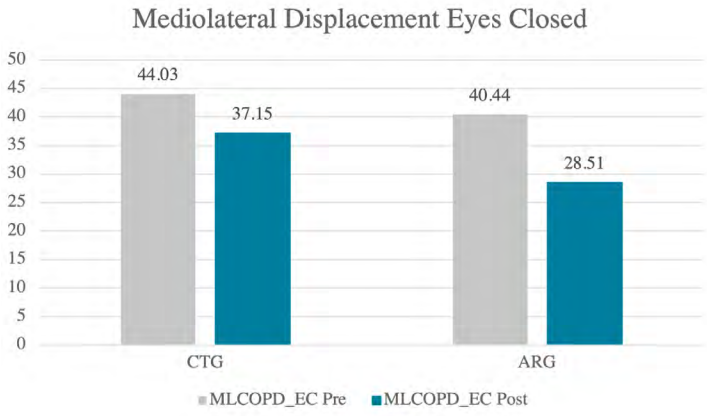


Figure 122. Medio-lateral Centre of Pressure Displacement eyes closed outcomes

AP_OE: The ANOVA revealed no significant changes in time (F=0.470; p=0.831; etap=0.002) nor in the time*group interaction (F=0.115; p=0.738; etap=0.006).

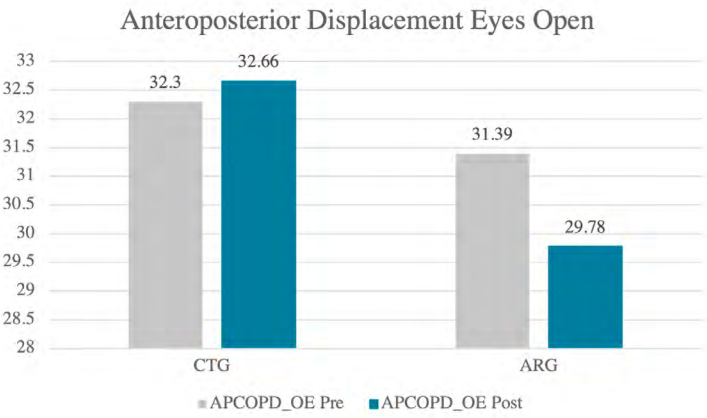


Figure 123. Antero-Posterior Centre of Pressure Displacement open eyes outcomes

AP_EC: The ANOVA revealed no significant changes in time (F=0.412; p=0.529; etap=0.021) nor in the time*group interaction (F=0.199; p=0.661; etap=0.010).

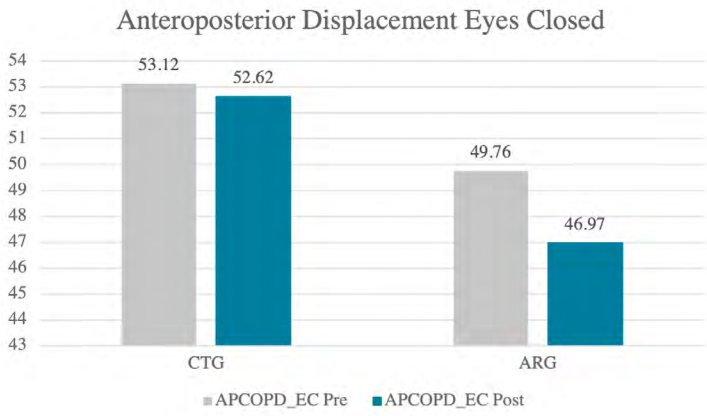


Figure 124. Antero-Posterior Centre of Pressure Displacement eyes closed outcomes

Sway area_OE: The ANOVA revealed no significant changes in time (F=0.018; p=0.896; etap=0.001) nor in the time*group interaction (F=0.212; p=0.651; etap=0.013).

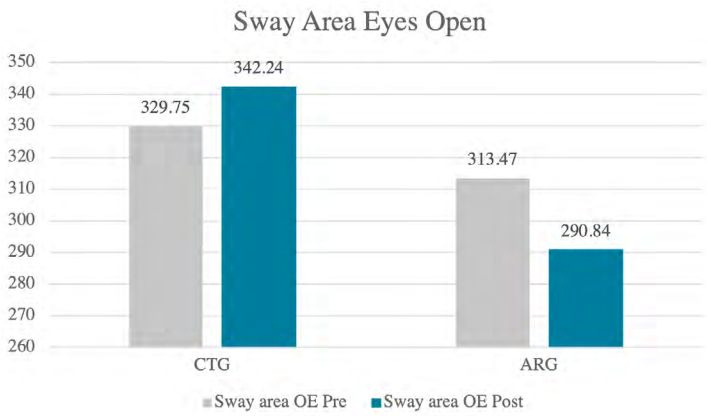


Figure 125. Sway Area open eyes outcomes

Sway area_EC: The ANOVA revealed no significant changes in time (F=0.682; p=0.426; etap=0.058) nor in the time*group interaction (F=0.756; p=0.403; etap=0.064).

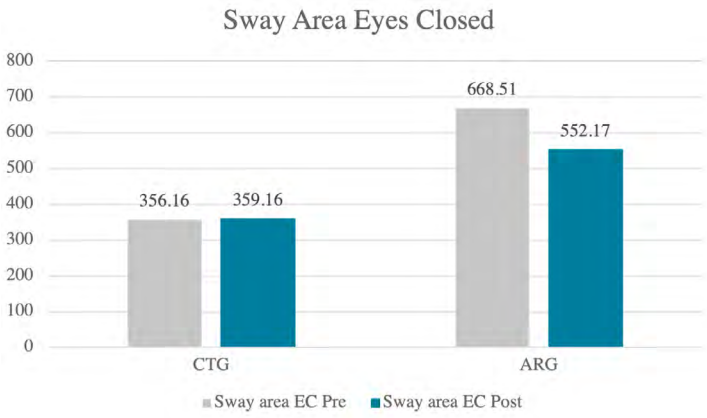


Figure 126. Sway Area eyes closed outcomes

Path_OE: The ANOVA revealed no significant changes in time (F=3.545; p=0.076; etap=0.165) nor in the time*group interaction (F=0.593; p=0.451; etap=0.032).

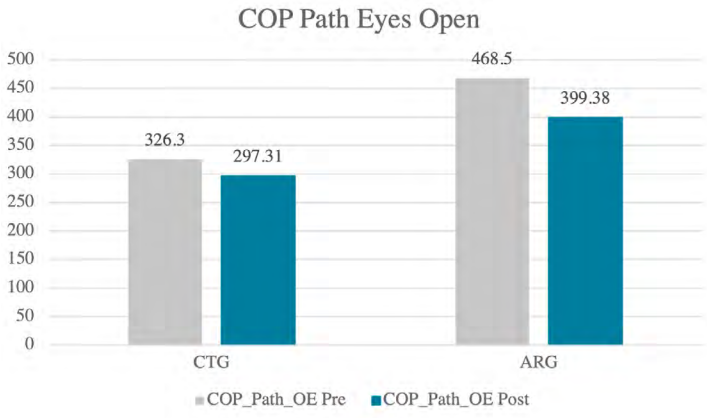


Figure 127. Centre of Pressure path open eyes outcomes

Path_EC: The ANOVA revealed significant changes in time (F=4.020; p=0.059; etap=0.167) but not, in the time*group interaction (F=0.628; p=0.438; etap=0.030). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in ARG (p=0.073; d=0.45 r=0.22). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

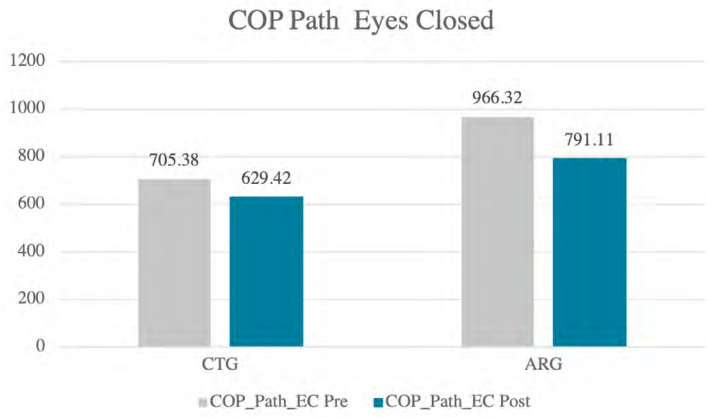


Figure 128. Centre of Pressure path eyes closed outcomes

Speed_OE: The ANOVA revealed significant changes in time (F=4.324; p=0.051; etap=0.178) but not, in the time*group interaction (F=1.791; p=0.196; etap=0.082). The *post hoc* analysis showed significant within-group differences between pre-post intervention with a small effect size in ARG (p=0.031; d=0.59 r=0.28). In addition, the *post hoc* analysis showed no significant between-group differences (p>0.05).

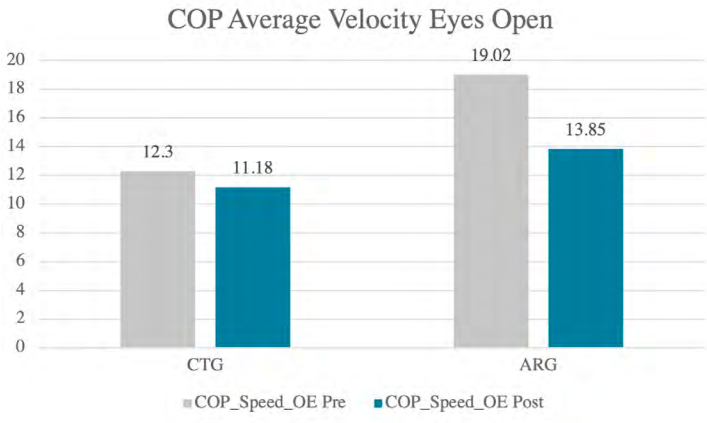


Figure 129. Centre of Pressure speed open eyes outcomes

Speed_OC: The ANOVA revealed no significant changes in time (F=4.022; p=0.059; etap=0.167) nor in the time*group interaction (F=0.635; p=0.435; etap=0.031).

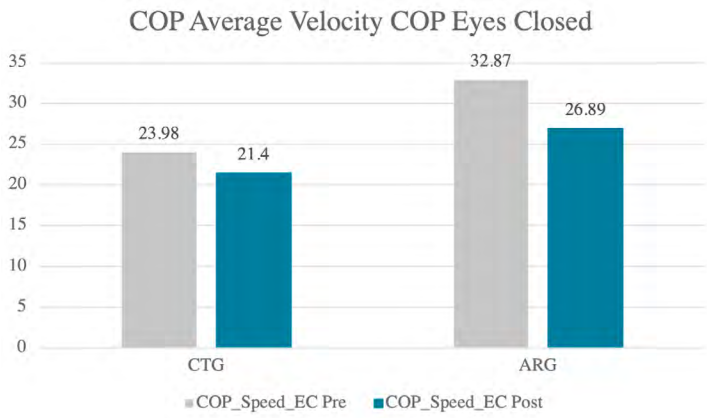


Figure 130. Centre of Pressure speed eyes closed outcomes

3.6 System Usability Scale

Lastly, the SUS was passed to the participants of the ARG in order to measure usability perception of BTS Nirvana. The mean and SD score of participants was 90,45 **(Figure 131)** which leads with to A grade and an "excellent" as adjective rating.

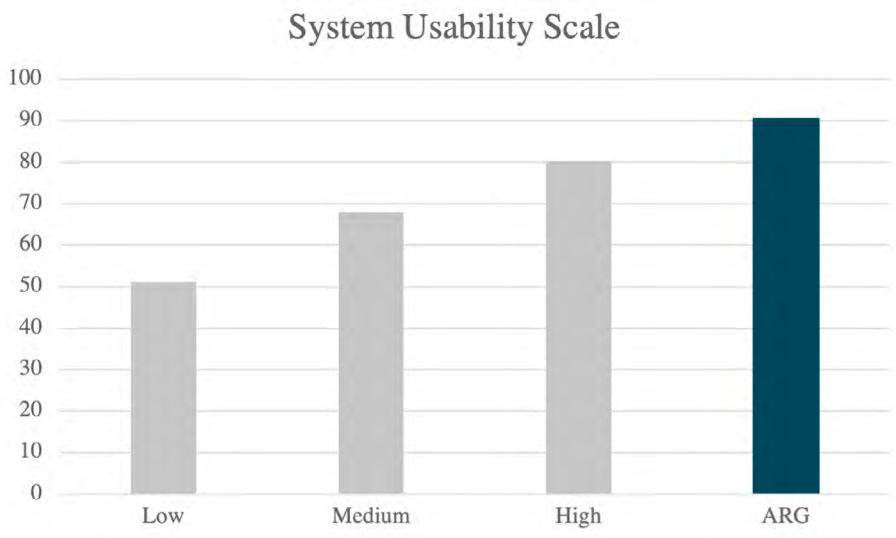
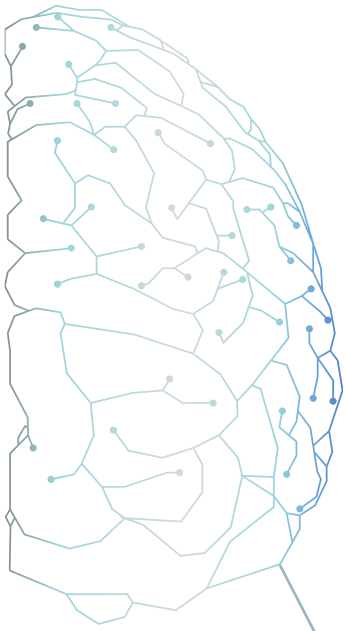


Figure 131. System Usability Scale Score of augmented reality group

Chapter 4

Discussion



4 DISCUSSION

The purpose of this study was to test the clinical usefulness of the AR using the NIRVANA BTS for improving UL, gait and balance impairments as well for improved the performance of dual task while walking. For this, the discussion will be subdivided in each category.

4.1 Upper-Limb

4.1.1 Clinical tests

In 9HPT ARG improved until -7.6s which is in line with other some previous studies that also found improvements after 4 weeks[190-191] and after 8 weeks of treatment[192] with a significant reduction in time, ranging from 3.5s [192] to 8.5s [190]. BBT and HGT were not as assessed in previous studies as much as the 9HPT, but still some studies reported clinically improvements. In other study, BBT increased from 3.5 to 4 blocks [190-191] while in our study the ARG improved until 12 more blocks at the assessment post-treatment. This triple difference can be justified because of the exercises performing during the treatment. In previous studies they used a Microsoft Kinect and a Nintendo Wii with the command, which is a distal movement, whereas in the NIRVANA games participants performed proximal movements where shoulder endurance was trained, and this could help to perform better in BBT. The HGT had an improvement of 3.43kg in ARG, minor in confront with the CTG which improved 3.71kg. A previous study reported 1.6kg for group which use VR even if the treatment lasted 8 weeks the double of ours. This could be lead with the fact that during the execution of UL exercises the participants were using weights on the wrists or griping an elastic band, where the grip force was also trained, even not statically significant between groups.

4.1.2 Instrumental tests

Even though the statistically significant improvements, 9HPT, BBT and HGT have limitations, being unable to detect minimal changes in motor skills influenced by testers[193] and cannot provide detailed and clinically important information as joint angles, velocities and accelerations[194-195].

For, CM, GP, AP, RP and IC both groups improved parallel. In CM reducing the execution time of the complete HTM cycle. Also, AS shows a more clinically improvement in ARG (-1.58s) than CTG (0.71s) which means that ARG reduced almost the half than CTG the sway area of the finger when reaching the target (mouth). However, GP, RP, and AS improved statistically significant in CTG in comparison with ARG Unfortunately, there is a lack in literature of kinematics assessment for HTM to measure changes after using VR in physical therapy. Thus, this data could be taken as a starting point. Nevertheless, changes in these parameters are expected, taking into consideration: the performance of HTM; the not badly affected arms of the participants, and the goal therapy in both groups, as no exercises for hand dexterity were included.

4.1.3 Questionnaires

For questionnaires, only MAM 36 can be compared with a previous study where participants only improved 3.6 points versus ours 2.5 in ARG and 4.6 CTG, which leads in the normality found previously. In contrast, DASH was not measured in any similar study. Participants, from both groups, experience subjectively the same improvements in their daily life.

4.2 Gait

4.2.1 Clinical tests

We found that both groups improved statistically significant more than 2s in T25FW, although they improved 20m (CTG) and 24m (ARG) in 2MWT. This could be because in T25FW, velocity and reaction is being considered, while in 2MWT resistance and fatigue are tested. Actually, during the intervention no reaction or velocity was trained, but the time to perform an exercise was always increased in order to make patients always have a chance during their treatment but avoiding frustrating.

4.2.2 Instrumental tests

All the different parameters of gait improved in both groups in our study, having better results in ARG in stance and swing phase, cadence, and hip ROM. This increment in hip FE can be justified because participants in ARG were able to work on stance phase with only one leg with the aim of raising with the knee the different balls in "balls" game. Working on balance on single leg has a correlation with a longer swinger phase, due to the fact they had trained the balance on the leg which is in stance phase. Obviously, when the swing phase last more, the stance phase is reduced. This is a very important result because gait patterns in pwMS had an increment in their stance phase and a reduction in swing phase, which leads with a correlation with reduced velocity, cadence, stride length and of course fatigue, because they need walk more steps for the same distance.

Actually, our outcomes show this correlation in cadence and less obvious but still clinically important in stride length, and velocity.

The lack of studies which compared a CT versus VR/AR and using objective and quantitative instruments to assess the differences between time and groups, hinders the discussion of the results. Improvements in gait analysis were only observed in one of the three included studies[196]compared with no intervention. Pooled effect analysis did not show significant differences in favour of the virtual group in line with the results of the present study. It is plausible that this occurred due to the fact that treatment was not focused on endurance or velocity but on quality of gait, taking into consideration the range of motion of the different LL joints during the gait cycle. Specially the heel as the first point of the cycle, working on the tibialis anterior, very weak in participants, no matter the group. No significant differences between groups were reported when virtual reality was compared with standard gait therapy [197-200].

4.2.3 Questionnaires

The questionnaire MSWS-12 showed in both groups a better perception from the participants in gait performance. Also here, we appreciated with almost 3 points of difference that ARG perceived better performance while walking than the CTG. This self-reported scale was also used in two other studies, one with no significant differences after the treatment and the other with statically significant differences. It must be highlighted that the study with no differences performed the exercises in Nintendo Wii for 30 minutes per session and the one with differences performed from 40 to 60 minutes, which is the double of time, even if participants trained the same number of sessions per week and in total. In our study, even there were not significantly changes between groups, there were shown on time.

In previous studies, only one self-reported measure was assessed in 6 of 11 studies. In this, in comparison with no intervention, VR training showed significant improvements for self-reported walking ability and for the perceived physical and psychological impact of MS. In comparison with standard training, significant differences were observed for flow experience, fatigue and fear of falling.

4.3 Dual Task

Despite the growing number of papers dealing with the DTC of gait in MS, there is a lack of standardized data. In particular, there is no indication about which gait parameters and cognitive tasks can be used in pwMS[187]. This is even more important considering that dual task walking is becoming not only an experimental setting but also a rehabilitative protocol[186]. Specially, for a functional rehabilitation, this is the main goal, so the patients can extrapolate the improvements in motor function during their DLA[201]. Experiencing more cognitive-motor demanding situations could be the reason for retention of cognitive-motor performance improvement in the ARG[202].

One study proved that pwMS showed a decreased gait speed and stride length and increase stride time, stance phase and double support duration in comparison with a healthy subjects sample[187]. Encouragingly, in our study all the spatiotemporal data, except the step width, in our sample improved in both groups. Actually, both groups were performing some exercise i.e. on the instable disks doing enhancing balance while doing other task at the same time.

4.4 Balance

4.4.1 Clinical tests

Nevertheless, the BBS was commonly used reporting also no significant overall effect. The BBS improved 6.18 points in CTG and 7 points in ARG, being the minimal detected change (MDT) in MS 3 in inpatients and 2 in outpatients [203]. Therefore, the improvement in balance was improved significantly. Actually, the improvement was parallel in both groups because the material used for reducing base support and adding instability was the same in both groups. In FSST the CTG improved in 4.06s and ARG in 3.67s. However, the MDC is estimated in 4.6s so not clinically improvement was actually reported for ARG. This can lead to the fact that patients did not train dynamic balance as much as the stable because performing way of the exercises in NIRVANA.

4.4.2 Instrumental tests

Posturographic systems have become more affordable and potentially useful for both clinical practice and research purposes. Nevertheless, they still represent a significant cost need a dedicated space and trained staff to run the tests. Further efforts are warranted to establish which parameters of balance should be evaluated, normative values for the force platform measures, how to standardize the posturographic assessment for multicentre study purposes and the ecological validity of this tool[204].

In previous studies compared with no intervention[125] significant postural control improvements in the ARG were observed in all measures in bipedal eyes opened tests [196], [198], [205]. It has also been shown that VR balance training is more effective than no intervention. However, when VR balance training was compared with conventional training, significant differences were only observed in two studies[205-206] and no differences between groups were reported in three studies [197-198], [207]. Regarding functional balance, this was only compared with no intervention in two studies [208-209], and no significant differences were observed between the VR and control groups. However, balance improvements in favor of ARG were found in two other studies [205], [207] while others did not [199], [206]. And in other study [200] the improvement was only significant in experimental group. It is not possible confront exactly because of the different balance measures used in other studies.

The parameter with best results in our study after the treatment was ML COP displacement in the ARG being 7.66mm less with open eyes and 11.93 mm with eyes closed than the T0. Meanwhile in CTG the reduction of was 2.2 mm with open eyes and 6.88 mm with closed eyes. Also the COP Path with and the COP speed, both with closed eyes, were improved statistically significant only in ARG. However, not statistically improvements in the other parameters were found.

Our study had no statistically significant differences between groups, but a better improvement clinically in ARG in the parameters mentioned before. Actually, exercise attributes might be a possible cause for these findings. In the ARG, the speed movement was externally imposed and participants had to react as fast as possible to successfully complete the tasks, while the control group performed the exercises at a self-selected pace that enables them to have more control on their movements. This may highlight the potential of two interventions to be used as complementary treatments.

4.5 Limitations and future work

The biggest limitations of this study were the small sample and the lack of consensus in literature for the exercise type and dose for both, functional training in conventional therapy and for VR/AR training.

It is worth mentioning that several previous studies had some limitations that made difficult to discuss our results. For instance, UL rehabilitation using VR all previous studies had relatively sample sizes from 5[210] to 60[192] participants. There were no comparisons of outcomes across MS types in any papers, with some articles not reporting the MS type of the participants[126]. All studies had different intervention protocols, with different commercially games or specifically tailored solutions, which difficulties the comparison of parameters and create homogenous protocols for clinical practice. Especially when some VR games included joysticks or commands. However, it must be highlighted the lack of consensus in exercise dosing. For example, the training frequency varied from one day[211] to 6 month programe [212] and also sessions lasted from 20 minutes [211]to an hour [210], with some studies not reporting the intervention duration at all [213].

Regarding the lack of literature of kinematics in UL, as being validated with a correlation with the clinical tests, this may represent a useful and objective quantitative measure of motor impairments potentially suitable for clinical purposes, such as assessment and planning of rehabilitative treatments.

For gait and balance rehabilitation, different commercial systems were used, different modalities of training were carried out and different training protocols were implemented. the total number of sessions ranged from 8 to 48, with a training frequency from 1 to 4 sessions per week and training time from 20 to 60 minutes per session. There is also a lack of description in the standard training protocols for balance and gait training, which means that can be a wide range of possibilities which we are comparing to VR groups, and of course the heterogeneity of different ways of measure different parameters.

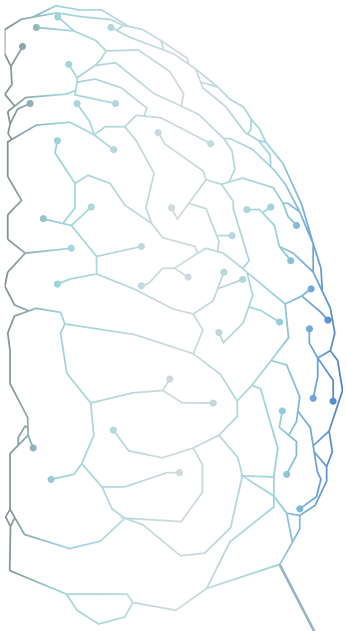
VR/AR training could be considered at least as effective as conventional training and more effective than no intervention to treat balance and gait impairments in MS rehabilitation[125]. However, these results should be interpretated with caution due to differences in the intensity of the therapy and differences in effect sizes among the studies. VR/AR has also been suggested as a more motivational and cost-effective alternative, although research supporting these benefits needed.

A variety of approaches including motor and sensory strategies, strengthening exercises, dual-task, cognitive and balance exercises have been employed to improve balance and decreases the risk of falling in pwMS. However, recent system reviews revealed that despite the efficacy of the conventional methods in improving balance of pwMS, these improvements are not sufficient enough to reduce the number of future falls[214]. Due to the chronic nature of the disease, pwMS, especially when

aimed at decreasing major consequences such as falling, is a long-term process[201]. The constant repetitive nature of conventional rehabilitation programs may decrease patient engagement in the long-term [197], [201]. Therefore, patients commitment and their motivation need to be preserved throughout the course of the program[201] This may raise the need for more effective and enjoyable rehabilitation programs to gain durable clinical improvements. A recent meta-analysis indicated that VR was at least as effective as conventional balance exercises in improving balance and reducing gait impairments in pwMS with no significant differences between the two types of training[125]. Even though other studies have shown the promising potential of VR to improve balance and gait in neurological conditions, such as MS[129], the small number of studies with matched groups in terms of training parameters (eg. duration of exercise in each treatment session, structure, and nature of the program), and the lack of follow-up make it hard to achieve a certain conclusion[125].

Chapter 5

Conclusions



5 CONCLUSIONS

1. AR is as efficient as CT in motor rehabilitation for pwMS.

2. AR is as efficient as CT in UL rehabilitation for pwMS evidenced with clinical, instrumental evaluation and self-questionnaires.

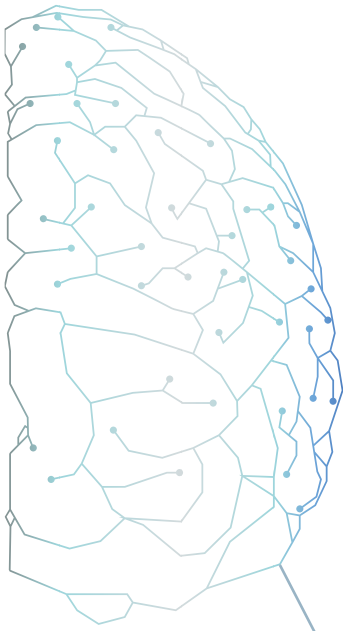
3. AR is as efficient as CT in gait rehabilitation for pwMS evidenced with clinical, instrumental evaluation and self-questionnaires.

4. AR is as efficient as CT in DT rehabilitation for pwMS with instrumental evaluation.

5. AR is as efficient as CT in balance rehabilitation for pwMS with clinical and instrumented evaluation.

Chapter 6

References



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Annexes

Appendix 1.
Registration form and assessment checklist

Nome				Data	
Patologia				Sesso	
Data di nascita		Peso	Kg	Altezza	cm

	Pre	Post
1. Valutazione cinematica del cammino con un sistema optoelettronico e piattaforme di forza.		
2. Valutazione cinematica dell'arto superiore con un sistema optoelettronico e piattaforme di forza.		
3. Test Romberg su una piattaforma baropodometrica		
4. Timed up and go con un sensore inerziale		
5. Test Handgrip		
6. Berg Balance Scale		
7. 2 Minute Walking Test		
8. Questionario sulla qualità della vita SF 36		
9. Questionario per l'arto superiore DASH		
10. Twelve Item Walking Scale		
11. MAM 36		
12. Test Usabilità del Sistema		

Appendix 2.
Berg Balance Scale

BERG BALANCE TESTS AND RATING SCALE

Patient Name _____
Date _____
Location _____
Rater _____

ITEM DESCRIPTION SCORE (0-4) Sitting to standing _____ Standing unsupported _____ Sitting unsupported _____ Standing to sitting _____ Transfers _____ Standing with eyes closed _____ Standing with feet together _____ Reaching forward with outstretched arm _____ Retrieving object from floor _____ Turning to look behind _____ Turning 360 degrees _____ Placing alternate foot on stool _____ Standing with one foot in front _____ Standing on one foot _____ TOTAL _____

GENERAL INSTRUCTIONS
Please demonstrate each task and/or give instructions as written. When scoring, please record the lowest response category that applies for each item.

In most items, the subject is asked to maintain a given position for a specific time. Progressively more points are deducted if the time or distance requirements are not met, if the subject's performance warrants supervision, or if the subject touches an external support or receives assistance from the examiner. Subjects should understand that they must maintain their balance while attempting the tasks. The choices of which leg to stand on or how far to reach are left to the subject. Poor judgment will adversely influence the performance and the scoring.

Equipment required for testing are a stopwatch or watch with a second hand, and a ruler or other indicator of 2, 5 and 10 inches (5, 12 and 25 cm). Chairs used during testing should be of reasonable height. Either a step or a stool (of average step height) may be used for item #12.

1. SITTING TO STANDING
INSTRUCTIONS: Please stand up. Try not to use your hands for support.
( ) 4 able to stand without using hands and stabilize independently
( ) 3 able to stand independently using hands
( ) 2 able to stand using hands after several tries
( ) 1 needs minimal aid to stand or to stabilize
( ) 0 needs moderate or maximal assist to stand

2. STANDING UNSUPPORTED
INSTRUCTIONS: Please stand for two minutes without holding.
( ) 4 able to stand safely 2 minutes
( ) 3 able to stand 2 minutes with supervision
( ) 2 able to stand 30 seconds unsupported
( ) 1 needs several tries to stand 30 seconds unsupported
( ) 0 unable to stand 30 seconds unassisted

If a subject is able to stand 2 minutes unsupported, score full points for sitting unsupported. Proceed to item #4.

3. SITTING WITH BACK UNSUPPORTED BUT FEET SUPPORTED ON FLOOR OR ON A STOOL
INSTRUCTIONS: Please sit with arms folded for 2 minutes.
( ) 4 able to sit safely and securely 2 minutes
( ) 3 able to sit 2 minutes under supervision
( ) 2 able to sit 30 seconds
( ) 1 able to sit 10 seconds
( ) 0 unable to sit without support 10 seconds

4. STANDING TO SITTING
INSTRUCTIONS: Please sit down.
( ) 4 sits safely with minimal use of hands
( ) 3 controls descent by using hands
( ) 2 uses back of legs against chair to control descent
( ) 1 sits independently but has uncontrolled descent
( ) 0 needs assistance to sit

5. TRANSFERS
INSTRUCTIONS: Arrange chairs(s) for a pivot transfer. Ask subject to transfer one way toward a seat with armrests and one way toward a seat without armrests. You may use two chairs (one with and one without armrests) or a bed and a chair.
( ) 4 able to transfer safely with minor use of hands
( ) 3 able to transfer safely definite need of hands
( ) 2 able to transfer with verbal cueing and/or supervision
( ) 1 needs one person to assist
( ) 0 needs two people to assist or supervise to be safe

6. STANDING UNSUPPORTED WITH EYES CLOSED
INSTRUCTIONS: Please close your eyes and stand still for 10 seconds.
( ) 4 able to stand 10 seconds safely
( ) 3 able to stand 10 seconds with supervision
( ) 2 able to stand 3 seconds
( ) 1 unable to keep eyes closed 3 seconds but stays steady
( ) 0 needs help to keep from falling

7. STANDING UNSUPPORTED WITH FEET TOGETHER
INSTRUCTIONS: Place your feet together and stand without holding.
( ) 4 able to place feet together independently and stand 1 minute safely
( ) 3 able to place feet together independently and stand for 1 minute with supervision
( ) 2 able to place feet together independently but unable to hold for 30 seconds
( ) 1 needs help to attain position but able to stand 15 seconds with feet together
( ) 0 needs help to attain position and unable to hold for 15 seconds

8. REACHING FORWARD WITH OUTSTRETCHED ARM WHILE STANDING
INSTRUCTIONS: Lift arm to 90 degrees. Stretch out your fingers and reach forward as far as you can. (Examiner places a ruler at end of fingertips when arm is at 90 degrees. Fingers should not touch the ruler while reaching forward. The recorded measure is the distance forward that the finger reaches while the subject is in the most forward lean position. When possible, ask subject to use both arms when reaching to avoid rotation of the trunk.)
( ) 4 can reach forward confidently >25 cm (10 inches)
( ) 3 can reach forward >12 cm safely (5 inches)
( ) 2 can reach forward >5 cm safely (2 inches)
( ) 1 reaches forward but needs supervision
( ) 0 loses balance while trying/requires external support

9. PICK UP OBJECT FROM THE FLOOR FROM A STANDING POSITION
INSTRUCTIONS: Pick up the shoe/slipper which is placed in front of your feet.
( ) 4 able to pick up slipper safely and easily
( ) 3 able to pick up slipper but needs supervision
( ) 2 unable to pick up but reaches 2-5cm (1-2 inches) from slipper and keeps balance independently
( ) 1 unable to pick up and needs supervision while trying
( ) 0 unable to try/needs assist to keep from losing balance or falling

10. TURNING TO LOOK BEHIND OVER LEFT AND RIGHT SHOULDERS WHILE STANDING
INSTRUCTIONS: Turn to look directly behind you over toward left shoulder. Repeat to the right. Examiner may pick an object to look at directly behind the subject to encourage a better twist turn.
( ) 4 looks behind from both sides and weight shifts well
( ) 3 looks behind one side only other side shows less weight shift
( ) 2 turns sideways only but maintains balance
( ) 1 needs supervision when turning
( ) 0 needs assist to keep from losing balance or falling

11. TURN 360 DEGREES
INSTRUCTIONS: Turn completely around in a full circle. Pause. Then turn a full circle in the other direction.
( ) 4 able to turn 360 degrees safely in 4 seconds or less
( ) 3 able to turn 360 degrees safely one side only in 4 seconds or less
( ) 2 able to turn 360 degrees safely but slowly
( ) 1 needs close supervision or verbal cueing
( ) 0 needs assistance while turning

12. PLACING ALTERNATE FOOT ON STEP OR STOOL WHILE STANDING UNSUPPORTED
INSTRUCTIONS: Place each foot alternately on the step/stool. Continue until each foot has touched the step/stool four times.
( ) 4 able to stand independently and safely and complete 8 steps in 20 seconds
( ) 3 able to stand independently and complete 8 steps in >20 seconds
( ) 2 able to complete 4 steps without aid with supervision
( ) 1 able to complete >2 steps needs minimal assist
( ) 0 needs assistance to keep from falling/unable to try

13. STANDING UNSUPPORTED ONE FOOT IN FRONT
INSTRUCTIONS: (DEMONSTRATE TO SUBJECT) Place one foot directly in front of the other. If you feel that you cannot place your foot directly in front, try to step far enough ahead that the heel of your forward foot is ahead of the toes of the other foot. (To score 3 points, the length of the step should exceed the length of the other foot and the width of the stance should approximate the subject's normal stride width)
( ) 4 able to place foot tandem independently and hold 30 seconds
( ) 3 able to place foot ahead of other independently and hold 30 seconds
( ) 2 able to take small step independently and hold 30 seconds
( ) 1 needs help to step but can hold 15 seconds
( ) 0 loses balance while stepping or standing

14. STANDING ON ONE LEG
INSTRUCTIONS: Stand on one leg as long as you can without holding.
( ) 4 able to lift leg independently and hold >10 seconds
( ) 3 able to lift leg independently and hold 5-10 seconds
( ) 2 able to lift leg independently and hold = or >3 seconds
( ) 1 tries to lift leg unable to hold 3 seconds but remains standing independently
( ) 0 unable to try or needs assist to prevent fall

TOTAL SCORE (Maximum = 56: _____

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Appendix 3.
Two Minute Walking Scale

Multiple Sclerosis Outcome Measures Taskforce
Compendium of Instructions for Outcome Measures

INSTRUMENT NAME: 2 Minute Walk Test

REVIEWER: Amy M. Yorke, PT, NCS

GENERAL INFORMATION:

- The 2 Minute Walk Test (MWT) is a submaximal measure of gait velocity and endurance – distance walked in 2 minutes
- Other versions include different time duration of test (3, 5, 6, 10, and 12 minutes)
- Minute walk tests have been used in various patient populations (e.g., neuromuscular, cardiopulmonary, peripheral vascular disease, cancer, amputation)

EQUIPMENT NEEDED:

- Stopwatch
- Two small cones to mark the turnaround point
- A chair that can be easily moved along the walking course
- Measuring device (e.g. calibrated wheel with counter or a digital measuring wheel)
- Pulse oximeter

ADMINISTRATION INSTRUCTIONS:

Time to administer and score:

- Two practice walks have been recommended prior to measurements secondary to initial training effects[1,2]
- 2 minutes, plus additional time needed for instructions and practice trials (if utilized)

General Rules:

- The 2MWT is a simple test that requires an approximately 100-ft, quiet, indoor, flat, straight rectangular hallway.
- Patient is allowed to wear regular footwear and an assistive device and/or orthotic
- Measurement of HR[3,4], respiratory rate[4,5], SaO_2[4,5], rating of perceived dyspnea (RPD)[4,5] and rating of perceived exertion (RPE)[4,5]

Definitions:

-

Instructions:

- Standardized verbal encouragement may be given at 30-second intervals[6-7] or may not be given[4-5]
- Patient may be instructed to "walk at your comfortable pace"[6-8] or "walk as far as you can"[3] or "walk as fast as you can, but walk safely"[6]

- For safety, a therapist may stand and guard the patient closely without impacting gait speed[3,6-7]
- After completion of the test, the distance walked and the number and duration of rests during the 2 minutes should be measured
- Rest breaks in between trials ranged from up to 2 minutes[5] to at least 30 minutes[4] in between trials

INTERPRETATION GUIDELINES:

- Longer distance walked indicates better performance
- Patient's value can be compared to normative data

Normative Data:

- In a group of 50 patients with MS, those patients with EDSS scores 1.5-4.0 ambulated 173 m ± 31 (40-172). Patients with EDSS scores 4.5-6.5 ambulated 104 m ± 41 (40-172).[5]

COPYRIGHT INFORMATION:

- Not applicable

WEB BASED RESOURCES / INFORMATION:

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Appendix 4.
Timed 25 Feet Walking test

Multiple Sclerosis Outcome Measures Taskforce
Compendium of Instructions for Outcome Measures

INSTRUMENT NAME: Timed 25-Foot Walk

REVIEWER: Diane D. Allen, PhD, PT

GENERAL INFORMATION:

- The Timed 25-foot walk (T25FW) is one of a number of measures of gait velocity. Similar measures include timed walks of 10 meters[1] or 30 feet. The instructions may be for self-selected walking speed or fastest safe walking speed. Time may be recorded manually with a stop watch or via more mechanized equipment such as photocells. Frequently, the course is set so that the individual walks a total of 35 feet (14 meters[1]): 5 feet (or 2 meters) prior to the beginning of the timed course and 5 feet (or 2 meters) after the end of the timed course, to minimize the acceleration/deceleration period within the recorded time.

EQUIPMENT NEEDED:

- Measured distance for a walking course and a stop watch or other timing device.

ADMINISTRATION INSTRUCTIONS:

Time to administer and score: Seconds

General Rules:

-

Definitions:

-

Instructions:

- A straight, level walking course is clearly marked, with 5 feet allowed before and after the 25 foot course for acceleration and deceleration. The participant is instructed to walk to the end of the entire course "at normal speed" (for comfortable or self-selected or normal gait speed) or "as fast as you can safely" (for fast gait). Record the number of seconds it takes to walk the 25 foot course (excluding the time it takes to accelerate and decelerate before and after the 25 feet). Record whether the participant had a practice walk before recording, and whether the score is for a single trial, the best of 2-3 trials, or the mean of 2-3 trials. (Instructions when used as part of the Multiple sclerosis functional composite are to walk "as quickly as possible, but safely"; the score is the mean of 2 trials.)

Scoring:

- Scored in seconds: higher numbers mean slower gait speed.

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Timed 25-Foot Walk

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- When converted to velocity in meters/second or centimeters/second, higher numbers mean faster gait speed.

INTERPRETATION GUIDELINES:

- Normative data for healthy males, females in different decades between ages 20 and 70 have been published for the 25-foot walk at comfortable (130-146 cm/sec) and maximum (175-253 cm/sec) speeds.[2]
- Median T25FW in 64 healthy controls (age 38.6 years, SD 11.8) was 4.4 seconds (SD = .6 seconds).[3]

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WEB BASED RESOURCES / INFORMATION:

- http://www.nationalmssociety.org/for-professionals/researchers/clinical-study-measures/t25-fw/index.aspx

REFERENCES:

1. Paltamaa J, West H, Sarasoja T, Wikstrom J, Malkia E. Reliability of physical functioning measures in ambulatory subjects with MS [corrected] [published erratum appears in PHYSIOTHER RES INT 2006;11(2):123]. *Physiother Res Int.* 2005;10(2):93-109.
2. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. *Age Ageing.* 1997;26(1):15-19.
3. Nieuwenhuis MM, Van Tongeren H, Sørensen PS, Ravnborg M. The six spot step test: a new measurement for walking ability in multiple sclerosis. *Mult Scler.* 2006;12(4):495-500.

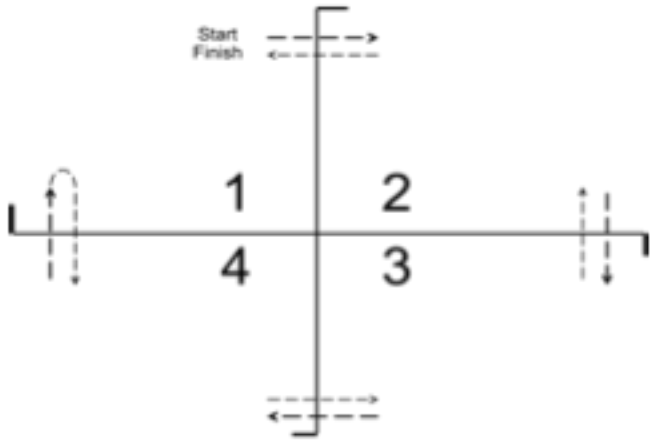
Appendix 5.
Four Square Step Test

Four Step Square Test Instructions

General Information:

- The patient is instructed to stand in square 1 facing square number 2 (see figure below)
- The patient is required to step as fast as possible into each square in the following sequence: 2, 3, 4, 1, 4, 3, 2, and 1
  - requires the patient to step forward, backward, and sideway to the right and left
- Equipment required for the FSST includes a stopwatch and 4 canes.

Set-up (derived from Dite and Temple 2002): A square is formed with the 4 canes by resting them flat on the floor.



Patient Instructions (derived from Dite and Temple 2002):

- "Try to complete the sequence as fast as possible without touching the sticks. Both feet must make contact with the floor in each square. If possible, face forward during the entire sequence."
- Demonstrate the sequence to the patient.
- Ask the patient to complete one practice trial to ensure the patient knows the sequence. Repeat the trial if the patient is unsuccessful

at completing the sequence, loses balance, or contacts a cane during the trial.
- Two FSST are completed with the best time taken as the score.
- A score is still provided if the patient is unable to face forward during the entire sequence.

Scoring:
- the best time of two FSST is the score
- stopwatch starts when the first foot contacts the floor in square 2
- stopwatch finishes when the last foot comes back to touch the floor in square 1

Four Step Square Test (FSST)

Name:_____

Assistive Device and/or Bracing Used:_____

Date:_____

Trial 1_____sec.___ Trial 1_____sec.___

FSST Score (best timed trial):_____sec.___

Date:_____

Trial 1_____sec.___ Trial 1_____sec.___

FSST Score (best timed trial):_____sec.___

Date:_____

Trial 1_____sec.___ Trial 1_____sec.___

FSST Score (best timed trial):_____sec.___

Date:_____

Trial 1_____sec.___ Trial 1_____sec.___

FSST Score (best timed trial):_____sec.___

Appendix 6.
Box and Blocks Test

NeurologySection

Multiple Sclerosis Outcome Measures Taskforce
Compendium of Instructions for Outcome Measures

INSTRUMENT NAME: Box and Blocks Test

REVIEWER: Evan Cohen, PT, MA, PhD, NCS

GENERAL INFORMATION:
- The Box and Blocks Test (BBT) is a test of manual dexterity.

EQUIPMENT NEEDED:
- A Box and Blocks testing unit
  - The wooden box with two equally-sized compartments separated by a 15.2 cm high divider
  - 150 wooden blocks (1"-square)
  - A stopwatch or timer

ADMINISTRATION INSTRUCTIONS:
Time to administer and score: The test for each hand takes one minute.

General Rules:
- Please see the article by Mathiowetz et al cited below for detailed instructions.

Definitions:
- N/A

Instructions:
- The patient has one minute to move as many blocks as possible, one at a time, from one compartment to the other.

Scoring:
- The score is the number of blocks transferred, with a score recorded separately for each hand.

INTERPRETATION GUIDELINES:
- Normative data is available.

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- N/A

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Box and Blocks Test

NeurologySection

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WEB BASED RESOURCES / INFORMATION:

- Box and Block test kits are available at http://www.pattersonmedical.com/app.aspx?cmd=get_product&id=79848 and other rehabilitation equipment sellers.

REFERENCES:

1. Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the Box and Block Test of manual dexterity. *Am J Occup Ther*. Jun 1985;39(6):386-391.

Appendix 7.
Nine Hole Peg Test

NeurologySection

Multiple Sclerosis Outcome Measures Taskforce
Compendium of Instructions for Outcome Measures

INSTRUMENT NAME: 9-Hole Peg Test (9HPT)

REVIEWER: Kathleen Brandfass, MS PT

GENERAL INFORMATION:

- 9HPT is timed test of upper extremity fine motor function.

EQUIPMENT NEEDED:

- 9HPT apparatus (available through the Rolyan 9 Hole Peg Test disturbed by Smith and Nephew Inc.) , stop watch.

ADMINISTRATION INSTRUCTIONS:

Time to administer and score: 5 to 10 minutes

General Rules:

- Both dominant and non-dominant hands are tested. Dominant hand is tested first. The apparatus is placed on a table with the well positioned on the side of the hand to tested

Definitions:

- 9HPT scores are based on the time it takes to complete the test activity.

Instructions:

- Administrator instructs the person performing the test to pick up the 9 pegs individually from the well and place the pegs one at a time into the holes and return them individually to the well.

Scoring:

- Timing is initiated when the person touches the first peg and is stopped when the person places the last peg back in the container. Test for each hand repeated twice.

INTERPRETATION GUIDELINES:

- Time is recorded for two successful trials; if person is unable to complete trial this is recorded by the test administrator.
- Healthy Sample Norms: (Grice et al, 2003)

Mean and Standard Deviation of Male (n = 314) & Female Participant's (n = 389)					
Male					
Age	***n***	**mean -right**	**mean -left**	**SD -right**	**SD -left**
21–25	41	16.41	17.5	1.65	1.73

26–30	32	16.88	17.84	1.89	2.22
31–35	31	17.54	18.47	2.70	2.94
36–40	32	17.71	18.62	2.12	2.30
41–45	30	18.54	18.49	2.88	2.42
46–50	30	18.35	19.57	2.47	2.69
51–55	25	18.9	19.84	2.37	3.10
56–60	25	20.90	21.64	4.55	3.39
61–65	24	20.87	21.60	3.50	2.98
66–70	14	21.23	22.29	3.29	3.71
71+	25	25.79	25.95	5.60	4.54
All Male	**314**	**18.99**	**19.79**	**3.91**	**3.66**
Female					
21–25	43	16.04	17.21	1.82	1.55
26–30	33	15.90	16.97	1.91	1.77
31–35	32	16.69	17.47	1.70	2.13
36–40	35	16.74	18.16	1.95	2.08
41–45	37	16.54	17.64	2.14	2.06
46–50	45	17.36	17.96	2.01	2.30
51–55	42	17.38	18.92	1.88	2.29
56–60	31	17.86	19.48	2.39	3.26
56–60	31	17.86	19.48	2.39	3.26
61–65	29	18.99	20.33	2.18	2.76
66–70	31	19.90	21.44	3.15	3.97
71+	31	22.49	24.11	6.02	5.66
All Female	**389**	**17.67**	**18.91**	**3.17**	**3.44**

COPYRIGHT INFORMATION:

- none

WEB BASED RESOURCES / INFORMATION:

National MS Society web site: www.nmss.org

REFERENCES:

1.Grice KO, Vogel KA,Mitchell A, Muniz S, Vollmer MA. Adult norms for a commercially available nine hole peg test for finger dexterity. Amer J Occup Ther 2003;53:570-573.
2. Mathiowetz V, Weber K, Kashman N, Volland G. Adult norms for the Nine Hole Peg Test of finger dexterity. Occup Ther J Res 1985; 5:24-38.

Appendix 8.
The Short Form 36 Health Survey Questionnaire (SF-36)

NeurologySection

Multiple Sclerosis Outcome Measures Taskforce
Compendium of Instructions for Outcome Measures

INSTRUMENT NAME: Short Form Health Survey of the Medical Outcome Study (SF-36)

REVIEWER: Susan E. Bennett, PT, DPT, EdD, NCS, MSCS

GENERAL INFORMATION:

- Generic measurement developed to measure health-related quality of life in patients and healthy persons. Consists of 8 sub-scales that are often used separately as outcome measures of various aspects of health-related-quality of life. It measures two main health concepts: physical and mental.

EQUIPMENT NEEDED:

- Pencil
- Survey

ADMINISTRATION INSTRUCTIONS:

Time to administer and score: 30 minutes

General Rules:

- Patient has to have the ability to adequately fill out the questionnaire, or have a proxy assist in completion.

Definitions:

-

Instructions:

- Patient or proxy has to fill out the questionnaire accurately.

Scoring:

- Nominal (yes/no) or ordinal scale, each response given a number of points.
- Each of the items are weighted and therefore software used to compile scores
- 8 sub-scales, all items are coded and transformed into percentage ranging from 0 (poor health) to 100 (optimal health)
  - Physical functioning (10 items)
  - Role limitations because of physical health (4 items)
  - Bodily pain (2 items)
  - Social functioning (2 items)
  - General mental health covering psychological distress and well-being (5 items)
  - Role limitations because of emotional problems (3 items)
  - Vitality, energy or fatigue (4 items)
  - General health perceptions (5 items)

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Short Form Health Survey of the Medical Outcome Study (SF-36)

- Change in health status in the past year (1 item)

INTERPRETATION GUIDELINES:

- Physical functioning in the SF-36 negatively and significantly correlated with duration of MS from onset (r= -0.37; p < 0.001) (Krokavcova)
- In patients with relapse remitting MS there was a relative risk of 1.9 (95% CI, 1.0 to 3.5) for experiencing a worsening EDSS score between those who evaluated their health as poor or fair versus those who evaluated their health as good, very good, or excellent. (Nortvedt 2)
- In an MS population a significant floor effect was seen in those people who walked with an aid (14.2%) and those who used wheelchairs (67.8%). (Riazi)
- There was a nine-fold decrease in physical function scores between patients with MS who walked independently and those who used a wheelchair. (Riazi)
- Less physically disabled individuals had significantly higher scores (p<0.05) on all SF- 36
- Is not a needs assessment tool, requires further investigation for actual management.
- Has limited validity as a measure of mental health in multiple sclerosis. Evidence shows that it underestimates the impact of multiple sclerosis on mental health.
- Patient variability
- Large floor and ceiling effects that do not differentiate between the dimensions of the disease (Freeman)
- Small effect size shows the responsiveness of the SF-36 to be poor in evaluating the effectiveness of inpatient rehabilitation in people with moderate to severe disability. (Freeman)

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-

WEB BASED RESOURCES / INFORMATION:

-

REFERENCES:

1. Dallmeijer A, Groot V, Roorda L, et al. Cross-diagnostic validity of the SF-36 physical functioning scale in patients with stroke, multiple sclerosis and amyotrophic lateral sclerosis: A study using rasch analysis. *J Rehabil Med*. 2007; 39: 163-169.
2. Krokavcova M, Dijk J, Nagy I, et al. Perceived health status as measured by the SF-36 in patients with multiple sclerosis: a review. *Scand J Caring Sci*. 2009; 23: 529-538.
3. Nortvedt M, Riise T, Myhr KH, et al. Performance of the SF-36, SF-12, and RAND-36 Summary Scales in a Multiple Sclerosis Population. *Medical Care*. 2000; 38(10): 1022-1028.

Short Form Health Survey of the Medical Outcome Study (SF-36)

Appendix 9.
Disabilities of the Arm, Shoulder and Hand (DASH)

Disabilities of the Arm, Shoulder and Hand

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. Open a tight or new jar.	1	2	3	4	5
2. Write.	1	2	3	4	5
3. Turn a key.	1	2	3	4	5
4. Prepare a meal.	1	2	3	4	5
5. Push open a heavy door.	1	2	3	4	5
6. Place an object on a shelf above your head.	1	2	3	4	5
7. Do heavy household chores (e.g., wash walls, wash floors).	1	2	3	4	5
8. Garden or do yard work.	1	2	3	4	5
9. Make a bed.	1	2	3	4	5
10. Carry a shopping bag or briefcase.	1	2	3	4	5
11. Carry a heavy object (over 10 lbs).	1	2	3	4	5
12. Change a lightbulb overhead.	1	2	3	4	5
13. Wash or blow dry your hair.	1	2	3	4	5
14. Wash your back.	1	2	3	4	5
15. Put on a pullover sweater.	1	2	3	4	5
16. Use a knife to cut food.	1	2	3	4	5
17. Recreational activities which require little effort (e.g., cardplaying, knitting, etc.).	1	2	3	4	5
18. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	1	2	3	4	5
19. Recreational activities in which you move your arm freely (e.g., playing frisbee, badminton, etc.).	1	2	3	4	5
20. Manage transportation needs (getting from one place to another).	1	2	3	4	5
21. Sexual activities.	1	2	3	4	5

Disabilities of the Arm, Shoulder and Hand

	NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
22. During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups? *(circle number)*	1	2	3	4	5

	NOT LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
23. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem? *(circle number)*	1	2	3	4	5

Please rate the severity of the following symptoms in the last week. *(circle number)*

	NONE	MILD	MODERATE	SEVERE	EXTREME
24. Arm, shoulder or hand pain.	1	2	3	4	5
25. Arm, shoulder or hand pain when you performed any specific activity.	1	2	3	4	5
26. Tingling (pins and needles) in your arm, shoulder or hand.	1	2	3	4	5
27. Weakness in your arm, shoulder or hand.	1	2	3	4	5
28. Stiffness in your arm, shoulder or hand.	1	2	3	4	5

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
29. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? *(circle number)*	1	2	3	4	5

	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
30. I feel less capable, less confident or less useful because of my arm, shoulder or hand problem. *(circle number)*	1	2	3	4	5

DASH DISABILITY/SYMPTOM SCORE = $\left[\frac{(\text{sum of n responses})}{n} - 1\right] \times 25$, where n is equal to the number of completed responses.

A DASH score may not be calculated if there are greater than 3 missing items.

DISABILITIES OF THE ARM, SHOULDER AND HAND

WORK MODULE (OPTIONAL)

The following questions ask about the impact of your arm, shoulder or hand problem on your ability to work (including home-making if that is your main work role).

Please indicate what your job/work is:_____

❒ I do not work. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week. Did you have any difficulty:

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for your work?	1	2	3	4	5
2. doing your usual work because of arm, shoulder or hand pain?	1	2	3	4	5
3. doing your work as well as you would like?	1	2	3	4	5
4. spending your usual amount of time doing your work?	1	2	3	4	5

SPORTS/PERFORMING ARTS MODULE (OPTIONAL)

The following questions relate to the impact of your arm, shoulder or hand problem on playing your musical instrument or sport or both. If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you.

Please indicate the sport or instrument which is most important to you:_____

❑ I do not play a sport or an instrument. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week. Did you have any difficulty:

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for playing your instrument or sport?	1	2	3	4	5
2. playing your musical instrument or sport because of arm, shoulder or hand pain?	1	2	3	4	5
3. playing your musical instrument or sport as well as you would like?	1	2	3	4	5
4. spending your usual amount of time practising or playing your instrument or sport?	1	2	3	4	5

SCORING THE OPTIONAL MODULES: Add up assigned values for each response; divide by 4 (number of items); subtract 1; multiply by 25.
An optional module score may not be calculated if there are any missing items.

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Appendix 10.
Twelve Item Multiple Sclerosis Walking Scal

Twelve Item MS Walking Scale (MSWS-12)

Record form

Subject ID Number | Subject Initials | Date Questionnaire Completed: Day / Month / Year

If you cannot walk at all, please tick this box ☐

In the past two weeks, how much has your MS . . .	Not at all	A little	Moderately	Quite a lot	Extremely
1. Limited your ability to walk?	1	2	3	4	5
2. Limited your ability to run?	1	2	3	4	5
3. Limited your ability to climb up and down stairs?	1	2	3	4	5
4. Made standing when doing things more difficult?	1	2	3	4	5
5. Limited your balance when standing or walking?	1	2	3	4	5
6. Limited how far you are able to walk?	1	2	3	4	5
7. Increased the effort needed for you to walk?	1	2	3	4	5
8. Made it necessary for you to use support when walking indoors (eg holding on to furniture, using a stick, etc.)?	1	2	3	4	5
9. Made it necessary for you to use support when walking outdoors (eg using a stick, a frame, etc.)?	1	2	3	4	5
10. Slowed down your walking?	1	2	3	4	5
11. Affected how smoothly you walk?	1	2	3	4	5
12. Made you concentrate on your walking?	1	2	3	4	5

From the numbers you circle against these questions, your healthcare professional can calculate your MSWS-12 score. This is done by adding the numbers you have circled, giving a total out of 60, and then transforming this to a scale with a range from 0 to 100. Higher scores indicate a greater impact on walking than lower scores.

To be completed by the healthcare professional

Total score _____ out of 60

Percentage _____ %

Mobility Matters in MS

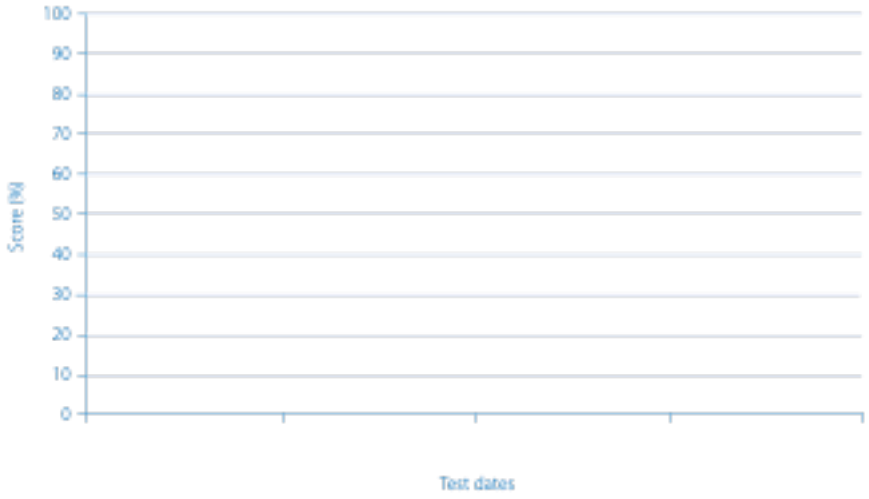
Twelve Item MS Walking Scale (MSWS-12)

Graph – Patient Progress Over Time

Subject ID Number | Subject Initials | First Visit Date: Day | Month | Year

Use the graphs below to plot the percentage score from the questionnaire at each visit. The higher the score/percentage, the greater the perceived impact MS is having on walking ability. A change will be indicated by a reduction or increase in the score over time.

Twelve Item MS Walking Scale



Mobility Matters in MS

Appendix 11.
Manual Ability Measurement

Manual Ability Measurement, MAM-36

Please choose one response regarding how easy or how hard it is for you to perform the following tasks, regardless which hand being used and without using assistive devices.

Easy (4)= I can do the activity without any problem.

A little hard (3)= I usually do the task myself, although it takes longer or more effort now than before (i.e., before the current diagnosis/condition/disability). Sometimes, there is pain or discomfort when I do the task.

Very hard (2)= It is very hard for me to do the task and I usually ask others to do it for me unless no one is around.

Cannot do (1)= I am unable to do the task all by myself.

Almost never do (0)= I have not or almost will never do the task, even though I think I can do it.

( ) Eat a sandwich.
( ) Drink a glass of water.
( ) Pick up a half full water pitcher.
( ) Use a spoon or fork.
( ) Butter bread (Put butter or jam on the bread).
( ) Cut meat on a plate with a knife.
( ) Squeeze toothpaste.
( ) Brush teeth.
( ) Brush or comb hair.
( ) Wash hands.
( ) Wring a towel.
( ) Zip pants.
( ) Zip a jacket.
( ) Button clothes.
( ) Fasten a clothes snap or hook.
( ) Cut nails with a nail clipper.
( ) Tie shoes with laces.
( ) Use a remote control.
( ) Key in telephone numbers.
( ) Turn door knob to open a door.
( ) Turn key to open a lock.
( ) Carry a shopping bag with a hand loop.
( ) Open a previously opened wide-mouth jar (jam, pickle).
( ) Open a previously unopened carton box (milk or cereal).

( ) Pour liquid from a bottle into a glass.
( ) Open a medication bottle with child-proof top.
( ) Open an envelop without a letter opener
( ) Peel vegetables or fruits.
( ) Count/handle money (bills and coins).
( ) Take things out of a wallet (bills, papers, credit cards).
( ) Write 3 to 4 sentences legibly.
( ) Turn pages of a book.
( ) Shuffle and deal cards.
( ) Use a hammer or screwdriver.
( ) Fold clothes after laundering.
( ) Take a CD/DVD out of its case and put it into a player/drive.

Internal agreements

- The MAM-36 is preferably handed to patient for self-completion; if impossible administer the questionnaire by interview.
- Item 30: take things out of a wallet (bills, papers, credit cards): examples of papers are driver's license, identity card, …
- Item 11: a towel may also be washcloth, floor cloth, cleaning cloth, …

Appendix 12.
System Usability Scale

Participant ID: _____ Site: _____ Date: ___/___/___

System Usability Scale

Instructions: For each of the following statements, mark one box that best describes your reactions to the website *today*.

		Strongly Disagree				Strongly Agree
1.	I think that I would like to use this website frequently.	☐	☐	☐	☐	☐
2.	I found this website unnecessarily complex.	☐	☐	☐	☐	☐
3.	I thought this website was easy to use.	☐	☐	☐	☐	☐
4.	I think that I would need assistance to be able to use this website.	☐	☐	☐	☐	☐
5.	I found the various functions in this website were well integrated.	☐	☐	☐	☐	☐
6.	I thought there was too much inconsistency in this website.	☐	☐	☐	☐	☐
7.	I would imagine that most people would learn to use this website very quickly.	☐	☐	☐	☐	☐
8.	I found this website very cumbersome/awkward to use.	☐	☐	☐	☐	☐
9.	I felt very confident using this website.	☐	☐	☐	☐	☐
10.	I needed to learn a lot of things before I could get going with this website.	☐	☐	☐	☐	☐

Please provide any comments about this website: