THE EFFECTS OF EXERCISE THERAPY ON PROPRIOCEPTION IN PATIENTS WITH MULTIPLE SCLEROSIS: A SYSTEMATIC REVIEW

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A Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of MSc (Med) in Biokinetics by dissertation.

Johannesburg, 2025

Declaration

I, Bokamoso Mthimkulu, declare that this dissertation is my own, unaided work. It is being submitted for the MSc (Med) in Biokinetics by dissertation at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Bokamoso Mthimkulu _____ 

Name of candidate Signature of candidate

09 day of September 20 25 in Sandton

Dedication

I dedicate this study to all the Multiple Sclerosis (MS) warriors working hard to have a normal life. Also, to my parents who have supported me throughout my MS journey. I know it has been challenging for me; I cannot imagine how it must be for them. Specifically, to my mother, Nthabiseng Motsepe, who started this journey with me, and is still by my side every step of the way. I promise to make you proud and help impact more lives and be a support to others exactly how you have been for me. You inspire me to be a better person. To my friends, and teammates for being considerate of the symptoms and off-days I experience. Your support will never go unnoticed.

To my doctors, Dr. Dominic Giampaolo (Neurologist), Dr. Heidi Frere (Integrative General Practitioner), Lindsay Dale (Psychologist), Dr. Thriya Ramasar (Psychiatrist), your support on my health journey will never go unnoticed. Thank you for picking me up when I was too tired to keep going. Lastly, I dedicate this to a special woman I had the opportunity of assisting as a Biokinetics professional, Moira Kolbe. Being a part of your MS journey was a blessing. You helped me establish my passion in helping people with MS have a few more years of independence. Your smile and laugh will always be remembered.

Acknowledgments

Dr. Natalia Neophytou, my supervisor, for helping me refine my topic and being my main supporter throughout the whole process.

Dr. Merling Phaswana, supervisor, for cheering me on when I felt like giving up. Her support got me through the challenging days.

Prof. Philippe Gradidge, supervisor, for guiding me on how to formulate a systematic review.

Elelwani Daphney Nevhufumba, Biokineticist, for explaining how to register and structure my systematic review.

Mr Devind Peter, The University of Witwatersrand Librarian, for assisting me with developing the search terms for the review.

Mr David Khumalo, PhD candidate, for assisting me with formatting the tables and figures.

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List of Abbreviations

ABC: Activities-specific Balance Confidence Scale
ACSM: American College of Sports Medicine
BT: Balance Therapy
BAL: Balance
BPNSF: Basic Psychological Need Satisfaction and Frustration
BBS: Berg Balance Scale
BBB: Blood-brain barrier
CV: Cardiovascular
CNS: Central nervous system
CSF: Cerebrospinal fluid
CIS: Clinically Isolated Syndrome
CBT: Cognitive Behavioural Therapy
CERT: Consensus on Exercise Reporting Template
C: Control group
CYC: Cycling
DMTs: Disease-modifying therapies
EBV: Epstein-Barre Virus
EXE: Exergaming
EXP: Experimental Group
HIT: High-intensity training
IMU: Inertial Measurement Units
INPLASY: International Platform of Registered Systematic Reviews and Meta-analysis Protocols
JBI: Joanna Briggs Institute
JC: John Cunningham
MRI: Magnetic Resonance Imaging
MBI: Modified Barthel Index
MFIS: Modified Fatigue Impact Scale
MSQoL-54: MS Quality of Life 54-Item Version
MSIS-29: Multiple Sclerosis Impact Scale
MusiQoL: Multiple Sclerosis International Quality of Life
MS: Multiple Sclerosis
MBP: Myelin basic protein

NMES: Neuromuscular Electrical Stimulation

NOS: Nitric Oxide Synthase

PICO: Population, Intervention, Comparators, Outcome

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols

PPMS: Primary Progressive Multiple Sclerosis

PML: Progressive Multifocal Leukoencephalopathy

PNF: Proprioceptive Neuromuscular Facilitation

PLP: Proteolipid protein

QoL: Quality of life

RCT: Randomized control trial

ROM: Range of motion

RRMS: Relapsing-Remitting Multiple Sclerosis

SPMS: Secondary Progressive Multiple Sclerosis

SOT: Sensory Organization Balance Test

SA: South Africa

TAT: Tinetti Assessment Tool

WBV: Whole-body Vibration

WHO: World Health Organisation

List of Definitions

Balance is defined as the ability to maintain and restore postural equilibrium during daily activities (1). It is a motor skill that involves the integration of sensory, motor, and cognitive systems to ensure postural stability (1).

Exercise therapy is defined as physical activity that is directed at postural corrections, the improvement or restoration of musculoskeletal function, and the maintenance of a healthy state of well-being (2). It is prescribed by a qualified health practitioner who specialises in exercise physiology and is mainly used by persons with injuries and/or an illness that affects their overall physical function and wellbeing (2).

Multiple Sclerosis is defined as an autoimmune neurodegenerative chronic disease that causes damage to the myelin sheath found around the axons of neurons leading to slower nerve impulses to and from the central nervous system (CNS) affecting communication between the sensory and motor systems (3–5).

Proprioception is defined as the ability of the body to detect the direction, motion, and position of muscles, joints, tendons, skin, and fascia in one part of the body relative to another part, as well as to its immediate environment (6–9).

Quality of life is defined as a state of well-being (physical, emotional, and social) that does not include the absence of disease (10). This definition is provided by the World Health Organisation (WHO) defining health.

1 Introduction

1.1 Background

Multiple Sclerosis (MS) is an autoimmune chronic disease that slows down the speed of nerve impulses in the central nervous system (CNS) by damaging the myelin sheath found around the axons of neurons (3–5). According to the Multiple Sclerosis International Federation, MS affects 2.9 million people worldwide and 4685 people in South Africa (SA) (11). Four forms of MS can be found: “Clinically Isolated Syndrome (CIS), Relapsing-Remitting (RRMS), Primary-Progressive (PPMS), and Secondary-Progressive (SPMS)” (3,12,13). The common form of MS, affecting 85% of patients, is RRMS which is characterised by periods of attacks and remission (3,14). Patients with RRMS may develop SPMS, which is characterised by the continuous decline in function that may lead to disability and death (3,14). Primary-Progressive MS is like SPMS, and it affects 15% of the MS population (3,14). Common symptoms experienced by MS patients affect the motor and sensory systems (15). These include visual impairments, muscle weakness, balance deficits, walking deficits, temperature and pressure changes, and memory loss (5,15,16). The effect of MS on the motor and sensory systems can impact the patient’s overall quality of life (QoL) related to their physical, social, and emotional well-being (17).

Injury to the nervous system, as seen in MS, can negatively impact sensory systems. Proprioception is one system that is affected through slowed nerve impulses, disrupted communication between nerves, and inaccurate body representations resulting in an increased risk of falls, and injuries experienced by individuals (9,18). Sensory impairments that impact proprioception, such as muscle weakness, tingling, numbness, and pain in the extremities, affect 80% of MS patients (19). Alterations in proprioception have been linked to decreased walking speed, postural control, and balance, and thus a reduced QoL of MS patients compared to healthy individuals has been observed (20–23). Proprioception is thus a key sensory system impacting balance and QoL in MS patients. Improving proprioception allows for more accurate representations of the body in the CNS enhancing an individual’s sense of self within their environment (internal and external), especially MS patients (9,18). This may be achieved with exercise therapy.

Management strategies that involve exercise therapy have positively impacted MS patients’ QoL through improved aerobic fitness, strength, cognition, walking ability, and efficiency, as

well as reduced fatigue, depressive symptoms, and stress (3,24–26). Studies done by Lozinski et al., (2022) and Rocca et al., (2024) provided evidence that exercise therapy influenced cortical brain matter and induced neuroplasticity of white matter structures in MS patients (27,28). This translated to improved motor control, energy levels, and balance (4,5). A qualitative study done by Carling et al., (2018) evaluated the role of core training in improving the balance and QoL of patients with MS. They concluded that training the core improves the balance and QoL of patients with MS (4). As proprioception is part of the sensory system, integrating sensory input into exercise therapy may result in clinically significant improvements in proprioceptive accuracy, providing MS patients with better balance, and QoL (29–32).

Studies have researched the effects of exercise therapy combined with proprioceptive training in the 21st century. What they found was enhanced proprioceptive accuracy in MS patients due to the stimulation of multiple CNS systems simultaneously (29–32). An example of how this has been achieved is by combining sensory stimuli and/or multitasking activities along with exercise (29–32). Hortobágyi et al., (2022), Prosperini et al., (2010), and Tosun et al., (2021) used Xbox gaming systems and other forms of visual input, showing improved QoL, gait parameters, and reduced falls in their participants. Tramontano et al., (2024) and Gandolfi et al., (2015) instructed their participants to perform an exercise with interference from additional sensory input. They found improvements in overall QoL in their participants.

Proprioception and exercise therapy have an immediate effect on the QoL of MS patients, and thus, working to improve proprioceptive accuracy using exercise may provide patients with therapeutic improvements. This is similar to studies analysing healthy populations where the effects of exercise therapy on proprioception for injury prevention and QoL showed improvements in proprioceptive accuracy and physical function (33,34). Limited research on the direct relationship between exercise therapy and proprioception in MS patients was found resulting in an intricate gap of knowledge on this topic (35). Documentation of systematic reviews were searched on INPLASY and PROSPERO. Further studies were searched on PubMed, CINAHL ultimate, ProQuest Central, SPORTDiscus, and SCOPUS. Understanding the connection between exercise and proprioception in individuals with MS will enable therapists to improve exercise management plans for their patients worldwide (35). A review on exercise therapy's effect on proprioception in individuals with MS has not yet been published, emphasising the need to critically review studies available on this topic (35). This

topic was chosen by the author after an incident where a sports player with MS had injured her ankle without any physical contact from another player.

1.2 Problem Statement

Proprioception plays an important role in building precise body images in the CNS that facilitate an individual's ability to enhance their conscious and unconscious body awareness, leading to better motor control and balance (9,18). Since MS impacts the integrity of the nerves located in the CNS, proprioception can be negatively impacted affecting the overall QoL of patients (36). The implementation of exercise therapy, which may include both proprioception-specific exercises and traditional muscle-strengthening exercises, has been shown to effectively lessen the risk of falls among individuals with MS (31,35,37). Consequently, these interventions contributed to an enhancement in the overall QoL experienced by patients. However, few studies have documented the implementation of exercise therapy in isolation to directly influence proprioception, as a primary outcome measure and therefore, improve the overall QoL of MS patients. Thus, the relationship between exercise and proprioception in MS patients worldwide needs to be highlighted. This will also be a stepping stone for exercise therapy for MS patients in SA, which has not been widely studied.

Compared to the worldwide statistics, only 4685 people of 2.9 million have been diagnosed with MS in SA (11). It is assumed that this low incidence rate has not brought enough interest to study the disease amongst South Africans leading to fewer available studies in this region (38,39). In SA, most studies have been concerned with understanding the epidemiology, and challenges associated with diagnosis and treatment, with very few analysing the impact exercise therapy has on proprioception in MS patients (38,39). This provides a gap in understanding the role exercise therapy plays in SA, leaving healthcare professionals with limited knowledge of effective management regimens for their patients (38). Implementing exercise therapy in SA may have a positive impact on disease outcomes as it has been shown to be clinically significant in Western countries. More research regarding exercise therapy, particularly exercise therapy on proprioception, on MS patients in SA is needed as it will allow for a more accurate understanding of how MS affects South Africans (38). Additionally, this will add to the body of knowledge worldwide providing other countries with information on how exercise therapies affect patients in certain climate regions and ethnic groups.

1.3 Research Question

What is the effect of exercise therapy on proprioception in patients with Multiple Sclerosis? Does improved proprioception lead to improvements in balance and QoL among patients with Multiple Sclerosis?

1.4 Aims and Objectives

This study aims to determine the effect of exercise on proprioception in patients with Multiple Sclerosis. Furthermore, it aims to establish common exercise modalities that have been used that positively or negatively impact proprioception.

The objectives of the study are:

- To identify studies done from 2003 to 2024 that have researched the effects of exercise on proprioception in adult Multiple Sclerosis patients worldwide.
- To systematically review the relevance of the studies identified, using the JBI critical appraisal tool, investigating exercise and proprioception in adult Multiple Sclerosis patients worldwide.
- To highlight and recommend a set of exercise modalities that positively and negatively affect proprioception in adult Multiple Sclerosis patients.

1.5 Rationale and Significance

Impaired balance, postural control, and frequent falls are common symptoms of MS that are closely linked to impaired proprioception (20–23). Increased instability experienced among patients with MS can lead to decreased physical activity as the fear of falling and injury is increased (40). Living a sedentary lifestyle can cause further health complications such as heart conditions, obesity, cancers, diabetes, depression, falls, and cognitive impairment, adding to the health burden in MS patients (41). Working to improve proprioception may be a key step to improving physical activity levels in MS patients mitigating the risk of further health complications and a reduced QoL experienced by patients. Studies have researched the effects of exercise interventions on balance, postural control, and frequent falls and found improvements in the QoL of MS patients (3,24–26). However, few have established the link between proprioception and impairments among MS patients. Reviewing current research establishing this link is imperative to improving the overall QoL of MS patients worldwide.

Conducting a systematic review will assist healthcare professionals and the public in knowing what has been studied in this field and whether the exercise therapy given has proved to be clinically significant for improving proprioception in MS patients worldwide. To date, few studies have investigated the benefit of exercise therapy in SA with none analysing the intricate relationship between proprioception and MS. This review has the potential to allow for more research on this topic in SA and to encourage researchers to study the effect of exercise therapy on proprioception in different diseases, injuries and disorders worldwide.

1.6 Conclusion

The next chapter will explore MS, proprioception, and exercise therapy in greater depth to provide a comprehensive understanding of the role of exercise therapy in addressing proprioceptive impairments in individuals with MS.

1.7 Outline of this Research Report/ Dissertation/ Thesis

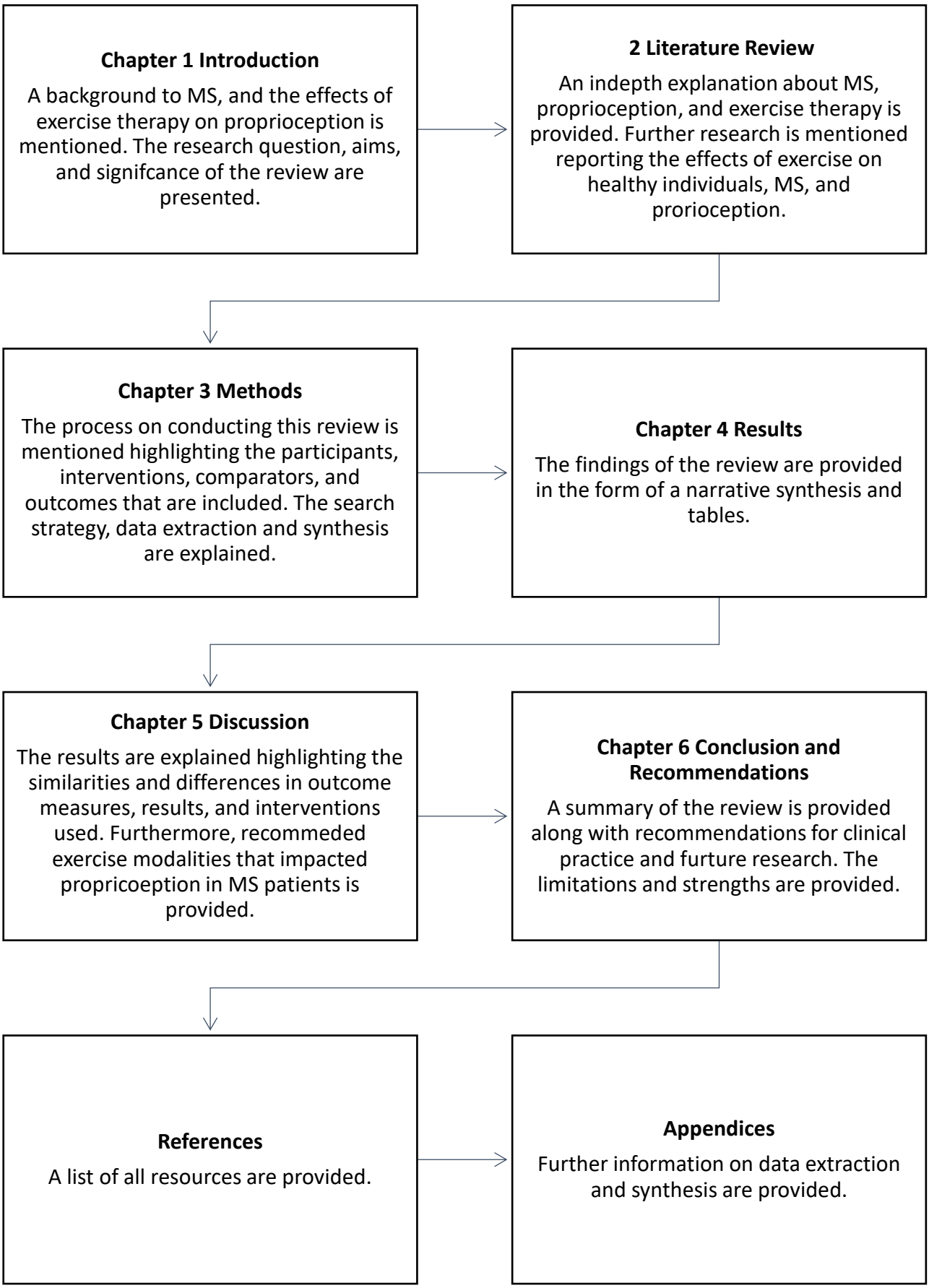

Figure 1. Outline of the thesis

2 Literature Review

2.1 Introduction

This chapter will review the current literature available on MS, its pathophysiology, symptoms, diagnosis, treatment, and management. Understanding how MS affects the body and the common symptoms that are experienced by patients will ensure accurate diagnosis, treatment, and management for patients. Providing an overview of MS will allow the reader to understand what knowledge is available on the disease. As proprioception plays a huge role in the overall quality of life (QoL) of MS patients, understanding what it is and its role in the body in healthy individuals and MS patients will be reviewed. This will help the reader better understand the differences in sensory functioning between both populations reiterating the effects of MS on the patients' QoL. Exercise therapy has emerged as a management strategy for MS patients. The benefits of exercise therapy for healthy individuals and MS patients will be summarised. Additionally, how it impacts proprioception will be summarised. This will provide the reader with knowledge of the role exercise therapy plays in both populations. Exercise therapy's impact on proprioception in MS patients will be reviewed. This combines exercise therapy, proprioception, and MS into one concept providing the reader with an overview of the purpose of this study. The databases that will be searched on include PubMed, SCOPUS, and the Witwatersrand Library. Keywords included MS, pathophysiology, symptoms, diagnosis, treatment, management, exercise, the body, proprioception, receptors, healthy adults.

2.2 Pathophysiology of Multiple Sclerosis

Multiple Sclerosis is inflammatory, mediating an immune response in the CNS (42). The exact cause of MS is not known, but it is suggested that the white blood cells, T helper cells and antibody B cells, play a crucial role in the onset and advancement of MS (13,15,43). T helper cells can become autoreactive and mimic molecules that attack "self-antigens, such as myelin basic protein (MBP) or proteolipid protein (PLP)", which both make up myelin (15). Autoreactive T helper cells also promote the dysfunction of the blood-brain barrier (BBB), increasing its permeability toward extracranial cells, pathogens, and viruses that can easily enter the CNS. The presence of T helper cells in the brain initiates an attack on the myelin sheath surrounding nerves by releasing proinflammatory cytokines and chemokines in the cerebrospinal fluid (CSF) (15). Cytokines and chemokines promote the recruitment of other

immune cells that contribute to the degeneration of oligodendrocytes, a cell responsible for making the myelin sheath. B cell antibodies are produced throughout this process, allowing for the constant attack on the myelin sheath in MS patients (15,43).

Studies have found that the Epstein-Barre Virus (EBV) is the main contributing factor to developing MS, and people who have had the virus at any given point in their lifetime are more likely to develop MS (13). The Epstein-Barre Virus a highly contagious virus that affects 95% of the world population and is contracted through saliva, bodily fluids, and organ transplantation (44). It is theorised that EBV-mediated B cells cross through the BBB and cause the inflammatory series of events that lead to MS disease diagnosis (13). Other factors that have been thought to contribute to the development of MS are vitamin D deficiency, gut microbiome dysfunction, and smoking (13,15,43). These factors will be reviewed below.

2.2.1 *Vitamin D deficiency*

Vitamin D is a fat-soluble vitamin that can be obtained through dietary sources, and supplements, and is produced in the skin through direct exposure to sunlight (45). The functions of vitamin D include supporting bone health and immune function, secreting hormones, and promoting cell growth and specialisation (45,46). When in the bloodstream, vitamin D binds to a specific receptor, known as vitamin D receptor, which allows the vitamin to carry out its functions. Low blood vitamin D levels have been linked to various health conditions, including Rickets, some cancers (namely prostate and colon), heart diseases, psychiatric disorders, infections, and autoimmune diseases such as MS, Diabetes Mellitus (45,47).

A review on vitamin D published by Sintzel et al., (2018) stated the role vitamin D has on the immune system. They found that active forms of vitamin D reduce proinflammatory T helper cell production and the cytotoxic effects of these cells on the body. Furthermore, it hinders the formation of antibodies in the body (45,47). As MS is thought to be caused by proinflammatory T helper cells, it is agreed that low vitamin D levels minimise its effect on the immune system and thus may increase the risk of developing MS (45,47). thus working to improve vitamin D levels is ideal for all populations.

Supplement therapy to increase vitamin D levels may lead to a lessened risk of developing MS and fewer relapses in MS patients. Therefore, prioritising vitamin D treatment is ideal (45,47).

2.2.2 Gut microbiome dysfunction

The gut has been shown to directly link to the CNS through the Vagus nerve. This allows for the intricate communication between the microbial world and the brain and spinal cord. An excess of proinflammatory microbiomes that are active in the gut has been associated with an increase in the immune activity from proinflammatory T helper cells in the brain (48). Multiple Sclerosis patients generally have low levels of *bifidobacteria,* which are known to correlate with increased proinflammatory T helper cells that cause a generalised state of subclinical inflammation in the body (48). It is agreed that improving the gut microbiome may decrease activity from proinflammatory T helper cells slowing down the progression of MS and enhancing the QoL of patients (49). This can be done by implementing certain therapies such as vitamin D and probiotic supplementation, antibiotic administration, and exercise therapy (49,50).

2.2.3 *Smoking*

Smoking is a lifestyle habit that can cause a proinflammatory effect in the body, specifically the lungs (48). When tobacco is burnt, it releases free radicals that are inhaled by the individual. These radicals can cause a proinflammatory immune response in the body, which leads to autoimmunity overtime (51). Auto-aggressive T cells, caused by irritation in the lungs from smoke, may interact with CNS antigens resulting in an autoimmune-mediated CNS attack that has been linked to the development of MS (51). Smoking after being diagnosed with MS has also been associated with a worsened disease progression with more frequent relapses, worsened symptoms, and greater disability (51). Further information on how MS is diagnosed will be discussed next.

2.3 Diagnosis of Multiple Sclerosis

The McDonald criteria was developed as a worldwide standardised diagnostic tool for MS (52,53). Based on the criteria, an individual must have more than two relapses that can be objectively seen during magnetic resonance imaging (MRI) (43,54). The neurologist looks for

the distribution of the lesions as well as the time difference between each lesion to be able to diagnose a person with MS (43,54). Conjunctively, a lumbar puncture may be used in the diagnosis of MS (54). The procedure includes the extraction of CSF from the lumbar spine, which is then tested for the presence of extra cranial immune cells as well as the immune cell composition in the sample (54).

Diagnosing MS in SA is more challenging as many other conditions that are highly prevalent in SA can cause neurological symptoms (55). These conditions include Human Immunodeficiency Virus, Tuberculosis, and Human Simplex Virus (55). Performing an MRI, analysing CSF, and assessing evoked potentials may assist in providing a more accurate diagnosis of MS (55). The neurologist will investigate for white matter lesions that are ovoid and near the “lateral ventricles, potentially in juxtacortical areas, the corpus callosum, the infratentorial area, or the spinal cord” in an MRI (consistent with the McDonald criteria) (55).

In the analysis of CSF, neurologists identify the presence of intrathecal immunoglobulin synthesis, which can be detected either by the “presence of oligoclonal bands or an increased immunoglobulin G index” (55). Oligoclonal bands are most looked for and provide a positive result if there are more than two bands present in the CSF, with none present in the serum sample that is collected. In conjunction with this, they examine evoked potentials that involve the stimulation of a nerve to test the speed and strength of the nerve in demyelinating conditions (55,56). Visual evoked potentials (stimulates the optic nerve), brainstem auditory evoked potentials (stimulate the “cochlear nerve, superior olive, lateral lemniscus, and inferior colliculus”) (55,56), and somatosensory evoked potentials (stimulation of the medial or tibial nerve) are used (55,56), but the visual evoked potentials are commonly used for diagnosing MS in SA, as optic neuritis is one of the common MS symptoms (55,56). Signs and symptoms of MS will be explained below.

2.4 Signs and Symptoms Associated with Multiple Sclerosis

There are no definite signs that a person can have that will classify them with MS and thus, further examination of CSF and the brain matter (via MRI) is required (55). The shapes and sizes of lesions seen on an MRI and the frequency and distribution of new lesions within three months (McDonald criteria), CSF analysis, as well as patient-reported symptoms, aid in a definite diagnosis of MS (55). Due to the inconsistent course of axonal damage each patient

may experience, symptoms and disease severity may differ with each patient making it an unpredictable disease. However, the most common symptoms a patient may experience include fatigue, sensory impairments affecting balance and walking, visual disturbances, trigeminal neuralgia, neuropathic pain and muscle spasms, depression, anxiety, and cognitive impairments (15,57). Sensory impairments, visual disturbances, cognitive impairments, and fatigue will be reviewed below.

2.4.1 Sensory impairments

Sensory impairments are known as abnormal sensations experienced in one or more senses (sight, hearing, taste, smell, touch, spatial awareness) (58). In this section, sensory impairments refer to motor dysfunction resulting from an abnormal sense of touch and spatial awareness, commonly referred to as sensorimotor dysfunction. Approximately 80% of MS patients report sensory disturbances that are attributable to musculoskeletal pain, altered sensations, allodynia, paraesthesia, Lhermitte's sign, dysaesthesia, and trigeminal neuralgia (19). These disturbances cause feelings of burning, sharp, shooting pain in the body, tingling sensations, numbness, pins and needles, and sensitivity to cold touch (19). The location of these symptoms depends on the location of the lesion in the brain and spinal cord (59). In comparison with healthy individuals, MS patients had significantly lower brain volumes and spinal cord composition that correlated with sensory impairment, as seen in a study done by Morozumi et al., (2024) (59).

2.4.2 Visual disturbances

Visual impairments are defined as a reduction in visual acuity and the ability to see objects caused by changes in the performance of the visual system (60). Inflamed eye muscles and the optic nerve is the cause of visual impairments in MS. Optic neuritis is commonly the initial symptom MS patients experience, with 40% of cases being reported (61). Common symptoms include blurry vision, blind spots, nystagmus, double vision, oscillopsia, partial or complete vision loss, and an inability to recognise the difference in light and colour (61).

2.4.3 Cognitive impairments

Cognitive impairment is known as the inability to obtain and process information through individual interactions, sensory inputs, and cognitive processing (62). It is caused by damage

to the composition of brain matter by toxins, plaques, proteins, and autoimmunity, such as MS (62). Impairments in MS patients are attributed to the location of specific brain lesions and the progression of atrophy over time. Common deficits include reduced attention, processing speed, memory, and verbal and communication skills, which affect approximately 70% of patients (19,57). Sleep disturbances and certain MS medications have also been associated with cognitive impairments (19).

2.4.4 Fatigue

Fatigue is known as the individual's perceived level of exhaustion that hinders them from being able to carry out their daily tasks, regardless of the amount of rest they have had (63). It is thought to be caused by reduced physical and mental capabilities and is described as a feeling of heaviness and an inability to interact in social interactions (63). Like MS, it is thought to have a direct link to immunity, presenting with a constant state of inflammation, causing inflammation-induced fatigue (63,64).

Fatigue is a widespread symptom in MS patients, affecting approximately 80% of patients (57). This is known to be one of the disabling symptoms impacting the overall QoL of MS patients. Motor symptoms have been found to be associated with the onset of MS fatigue. These symptoms include lack of coordination, muscle weakness, and exhaustion (19). Medications and psychiatric disorders, such as anxiety and depression, may also cause fatigue in MS patients (64).

All symptoms of MS are commonly treated with disease-modifying therapies (DMTs) and natural remedies (15,65). More information on the treatment of MS will be discussed below.

2.5 Modalities Used in the Treatment of Multiple Sclerosis

Disease-modifying therapies are used to lessen the rate of recurrence of relapses, and they aim to delay the advancement of the disease by suppressing or modulating the immune system (see Table 2.1). The downfall to this type of therapy has been reported to be a weakened immune system, leading to frequent infections and possibly the development of “progressive multifocal leukoencephalopathy (PML)”, a fatal, progressive brain disease caused by the “John Cunningham (JC) virus”, characterised by the demyelination of nerve cells (65–67).

Table 2.1 Disease-modifying therapies used to treat Multiple Sclerosis (13,68)

Name of the disease-modifying therapy	**Mechanism of action**
Beta Interferon	Downregulates proinflammatory T helper cells, and memory B cells. Increase T regulatory cells
Glatiramer acetate	Reduced memory of T and B cells, promotes anti-inflammatory cytokine changes, restored T regulatory cells
Daclizumab	Increases the size of natural killer cells and reduces proinflammatory T cells
Fingolimod	Affects the movement of C-C chemokine receptor type 7+ lymphocytes, naive and central memory T cells, and memory B cells from the lymph nodes
Teriflunomide	Immunomodulator inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase and targeting proliferating lymphocytes
Dimethyl fumarate	Reduces CD8+ T cells
Natalizumab	Prevents the movement of lymphocytes into the CNS
Alemtuzumab	Depletes circulatory lymphocytes
Ocrelizumab	Reduces B cells

Other studies have investigated non-DMTs as treatment options that encourage CNS repair in MS patients (69). “Bruton tyrosine kinase inhibitors, CD40L antibodies, and α-Lipoic acid” are thought to reduce CNS inflammation (69). “Masitinib, Ibudilast, Metformin, Clomipramine, and receptor-interacting protein kinase 1” are thought to portray neuroprotective properties (69). “Elezanumab, Opicinumab, Proteoglycans, Niacin, Muscarinic receptor antagonists, and Temelimab” are thought to promote CNS repair (69).

An additional study conducted by Jiménez-Jiménez et al., (2024) reviewed studies that used antioxidant substances to support the health and well-being of MS patients and animal models. They hypothesized that inflammation is caused by oxidative stress and thus reducing it in the body can present with anti-inflammatory properties. They found that green tea, melatonin, α-Lipoic acid, curcumin, resveratrol, pentoxifylline, vegetable and animal oils, coenzyme Q10, alpha-tocopherol, vitamin A, carotene, uric acid and bilirubin, nitric oxide synthase (NOS) inhibitors, carnitine and carnosine, and caffeic acid among others made a pronounced impact on the disease course of animal and human MS patients adding to their overall QoL (70). Natural remedies and non-DMTs provide non-harmful ways to slow the disease progression, and it is believed that it may assist in supporting patients who are on DMTs. Managing MS through diet, exercise, and psychosocial interventions have also been shown to improve the QoL of MS patients (25,71–73). These will be discussed below.

2.6 Management Strategies for Multiple Sclerosis

Managing MS symptoms has shown to enhance QoL. Encompassing healthy foods, exercise, and stress and psychological management is recommended (25,71–73). These will be expanded on below.

2.6.1 Management with food

The impact of food on the body can either promote harmony or stress. When humans consume foods that are high in toxins such as saturated and trans fats, red meat, sugar-containing beverages, refined carbohydrates, and high salt intake, excess stress is put on the body to break down these foods (71). The excess stress can activate proinflammatory immune cells. Excess consumption of these foods may lead to a chronic increase in immune activity and cell injury, as seen in MS (71). This chronic state of immune activity has been linked to a faster progression of the condition (74). A case-control study published on the effect of a 10-year-long dietary program on white matter lesion composition by Jaftha et al., (2024) found that patients who completed the program had a decreased volume of white matter lesions (74). They also found that the disability score measured with the Expanded Disability Status Scale (EDSS) score was mild-to-moderate in this population compared to MS patients who did not complete the program (74). The program is known as the “pathology-supported genetic–testing” program which is comprised of personalised dietary and

supplemental interventions based on a patient's medical and lifestyle history, genetic testing, and blood tests analysing deficiencies such as vitamin D, iron, and inflammation (74).

This suggests that increasing antioxidant and anti-inflammatory foods can aid cell healing and reduce overall stress leading to decreased inflammation in MS patients. This is mentioned by Stoiloudis et al., (2022) who have linked MS to oxidative stress and thus consuming foods that reduce oxidative stress have been shown to assist in slowing down the progression of the disease. This includes a diet that is rich in prebiotics and probiotics, polyphenols, fatty acids, vitamin A, vitamin D, and antioxidants such as curcumin (71).

2.6.2 Stress and psychological management

Being diagnosed with an unpredictable autoimmune degenerative disease can elevate one's stress levels. Elevated stress can impact the body's cortisol levels leading to a constant proinflammatory state (75). Drathen et al., (2024) concluded that a constant state of elevated cortisol (through post-traumatic stress disorder in military personnel) has been linked to increased disease activity and progression in MS patients (76). This was also seen in a review conducted by Jiang et al., (2022) who found stressors related to life and work were linked to increased disease activity (77). They also mentioned that positive stressors (patient-specific) were associated with a reduced risk of progression (77). Promoting stress management strategies is advised for improving the overall well-being of MS patients (75).

Taylor et al., (2020) reviewed studies that were interested in an intervention involving stress management in MS patients. They found that cognitive behavioural therapy (CBT), mindfulness, and psychoeducation were the most effective in improving perceived stress. They also found that these interventions positively impacted depression and anxiety symptoms (72). Cognitive behavioural therapy was also found to have a profound effect on fatigue over 12 months in a study conducted by Gay et al., (2023) (73). An intervention group (n = 27) was compared to a control group (n = 48). The intervention group underwent a programme that aimed to help them manage fatigue symptoms caused by MS (73). This comprised of theories related to CBT, managing energy effectively, improving self-management and self-efficacy strategies (73).

2.6.3 Management with exercise

Exercise is a form of structured and planned physical activity. It involves the repetitive movement of the body aimed at improving physical strength, fitness, and overall well-being (78). Examples of exercise include cardiovascular, flexibility, strength, and neuromuscular exercises (79). Exercise therapy is prescribed physical activity that is directed at improving posture, musculoskeletal function and maintaining a healthy state of wellbeing (2).

The American College of Sports Medicine associates the increased risk of mortality, heart conditions, obesity, cancers, diabetes, depression, falls, and cognitive impairment with a lack of exercise (80). Partaking in physical activity appears to be more beneficial to one's health. Some benefits include improvements in cardiovascular (CV) and respiratory function, reduction in CV risk factors, reduced psychiatric symptoms, improvements in cognitive and physical function leading to an improved level of independence especially in the elderly population, and decreased risk of falls and related injuries (80). Exercise therapy encompasses all the same benefits, but it is delivered in a safer environment for people with injuries and illnesses such as MS. Exercise therapy bridges the gap between the ability to exercise and the need to exercise for this population (2).

Exercise has many health benefits and has been shown to enhance the QoL of patients with MS (25). These benefits included improved aerobic fitness, strength, cognition, walking ability, and efficiency, as well as reduced levels of fatigue, depression, and stress (25,26). Different exercise modalities produced certain benefits amongst MS patients in a review conducted by Saedmocheshi et al., (2024). Aerobic exercises were associated with improved walking ability, balance, and QoL, while resistance exercises were associated with improved walking ability (81). Flexibility and mobility exercises improved balance and posture, and aquatic exercises, tai chi, and balance exercises improved balance and flexibility (81). These findings were similar to other reviews done by Reina-Gutiérrez et al., (2022) and Hao et al., (2022) (82,83). This is seen in healthy adults undergoing high-intensity functional training showing the clinical significance of exercise for all populations. Wang et al., (2023) reviewed 13 papers that researched high-intensity functional training (in the form of CrossFit training) in healthy adults and what they found was improved muscle strength, power, flexibility, and sport-specific performance in athletes but no improvements in agility and endurance (84). The sport types in the paper that were reviewed were volleyball, martial arts, and aerobic gymnastics. Eight papers included male participants and two included females.

This is similarly seen in ill populations such as adults with sarcopenia obesity. A review conducted by Chen et al., (2024) showed overall improvements in body fat percentage and muscle mass in participants who underwent aerobic exercise for a minimum of eight weeks. They reviewed three studies that used aerobic exercise (walking, cycling, jogging) as a modality (85). They further reviewed two studies that used anaerobic activity (dumbbells, sandbags, resistance bands) as an exercise modality. What they found was an increase in lean muscle mass and bone density, as well as improved grip strength, with a relatively minor difference in body fat between the two modalities (85). A minimum of 12 weeks was required to see improvements in physical health. Aerobic and anaerobic were used in four studies. A greater muscle mass and strength, along with a reduced body fat percentage and cardiovascular risk factors, was noted in participants (85). A minimum of 12 weeks was required to see improvements. Including combined exercise modalities appeared to be most beneficial in participants. All three studies showed positive results of exercise therapy on muscle mass and strength, with two also seeing improvements in body composition (84–86).

An additional benefit of exercise therapy is a slowed progression, fewer relapses, and neuroplasticity seen in MS patients (27,28) (see Point 2.4.1). However, these findings may be datable. A review done by Proschinger et al., (2022) found no short-term changes in the frequency of lesions in the CNS of MS patients who performed exercise therapy (87). They suggest that exercise therapy does not influence disease progression even though the annual relapse rate was decreased (87). Long-term studies assessing the impact of exercise therapy on the advancement of MS are required.

The effects of exercise therapy on MS will be discussed in more detail below.

2.7 The Effects of Exercise Therapy in Multiple Sclerosis

An RCT done by Gurpinar et al., (2020) investigated the outcome of water-based exercises on posture and hand function in MS patients. They compared Halliwick exercises to aquatic plyometric exercises. The study consisted of 28 MS patients aged between 47 and 66 years. They found that both training modalities improved postural control and hand function, with most improvements seen in the group doing Halliwick exercises. Similarly, a qualitative study done by Carling et al., (2018) evaluated the role of balance exercises in improving the QoL

of patients with MS. Twenty-seven patients with a mean age of 59 (7.9) years participated in a “CoDuSe program” which focused on core stability to improve balance. They concluded that training the core improves balance and thus overall QoL of patients with MS (4).

The exercise benefits seen in MS patients can similarly be seen in the elderly population (60 years and older). Boithias et al., (2024) conducted a pre-post-intervention study assessing the changes in the physiology and psychology of elderly participants performing recreational soccer. Fifteen adults (3 women and 12 men) participated in 60 minutes of physical activity (warm-up, soccer drills, and a short game) twice a week over 6 weeks. Anthropometric data, 2.5 up and go, 6-minute walk test (6MWT), Basic Psychological Need Satisfaction and Frustration (BPNSF) questionnaire, and a sit and reach test were assessed. Although there were improvements in all the outcome measures, none were significant (86). Studies with a longer intervention are needed to test if physiological and psychological changes can become significant.

An additional study researched the impact of exercise on brain function in MS patients (88), similar to the two studies mentioned below in point 2.4.1 (27,28). Riemenschneider et al., (2022) conducted an RCT examining the impact of aerobic exercise therapy on relapse frequency and brain atrophy in MS patients. The study included 84 adults with MS participating in an exercise program (n = 42) or health education (n = 42) over 48 weeks. The exercise group showed a decrease in relapse frequency, although the number was insignificant. They also showed changes in motor grey and white matter structures compared to the health education group, however, the results were insignificant (88). This suggests that short-term exercise interventions may be inadequate in noting changes in brain structures in MS patients. The findings were consistent with the above-mentioned studies (27,28).

Exercise therapy may have a clinical effect on vitamin D, gut health, and smoking in MS patients. It has additionally been shown to lessen the effect of symptoms experienced by MS patients. Further information will be presented below.

2.8 The Effects of Exercise Therapy on the Pathophysiology and Symptoms of Multiple Sclerosis

2.8.1 Vitamin D deficiency

Low levels of vitamin D have additionally been linked with reduced physical performance and an increased recovery time in athletes worldwide (89). Studies have explored how exercise therapy has a role in an individual's vitamin D levels. A review by Zhang et al., (2022) presented these findings, noting conflicting results on the impact exercise therapy has on vitamin D levels (90). They established studies that analysed the acute and chronic vitamin D levels following endurance and resistance activity. They found 14 studies that found an increase in vitamin D levels, six studies that found contradictory results, and three studies that did not note any changes in vitamin D levels (90). Similarly to the former, higher vitamin D levels correlated with daily physical activity in 38 MS patients who participated in a prospective observational study conducted by Bauer et al., (2020) (91). Three reviewed studies by Zhang et al., (2022) found significantly improved vitamin D levels in intervention groups that participated in exercise therapy and supplemented with vitamin D (90). This is like another study that saw changes in the overall QoL of MS patients who participated in endurance activity supplemented with vitamin D (92).

2.8.2 Gut microbiome dysfunction

Exercise therapy has been shown to have positive and negative effects on the gut depending on the type of exercise modality used (93,94). A study conducted by Clauss et al., (2021) reviewed the effects of high-intensity (more than 70% of their VO2max) and moderate-intensity (less than 70% of their VO2max) endurance activity in athletic, diseased, and overweight populations (93). They found that both intensities led to a positive change in gut microbiome diversity and composition, with more individuals having an increase in butyrate-producing species, which are known for improving an individual’s metabolic function and insulin responsiveness (93). Similar benefits of exercise on the gut were also mentioned by Monda et al., (2017) who reviewed studies that found an increased concentration of *butyrate* in the mice gut, which has correlated with a decreased risk for colon cancer, decreased gut permeability, and a decreased risk of obesity caused by an unhealthy diet (94). Contrary to this benefit, the authors found that low-intensity activity to be more beneficial as higher-intensity activities may cause a temporary reduction in oxygen supply to the gut, causing inflammation and increased gut permeability causing temporary harm to the microbial environment (93,94).

Based on the link between poor gut microbiomes (based on diversity as well as the type of microbiomes) and increased circulatory inflammation possibly leading to the development of MS, a study done by Mokhtarzade et al., (2021) hypothesised that exercise activity for MS patients for five days a week for six months would alter the gut composition of the patients and lead to decreased inflammation and better QoL of patients (95). The intervention group did resistance activity twice weekly and endurance activity thrice a week. No exercise was given to the control group. They found alterations in gut microbiome composition but no changes in the inflammatory markers of the patients (95). The authors believed that the insignificant change in inflammatory markers was due to the difficultly level of the exercise and the length of the study. It is agreed that exercise therapy may have a positive long-term effect on the gut microbiome composition of MS patients, but more long-term studies are required.

2.8.3 Smoking

Implementing exercise therapy to aid in smoking cessation has been studied in adults with and without nicotine replacement therapy (96,97). Both studies found no long-term effect of exercise on smoking cessation. Despite this, a recent review (98) found that exercises portrayed positive effects on the QoL, muscle strength, CV fitness, and body composition of adults who smoked. These effects may be seen in MS patients who smoke. Patients who quit smoking may also reduce disease progression and improve their overall QoL (99).

2.8.4 Sensory impairments

Exercise therapy may be a stepping stone to improving brain volumes in MS patients. Based on the above study (59), it is hypothesised that improvements in brain volume may lead to improvements in sensory function. Lozinski et al., (2022) and Rocca et al., (2024) reviewed the impact of exercise therapy on MS disease progression by examining changes in brain structures. They noted that aerobic exercise has a direct impact on preserving cortical brain structure volume. While other forms of exercise, such as resistance, balance, sensorimotor, and fine motor tasks, have been shown to produce white matter neuroplasticity (27,28). Additionally, sensorimotor exercise has been researched as a treatment modality by Solaro et al., (2020). They noted improvements in 59% of their participants who performed sensorimotor activities that involved quickly moving the affected hand to a target (100). No exercise therapy (resistance, aerobic, or neuromuscular) was added to their protocol. This

suggests that various avenues may be explored to enhance sensorimotor function in MS patients, thereby improving their QoL.

2.8.5 Visual disturbances

Visual training to improve visual performance linked to eye movements and attention has been implemented in neurologic disorders, including MS (101). These exercises included moving the head from side to side while keeping your eyes fixed on your finger in front of you, moving your finger and head in the same direction, and moving your finger while following it with your eyes, keeping your head still (102). This method was assessed by Son et al., (2024) who conducted an RCT on chronic stroke patients with visual impairments. They evaluated the impact of improved visual perception on gait and balance (102). The intervention group performed eye exercises in conjunction with exercise therapy, while the control group performed exercise therapy only. Both groups improved in balance and gait, but the intervention group presented greater improvements (102). The authors believe that all sensory information is processed together, enhancing physical performance. Eye exercises may improve visual acuity in stroke patients, potentially leading to enhanced gait and balance (102). Implementing eye exercises may also benefit MS patients. A study on this topic is needed, as no research can be found.

2.8.6 Cognitive impairments

Exercise therapy in the management of these impairments has been shown to improve processing speed, learning and working memory, and executive function (103). However, the RCTs that were reviewed by DeLuca et al., (2020) did not specifically recruit MS patients with a quantifiable level of cognitive impairment; and most of the studies did not specifically assess the effect of exercise on cognition but rather reported it as a consequence of exercise therapy (103). Understanding the direct link between exercise therapy and improved cognition in MS patients could not be made in this study. Despite this, an RCT conducted by Argento et al., (2023) on 48 patients with MS found that combined therapy (cognitive and motor training) showed improvements in both aspects in the participants (104). The intervention groups who respectively did cognitive training and motor training only saw improvements in cognition and motor abilities in their respective groups. Consequently, exercise without cognitive input did not result in better cognition. However, the types of exercises in these studies (103,104) were not documented or compared, and thus deciding whether exercise therapy directly affects

cognition cannot be made. Further research on the types of exercise modalities impacting cognition is thus needed.

2.8.7 Fatigue

Exercise therapy poses many benefits for MS patients, with a reduction in fatigue and improved QoL being one of them (105). This has been reviewed by Razazian et al., (2020) who found a substantial reduction in fatigue in MS patients who underwent physical therapy. They believed that this phenomenon was caused by better fitness levels, muscle strength, muscle endurance, and decreased psychosocial symptoms (105). Despite the positive effects of exercise mentioned, Rio et al., (2024) thematically explored how exercise affects fatigue in patients. Some patients expressed that exercise made their symptoms of fatigue worse (63). This confirms that each patient experiences and expresses fatigue differently, and management of fatigue with exercise should be personalised to the patient's capabilities.

Exercise and its benefit in MS patients show improvements in balance and QoL (4). Enhancing proprioceptive acuity may add to this benefit and better the lives of MS patients (106). Proprioception and its role in MS will be discussed in more detail below.

2.9 What is Proprioception

Proprioception, commonly known as the "sixth sense", is defined as the body's ability to detect the direction, motion, and position of muscles, joints, tendons, skin, and fascia in one part of the body relative to another part, as well as to its immediate environment (6–9). When stretch or pressure is applied to the body, special receptors known as proprioceptors are stimulated generating a nerve impulse that relays information about the body's position to the CNS for processing (6,107).

Proprioception is believed to be crucial for conscious and unconscious motor and reflex control (9,107). The conscious aspect of proprioception speaks to the awareness of joint position and movement, the perception of tension or force, the recognition of effort, and the perception of balance (9). Whilst the unconscious aspect of proprioception is formulated by ongoing schematic proprioceptive representations of the body image which allows for the unconscious awareness of daily motor and postural control (9).

Proprioceptors are in many parts of the body and are responsible for communicating different information about the environment to the brain. They are in the muscles, joints, and skin (6). Below is a table explaining the different types of receptors, their location, and stimulation.

Table 2.2 Types of proprioceptors found in the body (6)

Organ	Muscles	Joints	Skin
Types	Muscle spindles and Golgi tendon organs	Ruffini endings and Pacinian corpuscles	Meissner corpuscles, Pacinian corpuscles, Merkel endings, Ruffini endings
Location	Skeletal, extrafusal muscles, and musculotendinous junctions	External and inner layers of joint capsules, and ligaments	Skin
Stimulation	Change in the length and tension of the muscle	Slow adapting receptors, and fast and slow reactions to strain	Fast reaction to skin strain

2.10 The Role of Proprioception in the Body

Constant neural input is relayed to the brain when stretch is elicited in the muscles, tendons, joints, and skin, known as mechano-sensation (18). This mechanism allows individuals to continuously map out their environment (internal and external) through the formation of many body schemas that directly lead to better body awareness and movement patterns (9,18). Stretch force and speed, and muscle motor unit recruitment allow for more accurate proprioceptive input to the CNS. Therefore, certain situations can contribute to distorted proprioceptive input resulting in decreased motor control and balance.

This phenomenon is commonly seen in the geriatric population (9,18). During the aging process, peripheral and central neural systems are impacted. This is seen through the loss

of muscle motor units in the limbs, thus fewer muscle receptor recruitment, and the loss of afferent and efferent axons, thus a decline in impulse reception through slower speeds and fewer nerve recruitment (18). The loss of afferent and efferent axon integrity can also be seen in neurodegenerative diseases like MS and Parkinson's disease.

2.11 Proprioception and Multiple Sclerosis

Proprioceptive disturbances are commonly observed in patients with MS. This is due to damage to neurons influenced by proprioceptors, and symptoms that affect the musculoskeletal system, such as spasticity, tingling in the extremities, pain, and muscle weakness (18,20).

A recent case-control study conducted by Yaşa et al., (2024) assessed shoulder proprioception with balance, trunk control, and walking speed in MS patients. Eighty participants (40 with MS and 40 Healthy) aged between 18 and 60 years were assessed. They hypothesised that poor joint position sense of the shoulders, which are rich in proprioceptors, correlated with decreased balance, trunk control, and walking speed. They concluded that their hypothesis was correct as MS patients significantly had impairments in shoulder proprioception, balance (static and dynamic), trunk stability, and 10 m walking speed compared to healthy individuals (22). In a similar study conducted by Jules et al., (2024), 93 participants with RRMS (n = 32), PPMS (n = 7), SPMS (n = 24), and healthy individuals (n = 30) between the ages of 24 and 80 years were assessed for their sensorimotor function. Vibration sensation, proprioceptive function, and central motor function were assessed. Overall, MS patients had worse scores than healthy individuals, with PPMS and SPMS patients showing a greater decline than RRMS patients (23).

2.11.1 The effects of exercise therapy on proprioception

Existing evidence shows that exercise therapy as a treatment modality for injuries and conditions has a direct impact on proprioception (24,106). An RCT conducted by Hlaing et al., (2021) compared the impact of core stability and strength exercises on proprioception, balance, muscle thickness, and pain in patients experiencing subacute nonspecific low back pain in 36 participants aged between 20 and 50 years (33). Participants' lower back proprioceptive acuity, balance, and discomfort improved after repetitively activating the Transversus Abdominis and Lumbar Multifidus muscles (33)(33). Similarly, Ahmad et al.,

(2020) found that exercise therapy focusing on sensorimotor stimulation and walking improved proprioception in adult diabetic patients with peripheral neuropathy. In addition, proprioception was also improved in the trunk and the ankle of these patients (108).

2.11.2 The effects of exercise therapy on proprioception in Multiple Sclerosis patients

Research has shown how exercise therapy has a direct impact on proprioception, fall prevention, and the QoL of patients with MS (24). Sokhangu et al., (2021) conducted an eight-week RCT to examine the effects of neuromotor exercises on the strength, proprioception, and balance of 20 female MS patients aged 30 to 50 years. The experimental group experienced a notable increase in strength and a reduction in "proprioceptive error" (106). Similarly, Moghadasi et al., (2020) found that an eight-week full-body resistance exercise program involving 34 females with RRMS improved their mobility, proprioception, and knee strength.

The incorporation of sensory stimuli and/or multitasking activities along with exercise therapy has proved more beneficial in the overall well-being of MS patients (29–32). Hortobágyi et al., (2022) conducted an RCT examining the results of five different exercise modalities on 70 adult MS patients over 2 years. The modalities included exergaming, cycling, balance, proprioceptive neuromuscular facilitation (PNF), and a control group. They found greater improvements in the Multiple Sclerosis Impact Scale (MSIS-29) scores for the exergaming group, followed by the balance and cycling groups. The exergaming group received high-intensity agility training with sensory and visual input from an Xbox gaming system (30). Prosperini et al., (2010) and Tosun et al., (2021) primarily used visual stimulation along with exercise to improve the QoL of persons with MS. They examined 66 adult MS patients over 6 weeks. They found an improvement in proprioceptive acuity that facilitated a reduced risk of falls and improvements in gait parameters. Tramontano et al., (2024) and Gandolfi et al., (2015) tested multitasking activities on 111 adult MS patients over one month. Both studies had a conventional exercise group and an experimental group that underwent an exercise regimen along with sensory input. They noted an improvement in QoL in both groups with greater improvements seen in the experimental groups.

The effects of exercise in healthy and ill populations have been widely studied in Western populations with therapeutic efficacy being recognised. This may be readily translated to the SA population which has not been vastly studied (38,39). This provided a research gap in the understanding of the role of exercise therapy in developing countries, such as SA, minimising the therapeutic efficacy of MS management in this population.

2.12 Conclusion

Based on the reviewed literature, exercise therapy may play a significant role in the overall QoL of MS patients through enhanced proprioception. The upcoming chapter will discuss the methodological process in conducting this review to determine the link between exercise therapy and proprioception in MS patients.

3 Methods

3.1 Introduction

This chapter describes the methodology by which the systematic literature review was conducted. The type of study, inclusion criteria (stating the participants, interventions, comparators, and outcomes), search strategy, bias risk assessment, data collection and synthesis, conflicts of interest, and ethical considerations will be documented.

3.2 Type of Study

A systematic literature review was conducted following the “preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) reporting guideline” (109) (see Appendix A). It was registered onto the “International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY)” with registration number INPLASY2024110076 (see Appendix B). The PICO framework (110) was followed to construct this study. The acronym stands for P – population, I – intervention, C- comparator, and O – outcome (110).

3.3 Inclusion Criteria

3.3.1 Types of participants

The review included studies that investigated adult participants (≥ 18 years) who have been diagnosed with Relapsing-Remitting, Primary-Progressive, or Secondary-Progressive MS (35). Adult participants were not limited to a specific gender, ethnicity, or economic status.

3.3.2 Types of interventions

Studies that used all types of exercise therapy, alone or in conjunction with proprioceptive input, were reviewed. Exercise types included resistance, aerobic, proprioception, balance, and gait training. Interventions delivered at a hospital, gym, or home were included. Land-based and water-based interventions were reviewed. Studies that conducted the intervention for a minimum of 30 minutes, twice a week over three (3) weeks were preferred. No restrictions to intensity (low, moderate, or high) and progression were applied.

3.3.3 Comparators

Studies that compared the intervention group to a control group that either participated in exercise therapy without proprioception input or did not participate in any type of therapy were reviewed (35).

3.3.4 Outcomes

The outcome measures that were reviewed were proprioception, QoL, and balance in MS patients. Proprioception was analysed through the change in posture and/or positioning of the participant's joints mainly seen during standing and/or walking (29,30,111,112). The types of exercises and exercise activities that influenced their proprioception were noted (35). The results that measured balance using the Tinetti Assessment Tool (TAT), Berg Balance Scale (BBS), Activities-specific Balance Confidence Scale (ABC), Mini-BESTest test, and Sensory Organization Balance Test (SOT) (30–32) were analysed (35). Changes in the participant's QoL using the Multiple Sclerosis Impact Scale (MSIS-29), Modified Fatigue Impact Scale (MFIS), Multiple Sclerosis International Quality of Life (MusiQoL), Modified Barthel Index (MBI), MS Quality of Life 54-Item Version (MSQoL-54), and number of falls were also analysed (30,31,35,111,112).

3.3.5 Types of studies

Due to limited documentation of the effects of exercise therapy on proprioception, only randomised control trials and clinical case-control studies were found and thus reviewed.

3.4 Search Strategy

No studies on exercise therapy and proprioception were found prior to 2000. Therefore, studies done between 2003 and 2024 were sourced from five (5) databases, PubMed, CINAHL ultimate, ProQuest Central, SPORTDiscus, and SCOPUS, in July 2024 (35). The reviewers home language is English, and thus studies written in English, available in full text, peer-reviewed, and from reputable sources were included. Search terms included exercise therapy/ies, rehabilitation exercise/s, Multiple Sclerosis, MS, and proprioception (35). An initial search on PubMed was completed in November 2023 to determine an appropriate date range and keywords (see Appendix C). The librarian, Devind Peter, was consulted in July 2024 to refine the search terms (see Appendix D).

3.5 Study Selection

The first reviewer (Bokamoso Mthimkulu) and second reviewer (Natalia Neophytou) searched each database for research studies using the search terms stated in point 3.4. Search results were exported and stored in the reference manager Mendeley (version 2.131.0). Once all databases had been searched and results exported, the results were uploaded to Rayyan artificial intelligence software (software as a service or web application) (113) to effectively organise, manage, and screen all exported results for eligibility. The number of duplicate studies was noted and removed from the main results. The title and abstract of each study were screened for eligibility by both reviewers. Once all studies had been marked as included or excluded, included studies were finalised. A third reviewer (Merling Phaswana) was to be consulted on any disagreements on the studies to be included in the review. No disagreements arose between the first and second reviewer. A pilot study was not conducted due to time constraints.

3.6 Assessment of Methodological Quality

All eligible studies were screened further using the “JBI critical appraisal tool” (JBI) for randomized control trials, and clinical case-control studies for internal validity and trustworthiness (114,115) (see Appendix E). This was accompanied by the “Black’s and Down” (116) and “Consensus on Exercise Reporting Template (CERT)” (117) (see Appendix F and G) checklist to objectively assess the risk of bias, internal and external validity, and exercise intervention completeness and quality of each study (35). Included studies were selected based on internal reliability and validity and an overall score above 50%. Where the score was below 50%, studies were included based on internal reliability and validity only.

3.7 Data Collection

Relevant information from all eligible studies was tabulated by reviewer one to provide simplicity in analysing the results of each study. An updated JBI data extraction tool (118) was adapted and populated into Excel. The title, date of publication, author/s, study characteristics, location, participant characteristics, intervention characteristics, procedure per group, outcome measures, and similarities from each included study were documented (see Tables 4.3, 4.4, and 4.5). Recommendations on the best types of exercise modalities to improve the proprioception of MS patients were given (see Table 5.2). Missing data was not obtained due to time constraints. A pilot study was not conducted due to time constraints.

3.8 Data Synthesis

A narrative synthesis framework was used to analyse the data (119). This followed the guideline constituted by Popay et al., (2006) called the “Guidance on the Conduct of Narrative Synthesis in Systematic Reviews A Product from the ESRC Methods Programme Peninsula Medical School, Universities of Exeter and Plymouth” (119). It acknowledged the four fundamentals of a narrative synthesis which are “developing a theory of how the intervention works, why and for whom, developing a preliminary synthesis of findings of included studies, exploring relationships in the data, and assessing the robustness of the synthesis” (119). Key themes were formulated to effectively identify the similarities and discrepancies in the data. These included the study characteristics (i.e.: location, sample size, participant characteristics including age, gender, MS type, and duration), intervention characteristics (i.e.: intervention duration, session duration, frequency, and intensity), procedure characteristics (i.e.: exercise breakdown per treatment group), and study results based on the outcome measures of this review (i.e.: proprioception, balance, and QoL). Data was populated visually, in the form of tables, and descriptively. Due to time constraints, a meta-anaylsis was not advised.

3.9 Ethical Considerations

The study did not involve testing humans or animals. An ethical waiver form was submitted to and accepted by the University of the Witwatersrand Human Research Ethics Committee (see Appendix H). Only the researcher and supervisors had access to all collected data.

3.10 Conclusion

The upcoming chapter will present the results of the methodological process that was described.

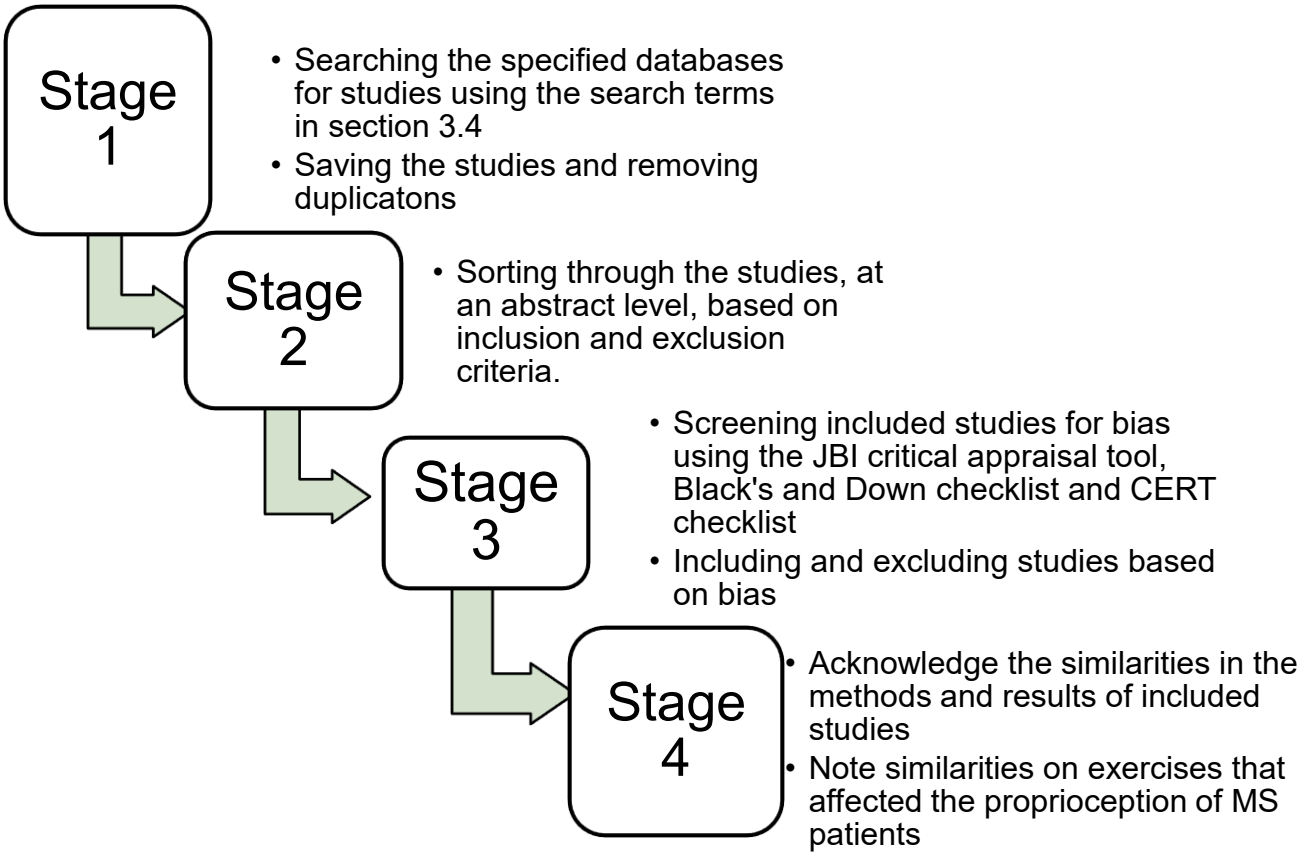

Figure 3.1 Diagram showing the process for conducting this study.

4 Results

4.1 Introduction

This chapter will present the findings of the review based on the process stated in the methods chapter. Firstly, the selection process for the included studies will be documented. This section enables the reader to view how each study was selected and the reasons for its inclusion or exclusion (see Figure 4.1 and Table 4.1). Secondly, the characteristics of the included studies will be documented, highlighting the types of participants (age, gender, MS type, and duration), location, sample size, exercise protocol (intervention procedure, duration, session duration, frequency, and intensity), and the outcome measures used (see Tables 4.2, 4.3, and 4.4). Similarities and differences will be noted. Thirdly, the results on proprioception, balance, and QoL (see Tables 4.5, 4.6, and 4.7) from each study will be documented, providing the reader with a summary of the findings. Fourthly, the key findings based on the objective will be presented. Data will be presented as a narrative synthesis and tables throughout this chapter.

4.2 Selection Process for Included Studies

Each reviewer (BM and NN) reviewed peer-reviewed English RCTs, and case-control trials of adults with MS. Four hundred and forty research papers were found. Forty-two duplicates were removed. Based on the inclusion criteria, 411 research papers were excluded at a title and abstract level. Nine research papers were reviewed for eligibility using the JBI critical appraisal tool, Black's and Down, and the CERT checklist (see Appendix E, F, and G). One study was excluded because the wrong study design was used. One study did not meet the inclusion criteria of this study and was excluded. One study had a risk of bias score below 50% making it ineligible for this review. Therefore, six of 420 studies were included. This information is presented below in Figure 4.1 and Table 4.1.

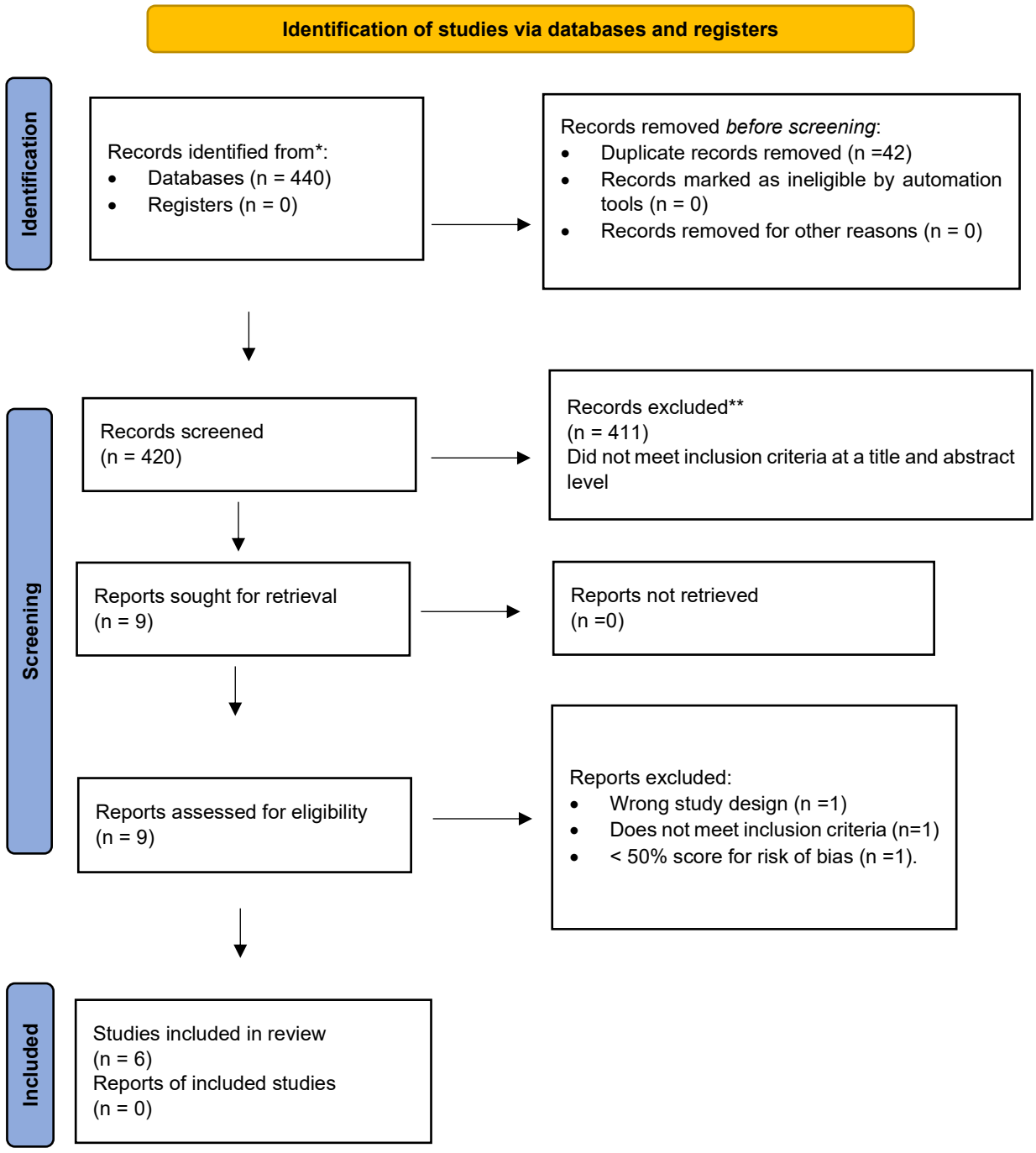

Figure 4.1 PRISMA flow diagram illustrating the selection process of the six included studies

Table 4.1 Quality assessment scoring of nine studies eligible for this review

Study	JBI critical appraisal result	Reason for inclusion	Black and Downs Checklist result	CERT checklist result	Total (Blacks and Downs, and CERT result)	Included /excluded	Reason for inclusion/exclusion	Final decision	Reason for exclusion
Hortobágyi, T et al.	Included	Good validity and reliability	17	6	23	Include	Combined score ≥50%	Include	
Escudero-Uribe, S et al.	Included	Good reliability	18	14	32	Include	Combined score ≥50%	Include	
Sames, C; DeBlois, A	Excluded	Not included	15	13	28	Include	Combined score ≥50%	Exclude	Wrong study design based on current systematic review design
Chotiyarnwong, C et al.	Excluded	Not included	22	6	28	Include	Combined score ≥50%	Exclude	Does not meet inclusion criteria
Tramontano, M et al.	Included	Good validity and reliability	22	6	28	Include	Combined score ≥50%	Include	
Tosun, A.T et al.	Included	Good reliability	18	7	25	Include	Combined score ≥50%	Include	
Prosperini, L et al.	Included	Good reliability	15	5	20	Exclude	Combined score ≤50%	Include	Good risk of bias score of more than 50% and the reliability of the study
Gandolfi, M et al.	Included	Good reliability	19	9	28	Include	Combined score ≥50%	Include	
Schyns, F et al.	Excluded	Not included	15	4	19	Exclude	Combined score ≤50%	Exclude	Overall low score and internal validity not well defined

4.2.1 Characteristics of the six studies included in this systematic review

Approximately 83.33% (n = 5) (29–32,111) of the studies were RCT studies and 16.67% (n = 1) (112) was a case-control study. Studies were published between 2010 and 2024. Interventions were completed at a university hospital (n = 3) (29,30,111), a neurological rehabilitation hospital (n = 1) (32), and a gym of neurological rehabilitation (n = 1) (31). One study did not state where the intervention was completed (112). The studies were conducted in Italy (n = 3) (31,32,112), Spain (n = 1) (111), and Turkey (n = 1) (29). One study did not state where the study was set (30). In all RCT studies, the outcome measures were measured by a blinded assessor, and adequate randomisation was completed. A total of 336 participants were recruited for the study, with 315 successfully completing it. The mean age of participants was 45.23±8.78 years. Females comprised 72.76% (n = 229) of participants, and 27.24% (n = 85.8) were male participants. Of 315 participants, 42.58 were diagnosed with PPMS, 120.42 were diagnosed with RRMS, 28 were diagnosed with SPMS, and 12 were healthy (two studies were not included as they did not state the type of MS the participants had and thus 119 participants were not accounted for). The mean duration each participant had MS was 13.36±6.76 years (one study was not included as they did not state the MS duration of the participants, and thus, 52 participants were not accounted for). This information is presented below in Table 4.2.

Table 4.2 Study and participant characteristics of six studies included in this systematic review

Title	Author/s	Publication date	Study design	Randomisation and Blinding	Location (facility, country)	Sample Size (n)	Age (years)	Gender (n) Female – F Male - M	MS type (n)	MS duration (years)
Comparative Effectiveness of 4 Exercise Interventions Followed by 2 Years of Exercise Maintenance in Multiple Sclerosis: A Randomized Controlled Trial (30).	Hortobágyi, T. et al.	2022	RCT	Completed and concealed by a therapist not involved in the study and Assessor-blinded	University Hospital, country unknown	70	47±5.95	F (61.2) M (6.8)	PPMS (41.58) RRMS (26.42)	13.1±3.89
Effect of Training Exercises Incorporating Mechanical Devices on Fatigue and Gait Pattern in Persons with Relapsing-Remitting Multiple Sclerosis (111).	Escudero-Uribe, S. et al.	2017	RCT	Randomly assigned using random numbers table and assessor-blinded	University Hospital, Spain	55	42.25±9.44	F (33) M (15)	RRMS	10.66±6.662
Cognitive-motor dual-task training improves dynamic stability during straight and curved gait in patients with multiple sclerosis: a randomized controlled trial (32).	Tramontano, M. et al.	2024	RCT	Completed by non-participating therapist and assessor-blinded	Neurological Rehabilitation Hospital, Italy	39	50.95±9.78	F (22) M (17)	RRMS and SPMS (n = unknown)	12.62±9.85
The efficiency of mirror therapy on drop foot in	Tosun, A.T. et al.	2020	RCT	Randomized via Microsoft Excel software and concealed from	University Hospital, Turkey	40	42.08±10.37	F (19) M (7)	RRMS (13) SPMS (14)	9.88±6.07

Multiple Sclerosis Patients (29).				assessor and assessor-blinded						
Visuo-proprioceptive training reduces risk of falls in patients with multiple sclerosis (112).	Prosperini, L. et al.	2010	Case-control trial	Not required	Facility unknown, Italy	40 cases, 12 control	39.26±11.44	F (35) M (19)	H (12) RRMS (26) SPMS (14) PPMS (1)	Unknown
Sensory integration balance training in patients with multiple sclerosis: A randomized, controlled trial (31).	Gandolfi, M. et al.	2015	RCT	The blinded therapist completed randomization using a computer-generated random numbers table and assessor assessor-blinded	Gym of Neurological Rehabilitation , Italy	80	48.41±6.83	F (59) M (21)	Unknown	13.78±7.28

RCT (Randomised control trial); age and MS duration presented as mean ± Standard deviation (SD), n refers to number of participants; H (healthy individuals); RRMS (Relapsing-Remitting Multiple Sclerosis); SPMS (Secondary Progressive Multiple Sclerosis); PPMS (Primary progressive Multiple Sclerosis).

The intervention duration ranged between one month (four weeks) and 24 months (104 weeks) with the majority completed in 12 weeks (n = 4) (29,32,111,112). Three of the studies had sessions at least three days per week (29,31,32). One study had sessions twice per week (111).

Table 4.3 Breakdown of the exercise protocol and study procedure of the six studies included in this systematic review

Study	**Exercise protocol** **Intervention duration (weeks), Frequency (days/week), Exercise duration (minutes), Intensity**	**Standardised procedure**	**Procedure: group one (n) = number of participants**	**Procedure: group two (n) = number of participants**	**Procedure: group three (n) = number of participants**	**Procedure: group four (n) = number of participants**	**Procedure: group five (n) = number of participants**
Hortobágyi, T. et al. (30)	104 weeks, 5 days/week for the initial 5 weeks then 3 days/week for the 99 maintenance weeks, 60 minutes, High-intensity (75% of age-predicted HR maximum, and RPE of 7/10).	Warm-up for 10 minutes. Interventions lasted 40 minutes. Cool down for 10 minutes.	EXE (14) - sensory and visual agility exercises with the Xbox 360 core system.	BAL (14) - balance exercises and stepping exercises.	CYC (14) - spinning class.	PNF (14) - delivered by a PNF-trained physical therapist.	C (12) – no exercise.
Escudero-Uribe, S. et al. (107)	12 weeks, 2 days/week, 60 minutes – 100 minutes (5-minute increase from week 1 -9) then 100 minutes (from week 9 -12), based on RPE 11–12 (light-intensity) to 13–15 (moderate to high intensity).	Warm-up for 5 minutes. Aerobic exercise for 15-30 minutes. Circuit exercise for 15-30 minutes. Stretching for 5 minutes. Cool down for 5 minutes.	WBV (16) - exercises performed using a Zeptor Med System.	BT (14) - exercises performed using BT software.	C (18) - no exercise.	n/a	n/a
Tramontano, M. et al. (32)	4 weeks, 3 days/week, 50 minutes, not reported.	30-minute stretching, mobilisation, neuromuscular assistance, gait, and balance exercises.	Conventional Training Group (16) - did the standard procedure only.	Dual Task Group (20) - cognitive exercise was added to the standardised	n/a	n/a	n/a

		20-minute postural stability exercises.		procedure for an extra 20 minutes			
Tosun, A.T. et al. (29)	12 weeks, 3 days/week (in person from week 1 – 6) and 2 days/week (at home from week 1 – 6) then 5 days/week (at home from week 7 – 12), 35 minutes, not reported.	20-minute NMES. 35-minute ROM, stretching, and resistive exercises (with a TheraBand) of the ankle.	EXP (13) - exercised with the mirror box.	C (13) - exercised without the mirror box.	n/a	n/a	n/a
Prosperini, L. et al. (108)	12 weeks, 0 days/week (from week 1 – 6) then 2 days/week (from week 7 – 12), 45 minutes, progressed based on participant's improvement.	None between the case and control group.	EXP (40) - Static and dynamic exercises with and without the equilibrium board. Performed with open and closed eyes with/out visual feedback, or with smooth pursuit.	C (12) - no exercise.	n/a	n/a	n/a
Gandolfi, M. et al. (31)	5 weeks, 3 days/week (week 1 to 5) then 0 days/week (week 6 -10), 50 minutes, progressed based on participant's improvement.	None between the case and control group.	EXP (39) - Graded exercises were performed at three levels of difficulty and repeated under three visual conditions: with free vision, blindfolded, and while wearing a visual-conflict dome.	C (41) - passive and active lower body mobilisation, stretching, and strengthening exercises.	n/a	n/a	n/a

			Unstable and stable surfaces were used when performing the exercises.				

BT (Balance Therapy) group; BAL (Balance) group; EXE (Exergaming) group; EXP (Experimental) group; C (Control group); CYC (Cycling) group; PNF (Proprioceptive Neuromuscular Facilitation) group; WBV (Whole-Body Vibration) group; HR (heart rate); RPE (rate of perceived exertion); NMES (Neuromuscular Electrical Stimulation); Xbox 360 core system (Kinect Adventures video game); GAITRite electronic walkway (a portable gait analysis system); Zeptor Med System (vibration system set at amplitude ¼ 3 mm, average frequency ¼ 4 Hze1 Hz/sec); BT software (mechanical device that provides a fall-safe balancing environment); instrument assessment with inertial measurement units (IMU) located on the head, sternum, and pelvis measuring three-dimensional linear accelerations and angular velocities. Number of participants in each group referred to as n.

Although all studies used different types of outcome measuring tools, they were all concerned with the physical and psychological function, and QoL of the participants. Approximately 67% (n = 4) assessed gait and balance (30–32,111), 33.33% (n = 2) assessed posture (32,111), and 83.33% (n = 5) directly assessed proprioception (29–32,111,112). All six studies found an improvement in the outcome measures of the experimental groups in at least one outcome measured. This is presented in Table 4.4 below.

Table 4.4 Outcome measures assessed and study findings of the six studies included in this systematic review

Study	Outcomes assessed	Study results (+) increase, (-) decrease, (/) no change
Hortobágyi, T. et al. (30)	MSIS-29	At 5 weeks, there was a (+) 11% in EXE group (P=<.001), (+) 6% in BAL and CYC group (P=.001), (/) in PNF and C group. At 104 weeks, there was a (+) 23% in the EXE group (P=<.001), (-) 6% in BAL and CYC group (P=<.001), (/) in PNF and C groups.
	TAT	At 5 weeks, there was a (+) 11% - 21% in EXE, BAL, and CYC groups (P=<.001), (/) in PNF and C groups. (/) in all groups at 104 weeks (P=<.001).
	BBS	At 5 weeks, there was a (+) 30% in EXE group (p=<.001), (+) 23% in BAL group (P=<.001), (+) 13% CYC group (P=<.001), (+) 8% in PNF group (P=<.001) and (-) 0.3 in C group (P=<.001). At 104 weeks, there was a 12-point difference between the EXE group and all other groups.
	Centre of pressure path	(/) change in all groups (P=>.05).
Escudero-Uribe, S. et al. (107)	MFIS	At 12 weeks, the WBV group (+) by 16.3%, the BT group (+) by 15.61%, and the C group (-) by 4.69% (P=0.21).
	MusiQoL	At 12 weeks, the WBV group (-) by 0.93%, the BT group (-) by 3.25%, and the C group (+) by 4.88% (P=0.145).
	GAITRite electronic walkway	At 12 weeks, the functional ambulation profile in the WBV group was (+) by 2.75%, the BT group (+) by 1.28%, and the C group (-) by 2.03% (P=0.005).
Tramontano, M. et al. (32)	Mini-BESTest	At 12 weeks, the DT group (+) by 3.03%, and the CT group (-) by 2.42% (P=<0.017). The DT group significantly improved from baseline to follow-up 1 at 6 weeks (P=0.013).

	MBI	At 12 weeks, the DT group (+) by 0.65%, and the CT group (+) by 1.69% (P=>0.05).
	Instrumental sensor-based assessment (IMU)	At 6 weeks, the DT group (+) for the 10mw test showing improvements in the ML axis for AC (S to H level) (U=88, P=0.021), LDLJa for P (U=89, P=0.041), and at 12 weeks, AP and CC axis for AC (S to H level) (U=60, P=0.01). At 6 weeks, the DT group (+) for the Fo8W in the ML axis for nRMS (H level) (U=89, P=0.023) and AC (S to H level) (U=62, P=0.001). At 12 weeks, the Fo8WT and FST showed differences in within-analysis for spatiotemporal parameters (P=<0.017).
Tosun, A.T. et al. (29)	Proprioception of ankle joint.	At 12 weeks, the MT group (+) by 72.64% (P=0.001), and the C group (+) by 9.61% (P=0.001).
Prosperini, L. et al. (108)	MSQoL-54	At 12 weeks, the EXP group (+) by 33.16% (P=0.04), with no pre-test data for the C group.
	Stabilometric test and monopodalic test	At 12 weeks, the EXP group (+) by 2.5% (P=<0.001), with no pre-test data for the C group.
Gandolfi, M. et al. (31)	BBS	At 10 weeks, the EXP group (+) by 10.32%, and the C group (+) by 3.96% (P=0.001).
	ABC	At 10 weeks, the EXP group (+) by 14.46%, and the C group (+) by 9.87% (P=>0.05).
	SOT	At 10 weeks, the EXP group (+) by 23.19%, and the C group (+) by 2.55% (P=<0.05).
	MSQOL-54	At 10 weeks, the EXP group (+) by 4.25% (physical and mental components only), and the C group (+) by 4.16% (physical and mental components only) (P=>0.05).
	Number of falls	At 10 weeks, the EXP group (+) by 86.44%, and the C group (+) by 27.43% (P=0.053).

ABC (Activities-specific Balance Confidence Scale); BBS (Berg Balance Scale); MFIS (Modified Fatigue Impact Scale); MSQoL-54 (MS Quality of Life 54-item version); MSIS-29 (Multiple Sclerosis Impact Scale); MusiQoL (Multiple Sclerosis International Quality of Life); SOT (Sensory Organization Balance Test); TAT (Tinetti Assessment Tool); NMES (Neuromuscular Electrical Stimulation); ROM (range of motion); GAITRite electronic walkway (a portable gait analysis system); instrument assessment with inertial measurement units (IMU) located on the head, sternum, and pelvis measuring three-dimensional linear accelerations and angular velocities. BT (Balance Therapy) group; BAL (Balance) group; EXE (Exergaming group); EXP (Experimental) group; C (Control) group; CYC (Cycling) group; PNF (Proprioceptive Neuromuscular Facilitation) group; WBV (Whole-Body Vibration) group; 10mWT (10-metre walk

test); Fo8WT (Figure of eight test); FST (Fukuda Stepping Test); AP (antero-posterior); ML (medio-lateral); CC (cranio-caudal); P (pelvis); S (sternum); H (head); AC (Attenuation coefficients); LDLJa (Log Dimensionless Jerk on acceleration); nRMS (normalized root mean square); $p<0.05$ shows statistical significance.

4.3 Findings Based on the Outcome Measures of this Study

This study was interested in the outcome measures that impacted proprioception, balance, and QoL in MS patients. This is further discussed below.

4.3.1 Changes in proprioception

Five studies reported on the proprioception tools that were reviewed. Prosperini, L et al., (2010) reported a 2.5% improvement in proprioceptive strategy concerning postural change (112). Tramontano, M et al., (2024) saw a significant improvement in posture using IMU sensors placed on the head, the sternum, the pelvis, and the outside of the ankle (32). Assessments were statistically presented. Hortobágyi, T et al., (2022) saw no change in the centre of pressure during a 20-second balance activity (30). Escudero-Uribe, S et al., (2017) noticed an improvement in spatiotemporal parameters in both experimental groups, while there was a slight decline in spatiotemporal parameters in the control group (111). Tosun, A.T et al., (2020) saw a significant increase in ankle proprioceptive acuity in the experimental group (29). This information is presented below in Table 4.5.

Table 4.5 Changes in proprioception in Multiple Sclerosis patients

Study	Parameters	Intervention group 1 (main study group) EXP, DT, EXE, WBV, and MT respectively		Intervention group 2 (participated in exercise therapy) CT, (BAL – CYC - PNF), BT, and C respectively		Intervention group 3 (no exercise therapy given) C	
		Baseline	**Final**	**Baseline**	**Final**	**Baseline**	**Final**
Prosperini, L. et al. (108)	Changes in proprioceptive strategy	0 (0–10.0)	2.5 (0–44.4)	-	-	Not measured	46.7 (10.0–76.3)
Tramontano, M. et al. (32)	Changes in postural control during dynamic motor tasks for 10mWT (AC in ML, CC and AP axis)	Not provided	30 (20-40)	Not provided	50 (30-70)	-	-
Hortobágyi, T. et al. (30)	Changes in centre of pressure (NEC, NEO, WEC, WEO)	12 (3.86), 11.6 (8.18), 8.6 (3.61), 12.3 (5.32)	Not reported due to insignificant result	11.7 (3.31), 11.8 (8.18), 9.3 (2.98), 13 (4.15) – 11.4 (5.03), 11.6 (3.86), 7.8 (2.7), 11.8 (3.81) – 10.4 (3.01), 9.2 (6.23), 8.7 (2.23), 11.4 (3.22)	Not reported due to insignificant result	10.1 (3.79), 10.3 (7.53), 8.9 (3.6), 13 (4.51)	Not reported due to insignificant result
Escudero-Uribe, S. et al. (107)	Functional ambulation profile	94.7 (6.7)	97.3 (4.5)	93.9 (7)	95.1 (8.3)	93.5 (5.8)	1.6 (9.1)
Tosun, A.T et al. (29)	Proprioception of the ankle	8.5 (2.94)	2.23 (1.83)	5.62 (1.82)	5.08 (1.89)	-	-

EXP (Experimental) group; C (Control) group; DT (Dual Task) group; CT (Conventional Training) group; ; EXE (Exergaming) group; EXP (Experimental) group; C (Control) group; CYC (Cycling) group; PNF(Proprioceptive Neuromuscular Facilitation) group MT (Mirror Therapy) group; BT (Balance Therapy) group; WBV (Whole-Body Vibration) group; 10mw test (10-metre walk test); NEC (narrow stance eyes closed); NEO (narrow stance eyes open); WEC (wide stance eyes closed); WEO (wide stance eyes open); AP (antero-posterior); ML (medio-lateral); CC (cranio-caudal); AC (Attenuation coefficients). Expressed as median (range) for the study conducted by Prosperini, L et al. or median (interquartile range) for the study conducted by Tramontano, M et al. or mean (SD) by all other studies.

4.3.2 Changes in balance

Three studies reported on the balance tools that were reviewed. In all studies, there was an overall improvement in balance in the experimental groups. One study reported a decline in balance of 2.42% in the conventional therapy group (32). One study reported no change in balance for the PNF group as well as the control group (30). Hortobágyi, T. et al., (2022) conducted their study over 24 months which resulted in the greatest improvements in balance (30%) (30). Two studies used more than one assessment tool allowing for a more accurate indication of the changes in balance in each group (30,31). This information is presented below in Table 4.6.

Table 4.6 Changes in balance in Multiple Sclerosis patients

Study	Parameters	Intervention group 1 (main study group) EXE, EXP, and DT respectively		Intervention group 2 (participated in exercise therapy) (BAL – CYC - PNF), C, and BT respectively		Intervention group 3 (no exercise therapy given) C	
		Baseline	**Final**	**Baseline**	**Final**	**Baseline**	**Final**
Hortobágyi, T. et al. (30)	TAT; BBS	15.9 (1.86); 21.7 (3.56)	(at 5 weeks) 18.3 (1.86); 27.8 (3.56)	16.4 (1.22) – 15.7 (1.89) – 16.4 (1.22); 21.9 (2.32) – 20.7 (3.79) – 21.1 (1.51)	(at 5 weeks) 18.8 (1.22) – 18.1 (1.89) – 16.4 (1.22); 26.5 (2.32) – 24.6 (3.79) – 23.6 (1.51)	16.7 (1.61); 22.5 (4.38)	(at 5 weeks) 16.7 (1.61); 22.3 (4.38)
Gandolfi, M. et al. (31)	BBS; ABC; SOT – on a firm surface (EO, EC, Dome) and a compliant surface (EO, EC, Dome)	47.97 (4.89); 63.99 (13.63); 111.69 (22.18), 64.98 (29.9), 55.83 (23.57) and 93.27 (27.84), 46.13 (23.36), 35.7 (11.56)	52.92 (2.97); 73.24 (12.97); 126.75 (20.03), 86.15 (34.21), 71.82 (30.85) and 107.5 (28.73), 68.93 (30.47), 63.15 (30.18)	46.49 (5.21); 58.99 (18.34); 109.44 (38.24), 57.56 (25.6), 59.4 (31.7) and 90.15 (32.93), 46.18 (24.72), 43.47 (29.97)	48.33 (5.88); 64.81 (20.6); 115.91 (35.91), 60.78 (27.96), 63.35 (34.11) and 87.44 (33.01), 48.06 (27.47), 41.02 (28.94)	-	-
Tramontano, M. et al. (32)	MINI-BESTest	18.49 (6.59)	21.75 (5.8)	18.15 (6.51)	17.71 (8.1)	-	-

BAL (Balance) group; EXE (Exergaming) group; EXP (Experimental) group; C (Control) group; CYC (Cycling) group; PNF (Proprioceptive Neuromuscular Facilitation) group; DT (Dual Task) group; CT (Conventional Training) group; ABC (Activities-specific Balance Confidence Scale); BBS (Berg Balance Scale); SOT (Sensory Organization Balance Test); TAT (Tinetti Assessment Tool); EO (eyes-open); EC (eyes-closed); Expressed as mean (SD).

4.3.3. Changes in quality of life

Five studies reported on the QoL tools that were reviewed. Two studies assessed the frequency of falls in the participants. This showed the greatest improvement in the experimental group (Gandolfi, M et al., (2015) improved by 86.44%, and Prosperini, L et al., (2010) improved by 76.05% with eyes open and 78.97% with eyes closed) (31,112). Three studies used more than one assessment tool. Escudero-Uribe, S et al., (2017) saw a significant improvement in the MFIS tool but a slight decline in the MusiQoL in both experimental groups. The control group improved in the MusiQoL assessment and declined in the MFIS assessment. Gandolfi, M et al., (2015) and Prosperini, L. et al., (2010) saw an improvement in the experimental groups (31,111,112). This information is presented below in Table 4.7.

Table 4.7 Changes in quality of life in Multiple Sclerosis patients

Study	Parameters	Intervention group 1 (main study group) EXE, WBV, DT, EXP, and MT respectively		Intervention group 2 (participated in exercise therapy) (BAL – CYC - PNF), CT, BT, and C respectively		Intervention group 3 (no exercise therapy given) C	
		Baseline	**Final**	**Baseline**	**Final**	**Baseline**	**Final**
Hortobágyi, T. et al. (30)	MSIS-29	108.7 (9.29)	(at 5 weeks) 97.7 (9.29)	110.7 (9.76) - 106 (10.35) - 110.1 (8.59)	(at 5 weeks) 104.7 (9.76) – 100 (10.35) – 110.1 (8.59)	109.8 (10.67)	(at 5 weeks) 109.8 (10.67)
Escudero-Uribe, S. et al. (107)	MFIS; MusiQoL	49.7 (13.3); 64.2 (11.6)	41.6 (14.3); 64.8 (12.8)	50.6 (17.4); 64.6 (12.2)	42.7 (20.8); 66.7 (13.7)	49 (11.1); 61.5 (10.6)	51.3 (18.4); 58.5 (15.1)
Tramontano, M. et al. (32)	MBI	96.86 (4.52)	96.23 (7.25)	96.92 (4.49)	95.35 (5.67)	-	-
Gandolfi, M. et al. (31)	MSQoL-54; number of falls	61.05 (20.15); 0.59 (0.99)	63.19 (17.94); 0.08 (0.27)	60.5 (16.62); 0.37 (0.54)	63.25 (13.18); 0.27 (0.55)	-	-
Prosperini, L. et al. (108)	MSQoL-54; risk of falls – stabilometric (EO, EC) and monopodalic (EO, EC)	75 (0–100); 0 (0–25.2), 0 (0–87.5) and 39.3 (0–88.4), 67.3 (26.8–99.1)	80 (40–11); 0 (0–20.4), 0 (0–37.0) and 15.7 (0–66.3), 52.6 (11–95.3)	-	-	Not measured	-; 0 (0–0), 0 (0–0) and 9.4 (0 - 41.7), 12.7 (0 - 47.1)

BT (Balance Therapy) group; BAL (Balance) group; EXE (Exergaming) group; EXP (Experimental) group; C (Control) group; CYC (Cycling) group; PNF (Proprioceptive Neuromuscular Facilitation) group; WBV (Whole-Body Vibration) group; DT (Dual Task) group; CT (Conventional Training) group; MBI (Modified Barthel Index); MFIS (Modified Fatigue Impact Scale);

MSQoL-54 (MS Quality of Life 54-item version); MSIS-29 (Multiple Sclerosis Impact Scale); MusiQoL (Multiple Sclerosis International Quality of Life); EO (eyes-open); E (eyes-closed). Expressed as median (range) for the study conducted by Prosperini, L et al. or mean (SD) by all other studies.

4.4 A Summary of findings based on the objectives

A summary of the findings, based on the objectives, is presented below in Table 4.8

Table 4.8 Summary of the findings of this study based on the objectives (35)

Objective	**Findings**
To identify studies done from 2003 to 2024 that have researched the effects of exercise on proprioception in adult Multiple Sclerosis patients worldwide.	Four hundred and forty studies across five databases (PubMed, CINAHL ultimate, ProQuest Central, SPORTDiscus, and SCOPUS) were collected. Formulated search terms were used to identify studies (exercise therapy/ies, rehabilitation exercise/s, Multiple Sclerosis, MS, and proprioception). Nine studies (2.05%) that researched exercise and proprioception in MS patients worldwide were identified.
To systematically review the relevance of the studies identified, the JBI critical appraisal tool was used to investigate exercise and proprioception in adult multiple sclerosis patients worldwide.	All nine studies were assessed for methodological quality using the JBI critical appraisal tool for RCTs and clinical case-control studies, Black's and Down, and the CERT checklist. Six studies (66.67%) out of nine were eligible to be included in this review. The three studies that were excluded were due to a wrong study design used (the study was not an RCT or case-control trial), did not meet the inclusion criteria (did not use exercise therapy and/or proprioceptive input), and had a high risk of bias.
To highlight and recommend a set of exercise modalities that positively and negatively affect proprioception in adult Multiple Sclerosis patients.	Five studies (83.33%) researched proprioceptive changes in their participants. Out of five studies, four (80%) had at least one intervention group (6 out of 16 groups) that performed exercise therapy without proprioceptive

	input. Exercise modalities included aerobic (n = 2), resistance (n = 2), flexibility (n = 3), mobility (n = 2), and neuromuscular (n = 4) exercises. Three studies (60%) showed that exercise therapy without proprioceptive input had a positive effect on proprioception in MS patients. One study (20%) showed that exercise therapy without proprioceptive input did not affect proprioception in MS patients. No study harmed proprioception in MS patients.

MS (Multiple Sclerosis); JBI (Joanna Briggs Institute); CERT (Consensus on Exercise Reporting Template). N – number of intervention groups that used only exercise as a modality.

4.5 Conclusion

Building upon these results, an in-depth critique of the findings will be presented in the upcoming chapter to assess their significance, and implications for future research and clinical practice.

5 Discussion

5.1 Introduction

This chapter will discuss the findings presented in the results chapter. The findings will be compared to existing evidence. This will help the reader acknowledge the gaps in the literature that were filled.

5.2 Study Findings

Only six studies exploring the direct relationship between exercise therapy and proprioception in MS patients in SA and worldwide have been documented. This review aimed to establish the direct link exercise therapy has on proprioceptive acuity. To our knowledge, this is the first review on this topic.

This review found that exercise therapy had a positive impact on proprioception in MS patients (see Table 4.5), and this correlated to improved balance and QoL (see Table 4.6 and 4.7). Despite this, exercise protocols that included proprioceptive input showed greater improvements in proprioception, balance, and QoL. This suggests that exercise therapy may be sufficient to impact proprioception, but the improvements may be delayed compared to exercise therapy protocols that include proprioceptive input.

5.2.1 Exercise therapy without proprioceptive input positively impacts proprioception in MS patients

The results of the study confirmed that exercise therapy, without proprioceptive input, positively impacts proprioception in MS patients with 60% (n = 3) of the studies reporting improvements in postural change or joint position sense in the intervention groups that consisted of exercise therapy only (29,111,112). This can be found in Tables 4.4 and 4.5. The findings of the review are consistent with a study conducted by Sokhangu et al., (2021) who conducted an RCT that concluded that neuromuscular exercises, in particular plyometric exercises, had a positive impact on proprioceptors indicating that exercise therapy, without proprioceptive input, may enhance proprioception in MS patients (106). Furthermore, a systematic review conducted by Lee et al., (2024) found similar results with nine stroke

patients who participated in weight training exercises that consisted of core stability exercises (120). The patients experienced improvements in trunk positioning error (120).

5.2.2 Certain exercise modalities impact proprioception in MS patients while others do not

This study found that aerobic (n = 2), resistance (n = 2), flexibility (n = 3), mobility (n = 2), and neuromuscular (n = 4) exercises positively impacted proprioception in MS patients (29,32,111,112). All four studies utilised neuromuscular exercises in at least one intervention group that performed exercise therapy without proprioceptive input. Neuromuscular exercises aim to improve sensorimotor function in individuals (121). In this study, these exercises included static and dynamic balance exercises (e.g. standing on one leg), stepping exercises (e.g. marching), PNF, and coordination exercises (e.g. Pilates ball exercises, bird dog). Three studies resulted in significant improvements in proprioception (P= 0.005, <0.017, and 0.001 respectively) (29,32,111). This can be seen in Tables 4.4 and 5.2. This suggests that exercise protocols that include neuromuscular exercises may produce the greatest results in proprioceptive improvements. This finding is consistent with a systematic review that found neuromuscular exercises (balance training, yoga, strength and flexibility training of the whole body) improved both proprioceptive acuity and motor performance in all populations (122).

Agility exercises performed using an Xbox 360 gaming system showed no improvements in the centre of pressure for the participants (30). This study indicates that agility exercises had no significant impact on proprioception, as observed in the research conducted by Hortobágyi et al., (2022). This absence of effect could be due to the center of pressure not being the primary outcome measure of the study. Furthermore, most research has analysed the effect of proprioceptive exercises on agility and has found improvements (123–126). Understanding the direct link between agility exercises and proprioceptive changes cannot be made as none that analysed the link between agility exercises (as a modality), and proprioception was found. Below is a table of all exercises used in the reviewed studies and their impact on proprioception.

Table 5.1 Exercise modalities that positively and negatively affect proprioception in Multiple Sclerosis patients.

Exercise Modality	**Examples of exercises**	**Effect on proprioception**	**Sensory input included**	**Impact from sensory input**
Aerobic	Cycling, treadmill walking, elliptical trainer	Positive	Whole body vibration (Zeptor Med system), Dynamic Balance System (Balance-Sift version 01.04.02), moving head toward the direction of a sound while opening and closing eyes	Enhanced proprioception
Resistance	Muscle activation with Therabands, body weight activities such as squatting	Positive	Mirror box, Whole body vibration (Zeptor Med system), Dynamic Balance System (Balance-Sift version 01.04.02), equilibrium board	Enhanced proprioception
Mobility	ROM exercises such as single leg raise, internal/external hip movement	Positive	Mirror box	Enhanced proprioception
Flexibility	Active and passive stretching in sitting, standing, and lying positions	Positive	Mirror box	Enhanced proprioception
Neuromuscular	Static and dynamic balance exercises (standing on one leg), stepping exercises (marching), PNF, coordination exercises (Pilates ball exercises, bird dog)	Positive	Whole body vibration (Zeptor Med system), Dynamic Balance System (Balance-Sift version 01.04.02), moving head toward the direction of a sound while opening and closing eyes on an uneven surface,	Enhanced proprioception

			equilibrium board, blindfolded or wearing a visual-conflict dome with exercises performed on a foam mat	
Agility	Exercise gaming system (Xbox 360 core)	Neutral	Sensorimotor and visuomotor on the gaming system	No impact on proprioception

Based on the outcome measures of this study, further findings on proprioception, balance, and QoL were found. This will be discussed in more detail below.

5.3 Effects of Exercise on Proprioception

Despite the positive impact exercise therapy had on proprioception, this study found that exercise therapy produced better results in proprioceptive acuity when it was combined with sensory input (29,32,111,112). This statement is agreed by Tramontano et al., (2024) who compared the outcomes of dual-task exercise and motor exercise on dynamic postural stability (32) and Tosun et al., (2021) compared the outcomes of exercise therapy with and without visual input (29).

A decreased proprioceptive acuity has been seen in other neurodegenerative diseases, mainly Parkinson's disease (127–129). Parkinson's disease is known as a disease that results in the progressive decline of neurons that produce dopamine located in the basal ganglia (CNS) (130). Similar to MS, patients with Parkinsons disease may experience decreased postural control and balance which may affect their QoL (127–129). A study assessed the effects of ankle proprioception in patients with mild-to-moderate disease on functional mobility (129). They found that ankle proprioception was not related to poor functional mobility (P=>0.05), while an alternative study researched the impact of ankle proprioception on function in MS patients and saw similar results (131). However, they did note that MS patients had a slower reaction time compared to healthy individuals (131). This may be the result of demyelinated neurons transmitting proprioceptive input to the CNS (20).

Exercise therapy (specifically Yoga, Tai Chi, and resistance exercises) may improve proprioception in patients with Parkinsons disease as seen in a systematic review conducted by Guo et al., (2024). This follows the findings that were seen in this review.

5.4 Effects of Exercise on Balance

Deficits in balance are a common symptom experienced by MS patients (4). This study hypothesised that an improvement in proprioceptive acuity will lead to an improvement in balance since balance helps maintain and restore postural equilibrium during daily activities and proprioception directly influences postural stability (1,9). Therefore, balance changes were assumed to be influenced by changes in proprioception. This study found that exercise therapy improved balance in MS patients (see Tables 4.4 and 4.6) (30,31). This is consistent with previous systematic reviews that found improvements in functional balance (83,132–134).

Although exercise therapy has a positive effect on balance, improvements were enhanced in groups that combined sensory input and exercise therapy (30–32). This suggests that exercise therapy, without proprioceptive input, may lead to delayed improvements in proprioception and thus improve balance in MS patients (31). However, a meta-analysis conducted on different exercise types on balance function in MS by Hao et al., (2022) found that yoga was the most effective at improving dynamic and static balance (83). This is achieved by stretching activities that improve the ROM of joints that affect postural control and the centre of gravity of patients. Yoga also incorporates positions that require your eyes to be closed which improves your sensory systems leading to better balance (83). Yoga is a form of exercise therapy that builds self-awareness while improving strength, flexibility, and mobility. It has been found to also improve proprioception (135), which may have a positive impact on balance.

All reviewed studies did not use yoga as a modality to impact proprioception suggesting that specific exercise modalities may have a direct link to proprioception and may impact balance in MS patients. This is demonstrated in one reviewed study that saw a decline in functional balance in the control group that participated in exercise therapy consisting of muscle stretching, joint mobility, neuromotor facilitation, gait, and balance exercises using swinging platforms (32). Limited use of various exercise modalities, such as yoga or Pilates, was acknowledged encouraging the further need for research on different exercise modalities that investigate the relationship between proprioception and balance in MS patients in SA and worldwide is needed.

5.5 Effects of Exercise on Quality of Life

Proprioception affects walking, postural control, and balance which are linked to the physical aspects of QoL, this study hypothesised that an improvement in proprioceptive acuity will lead to an improvement in QoL (36,136). This study found that exercise therapy improved QoL in MS patients (see Table 4.7) (31,32,112). This is despite one study that found a decline in QoL in their study but concluded that it was attributable to the type of QoL assessment tool that was chosen (MusiQoL compared to the MusiQoL-54) (111). Improvements in QoL seen in this review are consistent with previous reviews (133,137).

Although exercise therapy has a positive effect on QoL, improvements were enhanced in groups that combined sensory input and exercise therapy (31,32,112). This suggests that exercise therapy, without proprioceptive input, may lead to delayed improvements in proprioception and thus improve QoL in MS patients. This is agreed by Reina-Gutiérrez et al., (2022) who conducted a systematic review that concluded that sensorimotor training as an exercise modality was found to be more effective than other modalities (aerobic, combined, mind-body, resistance) at improving QoL related to health (physical and mental) in MS patients (82).

5.6 Types of Exercise Modalities Included in the Studies Reviewed

This study found that exercise modalities that included balance training on uneven surfaces, visual input, eyes open and closed, and/or mechanical stimulation (whole body vibration) showed greater improvements than the other intervention groups (29–32,111,112). This suggests that exercise therapy without proprioceptive input may be limiting to improve proprioception in MS patients despite the length of the intervention, as seen in the two-year-long study conducted by Hortobágyi et al., (2022) (30). This is agreed by Moghadasi et al., (2020) who suggested that total body resistance exercises may affect proprioception in the knee of MS patients at a 60-degree setting on a Biodex Isokinetic Dynamometer machine (24). However, no change in proprioception at 30 degrees was evident between experimental and control groups, further suggesting that exercise therapy without proprioceptive input may improve proprioception insignificantly (24).

All studies had a component of aerobic, strengthening, stretching, neuromuscular, and/or mobility exercises, which have been shown to improve QoL in MS patients (3,24–26).

Previous reviews found aerobic exercise, and yoga were most effective at improving balance and QoL in MS patients (83,137), but another study concluded that yoga did not significantly improve proprioception (which has been linked to balance and QoL in this review) (120), providing contradictory findings in the literature.

In this review, only one study was found that consisted of an intervention group that solely did aerobic activity (30). Balance and QoL improved but were not maintained for the full duration of the study (24 months). This is inconsistent with a study that showed severe disease progression of MS benefited from aerobic exercise to improve the physical component of QoL (82). Another study has linked improved QoL with aerobic activity (81). Further research on the impact of different exercise modalities on proprioception, balance, and QoL in MS patients in SA is needed, as all reviewed studies were not conducted in SA.

5.7 Similarities and Differences between Study Interventions Included in this Review

There were inconsistencies in the length and duration of the interventions between studies. This provides uncertainty in knowing what the preferred length of an intervention is. Despite this, all six studies were conducted within the recommended length (4 weeks – 12 weeks) (138) with one study extending its length to two years (30). The duration of all study protocols were 45-100 minutes. The reviewer (BM) agrees with the length of the intervention conducted by Hortobágyi et al., (2022) as the process of neuroplasticity is generally long with notable changes possibly after 48 weeks (28). Neuroplasticity allows for new nerve pathways in the brain that facilitate proprioception, balance, and QoL thus prioritising exercise regimens that support this change in MS patients long-term is beneficial (27,28). This is disagreed by Corrini et al., (2023) who conducted a systematic review and found that a few sessions a week (4 – 12 weeks, 2 - 3 days/week) of high-intensity training lasting for at least 40 minutes was sufficient to produce neuroplasticity (132). Further research determining the preferred length and duration of interventions is needed worldwide to provide healthcare professionals with a standardised management protocol for their patients.

One 12 week study (29) saw the greatest improvements in proprioception of the ankle joint (72.64%) suggesting that 12 week interventions may be sufficient to result in enhanced proprioceptive pathways in MS patients. All studies had supervised protocols, but intensity

was predominantly subjective. This suggests that the effectiveness of the study protocol may have produced varying results due to inconsistent intensities. Proprioception was the primary outcome measure in the study conducted by Tosun et al., (2021), and was the secondary outcome measure of all other included studies. The effectiveness of this study's intervention (29) could be attributed to proprioception being the primary outcome measured and the intervention length.

Only two studies (31,32) portrayed external validity with regards to the setting of the intervention, suggesting that the findings from each study do not provide adequate external validity for real-world application.

5.8 Similarities and Differences between Outcome Measures

All six studies measured two or more components that impact an MS patient's QoL. However, there were inconsistencies in the type of measuring tool that was used, with four common tools being used in more than one study (FSS, MSQoL-54, BBS, number of falls) (30,31,111,112). These measuring tools are concerned with balance and QoL, with none directly concerned with proprioception. The differences in the types of measuring tools for proprioception in each study may lead to inconsistent interpretations as a standard measuring tool is not established (139). Providing evidence that one type of measuring tool is more reliable than another is thus challenging; and aspects of balance, postural control, and joint position sense are commonly analysed, providing a theory of how proprioception may have been impacted (139). Further research to formulate a standardised measuring tool for proprioception is thus needed worldwide.

Despite the varying measuring tools that have been used for proprioception between studies (see Table 4.3), this may be seen positively as it allows for a selection of measuring tools that can be used in future studies, and it demonstrates that MS is a multifaceted disease that can be affected by different health components which may not be available in a standard measuring tool (111).

5.9 The Quality of Included Studies

5.9.1 Significance of interventions

All reviewed studies resulted in at least one clinically significant improvement in proprioception and/or balance and/or QoL with all intervention groups that partook in exercise therapy (29–32,111,112). This was determined by p-values of less than 0.05 for all outcome measures reviewed in this study (see Table 4.4). This shows that all reviewed studies had significant interventions for their study, indicating the validity of this study.

5.9.2 Significance of this study

All reviewed studies had good validity and/or reliability based on the JBI critical appraisal tool (see Table 4.1 and Appendix E). None displayed a low risk of bias based on the Blacks and Down's checklist (see Appendix F), indicating the validity of this study.

Four studies (n = 66.67%) conducted their interventions using minimal equipment, making these interventions more practical and feasible for real-world application (29,31,32,112). Rehabilitation protocols applied for a minimum of four weeks, three days/week for 50 minutes may produce minor significant changes in proprioception (32). However, protocols applied for 12 weeks, five days/week for 35 minutes may be ideal to produce greater significant changes in proprioception (29). For this reason, the exercise modalities stated in Table 5.2 can be used to improve proprioception in MS patients of European descent. It is recommended that further research on these exercise modalities is done in different regions and on different ethnic groups to examine their significance worldwide. Building on this, further recommendations for clinical practice and future research will be presented.

6 Conclusion and Recommendations

6.1 Conclusion

Previous studies have linked impaired proprioception to decreased gait speed, postural control, balance, and a reduced QoL of MS patients (20–23). Proprioception can thus be seen as a key sensory system that affects balance and QoL in MS patients. Management strategies that have included exercise therapy have positively impacted MS patients' QoL by improving the aerobic fitness, strength, cognition, walking ability, and efficiency of patients (3,24–26). Reduced fatigue, depressive symptoms, and stress were also noted leading to an improved overall QoL experienced by patients (3,24–26). This study aimed to establish a direct link between exercise therapy and proprioception in MS patients. A systematic literature review of narrative synthesis was conducted.

This study found six studies that conducted an RCT or case-control study on exercise therapy and proprioception in MS patients. The results showed that exercise therapy had a positive impact on proprioception, but more significant improvements were seen in intervention groups that included proprioceptive input to the exercise protocol. Improved balance and QoL in MS patients correlated with improvements in proprioception. The effect of sensorimotor input on balance and QoL was greater than that of motor input only. In this review, sensorimotor input included exercise with balance training on uneven surfaces, visual input, eyes open and closed, and/or mechanical stimulation (whole body vibration). Whereas motor input included exercise therapy only (aerobic, strengthening, stretching, neuromuscular, and/or mobility exercises).

Even though exercise therapy positively impacts proprioception and thus balance and QoL in MS patients, combining proprioceptive input to impact proprioception with the exercise protocol may ensure better improvements in balance and QoL in MS patients.

6.2 Clinical/Practical Recommendations

This study found that improvements in proprioception can improve the balance and QoL in MS patients. Prioritising exercise modalities that directly impact proprioception is recommended in clinical practice as it may enhance the QoL of MS patients. The preferred exercise modality in this study is neuromuscular exercise (i.e.: static and dynamic balance

exercises, stepping exercises, PNF, and coordination exercises). However, neuromuscular exercises were combined with other exercise modalities (i.e.: aerobic, resistance, and flexibility). Applying combination therapy (more than one exercise modality) in clinical practice may ensure greater improvements in proprioception, balance, and QoL of MS patients (see Table 4.3).

This study showed that adding sensory input, such as visual stimuli and vestibular stimuli, in conjunction with combined exercise modalities may provide greater improvements in proprioception, balance, and QoL. This study found that mirror therapy and balance exercises performed under various visual conditions (i.e.: with free vision, blindfolded, and while wearing a visual-conflict dome) produced the greatest results in proprioceptive acuity in MS patients. For this reason, applying combination exercise therapy with sensory input in MS rehabilitation programs is recommended (see Table 5.1).

Applying all these findings in resource-constraint environments, such as SA, could be challenging, but most exercise modalities that produced the greatest improvements in proprioception did not require expensive equipment such as an Xbox gaming system. This ensures that clinicians can provide effective rehabilitation programs with inexpensive equipment, for example, a Theraband, balance mat, and mirror, to their MS patients in SA.

6.3 Recommendation for Future Research

This review found studies that analysed proprioception in the European population. Research regarding exercise therapy's impact on proprioception is recommended in other populations (i.e.: the African, Asian, American, and Australian populations). This will contribute to a broader global understanding of how exercise therapy impacts proprioception, balance, and QoL in MS patients.

Future research should aim to identify different exercise modalities (for example, aerobic, combined, resistance, sensorimotor) that improve proprioception in MS patients in different regions, including SA, as improved proprioception has been linked to improved balance and QoL of patients. Understanding the most effective exercise modalities across different regions and ethnic groups will enhance the global body of knowledge essential for optimizing MS treatment worldwide.

It is recommended that multiregional 12+ week RCTs on MS patients analysing singular exercise modalities vs no intervention, using validated proprioceptive assessment tools, should be researched to identify ideal exercise modalities that will enhance proprioceptive acuity and QoL in MS patients. This may further be extended to wide-scale RCTs performed for a minimum of 12 months analysing the long-term physiological changes in the CNS which may correlate with improved proprioception, balance, and QoL.

6.4 Strengths and Limitations

6.4.1 Strengths

To the knowledge of the author, this study is the only study to systematically review the link between exercise and proprioception in MS patients, closing the gap in knowledge on this topic. This review can help pave the way for future research relevant to the SA context. All included studies were peer-reviewed RCTs and case-control trials adding to the credibility of this study. Five of the studies were published within the last 10 years suggesting their relevance to current research (see Table 4.2). All reviewed studies had good validity and/or reliability enhancing the significance of this study.

6.4.2 Limitations

The specific effects of exercise on proprioception have been minimally documented, resulting in limited research on this topic (see Figure 4.1). There is a clear need for more RCTs to establish a definitive link between exercise and proprioception on a global scale. Notably, none of the reviewed studies were conducted in SA, creating a gap in understanding the effectiveness of exercise interventions in this region. Instead, all studies were conducted in Europe, with the majority originating from Italy, limiting cross-regional comparisons of exercise therapy's impact on proprioception across different populations and climates.

Moreover, the studies varied in outcome measures, intervention durations, and participant groups, making direct comparisons difficult (see Tables 4.3 and 4.4). Inconsistent reporting of results further complicated the synthesis of findings, posing challenges in structuring the results chapter of this review. A pilot study was not completed prior to the systematic review.

6.5 Conclusion

This study confirms that exercise therapy has a positive effect on proprioception in MS patients. Although most results were clinically significant, omitting sensory input may result in delayed improvements. Exercise therapy that includes neuromuscular activation is seen as most effective. There were no studies found that explored the effect of exercise therapy in South African MS patients, leaving a gap in the literature for this population. The implication of this is limited understanding by healthcare professionals on the most effective rehabilitation strategies for their patients. Future research in SA should incorporate different exercise modalities to provide healthcare professionals with the varying therapeutic efficacy of different exercise modalities.

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8 Appendix

Appendix A: PRISMA-P checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al.: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

An Editorial from the Editors-in-Chief of Systematic Reviews details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 5:15

Point 2 has been updated to include the registration information.

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☑	☐	2,3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☑	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☑	☐	iv, 25
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☑	☐	Front page

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☑	☐	5
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☑	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☑	☐	9
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☑	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☑	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☑	☐	2,3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☑	☐	2
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☑	☐	3,4

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☑	☐	3
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☑	☐	3,4,5
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☑	☐	4,5
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☑	☐	5,6,7
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☑	☐	5,6,7
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☑	☐	6,7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☑	☐	6,7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☑	☐	5,6,7
DATA					

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☑	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐	☑	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☑	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☑	☐	6,7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☑	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☑	☐	5,6,7

Appendix B: INPLASY Registration

International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

The effects of exercise therapy on proprioception in patients with multiple sclerosis: a systematic review

INPLASY2024110076
doi: 10.37766/inplasy2024.11.0076
Received: 18 November 2024
Published: 18 November 2024

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Risk of bias assessment.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2024110076

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 November 2024 and was last updated on 18 November 2024.

INTRODUCTION

Review question / Objective Does engaging in muscle-strengthening activities in isolation have a direct impact on proprioception, and thus, resulting in a reduction in falls and an enhancement in the quality of life among individuals with Multiple Sclerosis?

Rationale MS has a direct impact on the body's sensory systems, including proprioception. Implementingexercisetherapy, which encompasses both proprioception specific exercises and traditional muscle strengthening exercises, has been shown to effectively mitigate the risk of falls among individuals with MS. To date, an overall review of all researched data on exercise therapy for proprioception in MS patients has not been published highlighting the need to critically review studies available on this topic. Moreover, understanding the relationship between proprioception and MS will allow therapists to better the exercise management plan for MS patients.

Condition being studied Multiple Sclerosis and proprioception.

METHODS

Search strategy Studies are sourced from PUBMED, CINAHL ultimate, ProQuest Central, ScienceDirect, and SCOPUS. Search terms used were exercise therap/ies, rehabilitation exercise/s, Multiple Sclerosis, MS, and proprioception. Searching all databases took place between November 2023 and 31 July 2024. Restrictions on the search include articles that are written in English and available in full text. Studies need to be peer-reviewed and reputable. The publication period is January 2003 to December 2023.

Participant or population Human participants 18 years and older that have been diagnosed with relapsing remitting, primary progressive or secondary progressive MS.

Intervention Exercise therapy and/or proprioception input that provided improvements in proprioceptive acuity, balance, and quality of life of MS patients.

Comparator The intervention will be compared to a control that either did not participate in any exercise therapy and/or proprioceptive training, or a control group that only did exercise therapy compared to the other groups.

Study designs to be included Randomized control trials, and clinical case control studies.

Eligibility criteria Research papers that are written in English, available in full text, peer-reviewed and reputable, conducted between 2003 and 2023, provide the outcomes/results of what was being tested, and investigate the effect of exercise on proprioception, balance and/or fall risk in adult Multiple Sclerosis patients worldwide.

Information sources Electronic databases PUBMED, CINAHL ultimate, ProQuest Central, ScienceDirect, and SCOPUS were the only information sources.

Main outcome(s) Main outcome measures are proprioception and exercise therapy in MS patients, looking specifically at proprioception through the change in posture and/or positioning of the participant's joints mainly seen during standing and/or walking.

Additional outcome(s) Additional outcome measures are quality of life (QoL) and balance in MS patients, looking specifically at Tinetti Assessment Tool (TAT), Berg Balance Scale (BBS), Activities-specific Balance Confidence Scale (ABC), Mini-BESTest test, and Sensory Organization Balance Test (SOT), Multiple Sclerosis Impact Scale (MSIS-29), Modified Fatigue Impact Scale (MFIS), Multiple Sclerosis International Quality of Life (MusiQoL), Modified Barthel Index (MBI), MS Quality of Life 54-item version (MSQoL-54), and number of falls.

Quality assessment / Risk of bias analysis All eligible studies will be screened further using the JBI critical appraisal tool for randomized control trials, and clinical case control studies. This was accompanied by the Black's and Down's and Consensus on Exercise Reporting Template checklist.

Strategy of data synthesis Descriptive narrative summary will be used.

Subgroup analysis No subgroups to be analyze.

Sensitivity analysis The reliability and validity of each study will be noted to assess the quality of this review.

Language restriction English.

Country(ies) involved South Africa.

Keywords Multiple Sclerosis (MS), Quality of life (QoL).

Contributions of each author
Author 1 - Bokamoso Mthimkulu.
Author 2 - Natalia Neophytou.
Author 3 - Merling Phaswana.
Author 4 - Philippe Gradidge.

Appendix C: Database search

Initial search

Date	Database	Search terms	Results
9 November 2023	PUBMED	exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Multiple Sclerosis AND Proprioception	93 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Multiple Sclerosis AND Vestibular Sense	92 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Multiple Sclerosis AND Position Sense	92 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Multiple Sclerosis AND Posture Sense	92 studies on clinical trials, randomised control trials, and books and documents
9 November 2023	PUBMED	exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND disseminated sclerosis AND proprioception	93 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND disseminated sclerosis AND vestibular sense	92 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND disseminated sclerosis AND posture sense	92 studies on clinical trials, randomised control trials, and books and documents

		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND disseminated sclerosis AND position sense	92 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND MS AND position sense	128 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND MS AND posture sense	127 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND MS AND vestibular sense	127 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND MS AND proprioception	129 studies on clinical trials, randomised control trials, and books and documents
9 November 2023	PUBMED	exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Multiple Sclerosis, Acute Fulminating AND proprioception	93 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Multiple Sclerosis, Acute Fulminating AND vestibular sense	92 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Multiple Sclerosis, Acute Fulminating AND posture sense	92 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Multiple Sclerosis, Acute Fulminating AND position sense	92 studies on clinical trials, randomised control trials, and books and documents

		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Remitting-Relapsing Multiple Sclerosis OR Multiple Sclerosis, Relapsing Remitting AND proprioception	21 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Remitting-Relapsing Multiple Sclerosis OR Multiple Sclerosis, Relapsing Remitting AND vestibular sense	21 studies on clinical trials, randomised control trials, and books and documents
9 November 2023	PUBMED	exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Remitting-Relapsing Multiple Sclerosis OR Multiple Sclerosis, Relapsing Remitting AND position sense	21 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Remitting-Relapsing Multiple Sclerosis OR Multiple Sclerosis, Relapsing Remitting AND posture sense	21 studies on clinical trials, randomised control trials, and books and documents
12 November 2023	PUBMED	exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Multiple Sclerosis, Acute Relapsing AND proprioception	14 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Multiple Sclerosis, Acute Relapsing AND vestibular sense	14 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Multiple Sclerosis, Acute Relapsing AND posture sense	14 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Multiple Sclerosis, Acute Relapsing AND position sense	4 studies on clinical trials, randomised control trials, and books and documents

		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Chronic Progressive Multiple Sclerosis AND proprioception	4 studies on clinical trials, randomised control trials, and books and documents
12 November 2023	PUBMED	exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Chronic Progressive Multiple Sclerosis AND Vestibular sense	4 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Chronic Progressive Multiple Sclerosis AND position sense	4 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Chronic Progressive Multiple Sclerosis AND posture sense	4 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Multiple Sclerosis, Remittent Progressive OR Progressive Relapsing Multiple Sclerosis AND proprioception	11 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Multiple Sclerosis, Remittent Progressive OR Progressive Relapsing Multiple Sclerosis AND Vestibular sense	11 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Multiple Sclerosis, Remittent Progressive OR Progressive Relapsing Multiple Sclerosis AND position sense	11 studies on clinical trials, randomised control trials, and books and documents
12 November 2023	PUBMED	exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Multiple Sclerosis, Remittent Progressive OR Progressive Relapsing Multiple Sclerosis AND posture sense	11 studies on clinical trials, randomised control trials, and books and documents

		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Secondary Progressive Multiple Sclerosis OR Primary Progressive Multiple Sclerosis AND proprioception	14 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Secondary Progressive Multiple Sclerosis OR Primary Progressive Multiple Sclerosis AND Vestibular sense	14 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Secondary Progressive Multiple Sclerosis OR Primary Progressive Multiple Sclerosis AND position sense	14 studies on clinical trials, randomised control trials, and books and documents
		exercise therapy OR exercise therapies OR rehabilitation exercise OR rehabilitation exercises OR remedial exercise OR remedial exercises AND Secondary Progressive Multiple Sclerosis OR Primary Progressive Multiple Sclerosis AND posture sense	14 studies on clinical trials, randomised control trials, and books and documents

Refined search

Date	**Database**	**Search terms**	**Results**
18-Jul-24	CINAHL ultimate	"Exercise therapy" OR "exercise therapies" AND "multiple sclerosis" OR "MS" AND proprioception	116 articles found
		"Rehabilitation exercise" OR "rehabilitation exercises" AND "multiple sclerosis" OR "MS" AND proprioception	68 articles found
			135 total
18-Jul-24	SPORTDiscus	"Exercise therapy" OR "exercise therapies" AND "multiple sclerosis" OR "MS" AND proprioception	31 articles found

		"Rehabilitation exercise" OR "rehabilitation exercises" AND "multiple sclerosis" OR "MS" AND proprioception	142 articles found
			171 total
18-Jul-24	PUBMED	"Exercise therapy" OR "exercise therapies" AND "multiple sclerosis" OR "MS" AND proprioception	68 articles found
		"Rehabilitation exercise" OR "rehabilitation exercises" AND "multiple sclerosis" OR "MS" AND proprioception	67 articles found
			68 total
19-Jul-24	SCOPUS	"Exercise therapy" OR "exercise therapies" AND "multiple sclerosis" OR "MS" AND proprioception	6 articles found
		"Rehabilitation exercise" OR "rehabilitation exercises" AND "multiple sclerosis" OR "MS" AND proprioception	0 articles found
			6 total
19-Jul-24	ProQuest Central	"Exercise therapy" OR "exercise therapies" AND "multiple sclerosis" OR "MS" AND proprioception	98 articles found
		"Rehabilitation exercise" OR "rehabilitation exercises" AND "multiple sclerosis" OR "MS" AND proprioception	32 articles found
			118 total

Appendix D: Refined Search Strategy

Initial search terms:

Exercise Therapy, Remedial Exercise/s, Exercise Therapies, Rehabilitation Exercise/s, Multiple Sclerosis, Disseminated Sclerosis, MS, Multiple Sclerosis, Acute Fulminating, Remitting-Relapsing Multiple Sclerosis, Multiple Sclerosis, Relapsing Remitting, Multiple Sclerosis, Acute Relapsing, Chronic Progressive Multiple Sclerosis, Multiple Sclerosis, Remittent Progressive, Progressive Relapsing Multiple Sclerosis, Secondary Progressive Multiple Sclerosis, Primary Progressive Multiple Sclerosis, Proprioception, Vestibular Sense, Position Sense, and Posture Sense

Refined search terms:

Exercise Therapy/ies, Rehabilitation Exercise/s, Multiple Sclerosis, MS, and Proprioception

Appendix E: JBI Critical Appraisal Tool

Assessor: Bokamoso Mthimkulu	Date of Appraisal: 3 September 2024	Record Number: 01
Study Author: Hortobágyi, T; Ács, P; Baumann, P; Borbély, G; Áfra, G; Reichardt-Varga, E; Sántha, G; Tollár, J	Study Title: Comparative Effectiveness of 4 Exercise interventions Followed Years of Exercise Maintenance in Multiple Sclerosis: A Randomized Controlled T	Study Year: 2022

Internal Validity		Choice - Comments/Justification	Yes	No	Unclear	N/A
Bias related to selection and allocation						
1	**Was true randomization used for assignment of participants to treatment groups?**	An outside therapist, that did not participate in the study did the randomisation of the groups	☒	☐	☐	☐
2	**Was allocation to treatment groups concealed?**	Outside therapist did the concealing of the groups. They did not participate in the study	☒	☐	☐	☐
3	**Were treatment groups similar at the baseline?**	The scores for EDSS, MSIS-29, MS duration, age and sex, heigh, mass and BMI were similar.	☒	☐	☐	☐
Bias related to administration of intervention/exposure						
4	**Were participants blind to treatment assignment?**	Participants were familiar with the treatment	☐	☒	☐	☐
5	**Were those delivering the treatment blind to treatment assignment?**	Up to 3 trained therapists and a supervisor were monitoring the treatment for the participants	☐	☒	☐	☐

6	**Were treatment groups treated identically other than the intervention of interest?**	However, a limitation about assessor cooperations over 2 years was stated in the study.	☒	☐	☐	☐
Bias related to assessment, detection and measurement of the outcome						
7	**Were outcome assessors blind to treatment assignment?**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	Changes in outcome were measured by assessors who were blinded to treatment allocation.	☒	☐	☐	☐
	Outcome 2	Changes in outcome were measured by assessors who were blinded to treatment allocation.	☒	☐	☐	☐
	Outcome 3	Changes in outcome were measured by assessors who were blinded to treatment allocation.	☒	☐	☐	☐
	Outcome 4	Changes in outcome were measured by assessors who were blinded to treatment allocation.	☒	☐	☐	☐
	Outcome 5	Changes in outcome were measured by assessors who were blinded to treatment allocation.	☒	☐	☐	☐
	Outcome 6	Changes in outcome were measured by assessors who were blinded to treatment allocation.	☒	☐	☐	☐
	Outcome 7	Changes in outcome were measured by assessors who were blinded to treatment allocation.	☒	☐	☐	☐

8	**Were outcomes measured in the same way for treatment groups?**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	Order of the tests was standardized among patients and testing sessions.	☒	☐	☐	☐
	Outcome 2	Order of the tests was standardized among patients and testing sessions.	☒	☐	☐	☐
	Outcome 3	Order of the tests was standardized among patients and testing sessions.	☒	☐	☐	☐
	Outcome 4	Order of the tests was standardized among patients and testing sessions.	☒	☐	☐	☐
	Outcome 5	Order of the tests was standardized among patients and testing sessions.	☒	☐	☐	☐
	Outcome 6	Order of the tests was standardized among patients and testing sessions.	☒	☐	☐	☐
	Outcome 7	Order of the tests was standardized among patients and testing sessions.	☒	☐	☐	☐

9	**Were outcomes measured in a reliable way**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	3 Physical therapists were trained and supervised by a principal investigator. Separate assessors were used to assess outcome.	☒	☐	☐	☐

Outcome 2	3 Physical therapists were trained and supervised by a principal investigator. Separate assessors were used to assess outcome.	☒	☐	☐	☐
Outcome 3	3 Physical therapists were trained and supervised by a principal investigator. Separate assessors were used to assess outcome.	☒	☐	☐	☐
Outcome 4	3 Physical therapists were trained and supervised by a principal investigator. Separate assessors were used to assess outcome.	☒	☐	☐	☐
Outcome 5	3 Physical therapists were trained and supervised by a principal investigator. Separate assessors were used to assess outcome.	☒	☐	☐	☐
Outcome 6	3 Physical therapists were trained and supervised by a principal investigator. Separate assessors were used to assess outcome.	☒	☐	☐	☐
Outcome 7	3 Physical therapists were trained and supervised by a principal investigator. Separate assessors were used to assess outcome.	☒	☐	☐	☐

Bias related to participant retention

10	**Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Two withdrawals noted before the intervention started (in the control group)	☒	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Two withdrawals noted before the intervention started (in the control group)	☒	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Two withdrawals noted before the intervention started (in the control group)	☒	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Two withdrawals noted before the intervention started (in the control group)	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Two withdrawals noted before the intervention started (in the control group)	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Two withdrawals noted before the intervention started (in the control group)	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Two withdrawals noted before the intervention started (in the control group)	☐	☐	☐	☐

	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

Statistical Conclusion Validity

11	**Were participants analysed in the groups to which they were randomized?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Assessors were blinded to allocation	☒	☐	☐	☐

Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐

	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

12	**Was appropriate statistical analysis used?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Continuous data was expressed using the Shapiro-Wilk test. 1-way analysis of variance and Kruskal test.	☒	☐	☐	☐
	Result 2	Baseline and gain score was measured using 1-way analysis	☒	☐	☐	☐
	Result 3	A significant effect, characterized by partial eta squared (ph2) effect size, was interpreted as a group by time interaction and was followed by a Tukey's post hoc or a Mann-Whitney test to determine the means that were different. Within group differences were quantified by Cohen effect size.	☒	☐	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Continuous data was expressed using the Shapiro-Wilk test. 1-way analysis of variance and Kruskal test.	☒	☐	☐	☐
	Result 2	Baseline and gain score was measured using 1-way analysis	☒	☐	☐	☐

Result 3	A significant effect, characterized by partial eta squared (ph2) effect size, was interpreted as a group by time interaction and was followed by a Tukey's post hoc or a Mann-Whitney test to determine the means that were different. Within group differences were quantified by Cohen effect size.	☒	☐	☐	☐
Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Continuous data was expressed using the Shapiro-Wilk test. 1-way analysis of variance and Kruskal test.	☒	☐	☐	☐
Result 2	Baseline and gain score was measured using 1-way analysis	☒	☐	☐	☐
Result 3	A significant effect, characterized by partial eta squared (ph2) effect size, was interpreted as a group by time interaction and was followed by a Tukey's post hoc or a Mann-Whitney test to determine the means that were different. Within group differences were quantified by Cohen effect size.	☒	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Continuous data was expressed using the Shapiro-Wilk test. 1-way analysis of variance and Kruskal test.	☒	☐	☐	☐
Result 2	Baseline and gain score was measured using 1-way analysis	☒	☐	☐	☐

Result 3	A significant effect, characterized by partial eta squared (ph2) effect size, was interpreted as a group by time interaction and was followed by a Tukey's post hoc or a Mann-Whitney test to determine the means that were different. Within group differences were quantified by Cohen effect size.	☒	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Continuous data was expressed using the Shapiro-Wilk test. 1-way analysis of variance and Kruskal test.	☒	☐	☒	☐
Result 2	Baseline and gain score was measured using 1-way analysis	☒	☐	☐	☐
Result 3	A significant effect, characterized by partial eta squared (ph2) effect size, was interpreted as a group by time interaction and was followed by a Tukey's post hoc or a Mann-Whitney test to determine the means that were different. Within group differences were quantified by Cohen effect size.	☒	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Continuous data was expressed using the Shapiro-Wilk test. 1-way analysis of variance and Kruskal test.	☒	☐	☐	☐
Result 2	Baseline and gain score was measured using 1-way analysis	☒	☐	☐	☐

Result 3	A significant effect, characterized by partial eta squared (ph2) effect size, was interpreted as a group by time interaction and was followed by a Tukey's post hoc or a Mann-Whitney test to determine the means that were different. Within group differences were quantified by Cohen effect size.	☒	☐	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Continuous data was expressed using the Shapiro-Wilk test. 1-way analysis of variance and Kruskal test.	☒	☐	☐	☐
Result 2	Baseline and gain score was measured using 1-way analysis	☒	☐	☐	☐
Result 3	A significant effect, characterized by partial eta squared (ph2) effect size, was interpreted as a group by time interaction and was followed by a Tukey's post hoc or a Mann-Whitney test to determine the means that were different. Within group differences were quantified by Cohen effect size.	☒	☐	☐	☐

			Yes	No	Unclear	N/A
13	**Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?**		☒	☐	☐	☐

Overall appraisal:	**Include: ☒**	**Exclude: ☐**	**Seek Further Info: ☐**

Comments:

Table 3 – The JBI Critical Appraisal Tool for RCTs

Assessor: Bokamoso Mthimkulu	**Date of Appraisal: 4 September 2024**	**Record Number: 02**
Study Author: Escudero-Uribe, S; Hochsprun Heredia-Camacho, B; Izquierdo-Ayuso, G	**Study Title: Effect of Training Exercises Incorporating Mechanical Devices on Fatigue and Gait Pattern in Persons with Relapsing-Remitting Multiple Sclerosis**	**Study Year: 2017**

Internal Validity		Choice - Comments/Justification	Yes	No	Unclear	N/A
Bias related to selection and allocation						
1	**Was true randomization used for assignment of participants to treatment groups?**	A randomization table was used to assign participants to groups.	☒	☐	☐	☐
2	**Was allocation to treatment groups concealed?**	A neurologic physiotherapist allocated participants to one of 3 groups. Does not state how the assignment was concealed after that.	☐	☐	☒	☐

3	**Were treatment groups similar at the baseline?**	The scores for EDSS, MS duration, age and BMI	☒	☐	☐	☐
Bias related to administration of intervention/exposure						
4	**Were participants blind to treatment assignment?**	Does not state.	☐	☐	☒	☐
5	**Were those delivering the treatment blind to treatment assignment?**	A guided neurologic physiotherapist supervised the activity	☐	☒	☐	☐
6	**Were treatment groups treated identically other than the intervention of interest?**	All treatment groups followed the same circuit.	☒	☐	☐	☐
Bias related to assessment, detection and measurement of the outcome						
7	**Were outcome assessors blind to treatment assignment?**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	A separate pretest and posttest assessor was used and performed the tests in the same way	☒	☐	☐	☐
	Outcome 2	A separate pretest and posttest assessor was used and performed the tests in the same way	☒	☐	☐	☐
	Outcome 3	A separate pretest and posttest assessor was used and performed the tests in the same way	☒	☐	☐	☐
	Outcome 4	A separate pretest and posttest assessor was used and performed the tests in the same way	☒	☐	☐	☐
	Outcome 5		☐	☐	☐	☐

	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

8	**Were outcomes measured in the same way for treatment groups?**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	Order of the tests was standardized among patients and testing sessions.	☒	☐	☐	☐
	Outcome 2	Order of the tests was standardized among patients and testing sessions.	☒	☐	☐	☐
	Outcome 3	Order of the tests was standardized among patients and testing sessions.	☒	☐	☐	☐
	Outcome 4	Order of the tests was standardized among patients and testing sessions.	☒	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

9	**Were outcomes measured in a reliable way**		**Yes**	**No**	**Unclear**	**N/A**

	Outcome 1	Standardized protocol used to measure outcomes	☒	☐	☐	☐
	Outcome 2	Standardized protocol used to measure outcomes	☒	☐	☐	☐
	Outcome 3	Standardized protocol used to measure outcomes	☒	☐	☐	☐
	Outcome 4	Standardized protocol used to measure outcomes	☒	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

Bias related to participant retention

10	**Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Reason for exclusion was noted. Data of the excluded participants was removed from baseline and result.	☐	☒	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Reason for exclusion was noted. Data of the excluded participants was removed from baseline and result.	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Reason for exclusion was noted. Data of the excluded participants was removed from baseline and result.	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Reason for exclusion was noted. Data of the excluded participants was removed from baseline and result.	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐

	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

Statistical Conclusion Validity

11	**Were participants analysed in the groups to which they were randomized?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Assessors were blinded to allocation	☒	☐	☐	☐

Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐

	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
12	**Was appropriate statistical analysis used?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Parameters for normal distribution was expressed using the Shapiro-Wilk test.	☒	☐	☐	☐
	Result 2	Differences in demographic characteristics among the three groups were examined using the x2 test for	☐	☐	☐	☐

	qualitative variables and one-way analysis of variance. Intergroup analysis was done using one-way analysis				
Result 3	pre- and post-intervention (intra-group analysis), were assessed using the paired-samples t test. Effect size impact was measured using Cohen d analysis.	☐	☐	☐	☐
Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Parameters for normal distribution was expressed using the Shapiro-Wilk test.	☒	☐	☐	☐
Result 2	Differences in demographic characteristics among the three groups were examined using the x2 test for qualitative variables and one-way analysis of variance. Intergroup analysis was done using one-way analysis	☐	☐	☐	☐
Result 3	pre- and post-intervention (intra-group analysis), were assessed using the paired-samples t test. Effect size impact was measured using Cohen d analysis.	☐	☐	☐	☐
Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Parameters for normal distribution was expressed using the Shapiro-Wilk test.	☒	☐	☐	☐
Result 2	Differences in demographic characteristics among the three groups were examined using the x2 test for qualitative variables and one-way analysis of variance. Intergroup analysis was done using one-way analysis	☐	☐	☐	☐

Result 3	pre- and post-intervention (intra-group analysis), were assessed using the paired-samples t test. Effect size impact was measured using Cohen d analysis.	☐	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Parameters for normal distribution was expressed using the Shapiro-Wilk test.	☒	☐	☐	☐
Result 2	Differences in demographic characteristics among the three groups were examined using the x2 test for qualitative variables and one-way analysis of variance. Intergroup analysis was done using one-way analysis	☐	☐	☐	☐
Result 3	pre- and post-intervention (intra-group analysis), were assessed using the paired-samples t test. Effect size impact was measured using Cohen d analysis.	☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☒	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐

Result 3		☐	☐	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐

		Yes	**No**	**Unclear**	**N/A**
13	**Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?**	☒	☐	☐	☐

Overall appraisal: **Include: ☒** **Exclude: ☐** **Seek Further Info: ☐**

Comments:

Table 3 – The JBI Critical Appraisal Tool for RCTs

RoB Assessor: Bokamoso Mthimkulu	**Date of Appraisal: 11 September 2024**	**Record Number: 03**

Study Author: Sames, C; DeBlois, A	Study Title: Pilot Study to Investigate the Effect of a 1 Week Aquatic Exercise Program on Individuals with H Levels of Disability Due to Multiple Sclerosis	Study Year: 2021

Internal Validity		Choice - Comments/Justification	Yes	No	Unclear	N/A
Bias related to temporal precedence						
1	**Is it clear in the study what is the "cause" and what is the "effect" (i.e. there is no confusion about which variable comes first)?**	**10-week Aquatic Exercise program leads to improved walking speed, fatigue levels, and overall QOL**	☒	☐	☐	☐
Bias related to selection and allocation						
2	**Was there a control group?**	One group pre-/posttest study	☐	☒	☐	☐
Bias related to confounding factors						
3	**Were participants included in any comparisons similar?**	They all have moderate to severe disability caused by MS.	☒	☐	☐	☐
Bias related to administration of intervention/exposure						
4	**Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?**	All participants received the same treatment	☒	☐	☐	☐

Bias related to assessment, detection and measurement of the outcome						
5	**Were there multiple measurements of the outcome, both pre and post the intervention/exposure?**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	Day 9 and 10 prior to and within 5 days after the 10-week aquatic intervention.	☒	☐	☐	☐
	Outcome 2	Day 9 and 10 prior to and within 5 days after the 10-week aquatic intervention.	☒	☐	☐	☐
	Outcome 3	Day 9 and 10 prior to and within 5 days after the 10-week aquatic intervention.	☒	☐	☐	☐
	Outcome 4		☐	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

6	**Were the outcomes of participants included in any comparisons measured in the same way?**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	Day 9 and 10 prior to and within 5 days after the 10-week aquatic intervention.	☒	☐	☐	☐

	Outcome 2	Day 9 and 10 prior to and within 5 days after the 10-week aquatic intervention.	☒	☐	☐	☐
	Outcome 3	Day 9 and 10 prior to and within 5 days after the 10-week aquatic intervention.	☒	☐	☐	☐
	Outcome 4		☐	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

7	**Were outcomes measured in a reliable way?**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	Same instructor did all the assessing	☒	☐	☐	☐
	Outcome 2	Same instructor did all the assessing	☒	☐	☐	☐
	Outcome 3	Same instructor did all the assessing	☒	☐	☐	☐
	Outcome 4		☐	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐

	Outcome 7		☐	☐	☐	☐

Bias related to participant retention

8	**Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Participants that did not complete the study were excluded from the final analysis	☐	☒	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Participants that did not complete the study were excluded from the final analysis	☐	☒	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 3		**Yes**	**No**	**Unclear**	**N/A**

Result 1	Participants that did not complete the study were excluded from the final analysis	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐

	Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

Statistical Conclusion Validity

9	**Was appropriate statistical analysis used?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	nonparametric tests were applied using Wilcoxon's signed rank test for within-group comparisons (baseline and postintervention data for 10 subjects) and the Mann-Whitney *U* test for between-group comparisons (completers vs withdrawal)	☒	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	nonparametric tests were applied using Wilcoxon's signed rank test for within-group comparisons (baseline and postintervention data for 10 subjects) and the Mann-	☒	☐	☐	☐

	Whitney *U* test for between-group comparisons (completers vs withdrawal)				
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	nonparametric tests were applied using Wilcoxon's signed rank test for within-group comparisons (baseline and postintervention data for 10 subjects) and the Mann-Whitney *U* test for between-group comparisons (completers vs withdrawal)	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐

Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐

Overall appraisal: **Include: ☐** **Exclude: ☒** **Seek Further Info: ☐**

Comments: Not part of inclusion criteria of Systematic Review being done.

Assessor: Bokamoso Mthimkulu	**Date of Appraisal: 4 September 2024**	**Record Number: 04**

Study Author: Chotiyarnwong, C; Nair, Angelini, L; Buckley, E; Mazza, C; Heyes Ramiz, R; Baster, K; Ismail, A; Das, J; Al Lindert, R; Sharrack, B; Price, S; Paling, D	Study Title: Effect of remote ischaemic preconditioning on walking in pe with multiple sclerosis: double-blind randomised controlled trial	Study Year: 2020

Internal Validity		Choice - Comments/Justification	Yes	No	Unclear	N/A
Bias related to selection and allocation						
1	**Was true randomization used for assignment of participants to treatment groups?**	By use of a random number table	☒	☐	☐	☐
2	**Was allocation to treatment groups concealed?**	To participants and assessors	☒	☐	☐	☐
3	**Were treatment groups similar at the baseline?**	The scores for EDSS, MS duration, sex was not too similar. Age was the only similar characteristic	☐	☒	☐	☐
Bias related to administration of intervention/exposure						
4	**Were participants blind to treatment assignment?**	To participants and assessors	☒	☐	☐	☐
5	**Were those delivering the treatment blind to treatment assignment?**	Double-blinded study design	☒	☐	☐	☐
6	**Were treatment groups treated identically other than the intervention of interest?**	All treatment groups followed the same protocol	☒	☐	☐	☐
Bias related to assessment, detection and measurement of the outcome						

7	Were outcome assessors blind to treatment assignment?		Yes	No	Unclear	N/A
	Outcome 1	Researcher performing the assessments was blinded to the study	☒	☐	☐	☐
	Outcome 2	Researcher performing the assessments was blinded to the study	☒	☐	☐	☐
	Outcome 3	Researcher performing the assessments was blinded to the study	☒	☐	☐	☐
	Outcome 4	Researcher performing the assessments was blinded to the study	☒	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

8	Were outcomes measured in the same way for treatment groups?		Yes	No	Unclear	N/A
	Outcome 1	Order of the tests was standardized among patients	☒	☐	☐	☐
	Outcome 2	Order of the tests was standardized among patients	☒	☐	☐	☐
	Outcome 3	Order of the tests was standardized among patients	☒	☐	☐	☐

	Outcome 4	Order of the tests was standardized among patients	☒	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

9	**Were outcomes measured in a reliable way**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	One patient was seen by the assessor at a time	☒	☐	☐	☐
	Outcome 2	One patient was seen by the assessor at a time	☒	☐	☐	☐
	Outcome 3	One patient was seen by the assessor at a time	☒	☐	☐	☐
	Outcome 4	One patient was seen by the assessor at a time	☒	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

Bias related to participant retention

10	**Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Reason for exclusion was noted. Data on both groups state the exclusion during analysis was done. All tables with results show the original number before exclusion.	☐	☒	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Reason for exclusion was noted. Data on both groups state the exclusion during analysis was done. All tables with results show the original number before exclusion.	☐	☒	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Reason for exclusion was noted. Data on both groups state the exclusion during analysis was done. All tables with results show the original number before exclusion.	☐	☒	☐	☐

Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Reason for exclusion was noted. Data on both groups state the exclusion during analysis was done. All tables with results show the original number before exclusion.	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**

	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

Statistical Conclusion Validity

11	**Were participants analysed in the groups to which they were randomized?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 3		**Yes**	**No**	**Unclear**	**N/A**

Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**

	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

12	**Was appropriate statistical analysis used?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Continuous data was expressed using the Shapiro-Wilk and Kolmogorov-Smirnov test.	☒	☐	☐	☐
	Result 2	Independent t-test was used for normally distributed data, and Mann-Whitney U-test was employed to analyse for non-normally distributed data	☒	☐	☐	☐
	Result 3	Pearson χ2 test was used to compare the numbers of responders between groups. No effect size stated.	☐	☒	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Continuous data was expressed using the Shapiro-Wilk and Kolmogorov-Smirnov test.	☒	☐	☐	☐
	Result 2	Independent t-test was used for normally distributed data, and Mann-Whitney U-test was employed to analyse for non-normally distributed data	☒	☐	☐	☐

Result 3	Pearson χ2 test was used to compare the numbers of responders between groups. No effect size stated.	☐	☒	☐	☐
Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Continuous data was expressed using the Shapiro-Wilk and Kolmogorov-Smirnov test.	☒	☐	☐	☐
Result 2	Independent t-test was used for normally distributed data, and Mann-Whitney U-test was employed to analyse for non-normally distributed data	☒	☐	☐	☐
Result 3	Pearson χ2 test was used to compare the numbers of responders between groups. No effect size stated.	☐	☒	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Continuous data was expressed using the Shapiro-Wilk and Kolmogorov-Smirnov test.	☒	☐	☐	☐
Result 2	Independent t-test was used for normally distributed data, and Mann-Whitney U-test was employed to analyse for non-normally distributed data	☒	☐	☐	☐
Result 3	Pearson χ2 test was used to compare the numbers of responders between groups. No effect size stated.	☐	☒	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☒	☐

Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐

			Yes	**No**	**Unclear**	**N/A**
13	**Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?**		☒	☐	☐	☐

Overall appraisal: **Include: ☐** **Exclude: ☒** **Seek Further Info: ☐**

Comments: Study does not use sensory and motor aspects for improvement.		
Assessor: Bokamoso Mthimkulu	**Date of Appraisal: 9 September 2024**	**Record Number: 09**
Study Author: Schyns, F; Paul, L; Finlay Ferguson,C; Noble, E	**Study Title: Vibration therapy in multiple sclerosis: a pilot study exploring its effects on tone, muscle force, sensation and functi performance**	**Study Year: 2009**

Internal Validity		Choice - Comments/Justification	Yes	No	Unclear	N/A
Bias related to selection and allocation						
1	**Was true randomization used for assignment of participants to treatment groups?**	By a physiotherapist drawing a number from an envelope	☒	☐	☐	☐
2	**Was allocation to treatment groups concealed?**	Does not state	☐	☐	☒	☐
3	**Were treatment groups similar at the baseline?**	Varied	☐	☒	☐	☐
Bias related to administration of intervention/exposure						
4	**Were participants blind to treatment assignment?**	Does not state	☐	☐	☒	☐
5	**Were those delivering the treatment blind to treatment assignment?**	Does not state	☐	☐	☒	☐

6	**Were treatment groups treated identically other than the intervention of interest?**	All treatment groups followed the same study method	☒	☐	☐	☐

Bias related to assessment, detection and measurement of the outcome

7	**Were outcome assessors blind to treatment assignment?**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 2	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 3	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 4	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 5	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 6	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

8	**Were outcomes measured in the same way for treatment groups?**		**Yes**	**No**	**Unclear**	**N/A**

	Outcome 1	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 2	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 3	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 4	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 5	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 6	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

9	**Were outcomes measured in a reliable way**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	One blinded assessor at all assessment stages	☒	☐	☐	☐
	Outcome 2	One blinded assessor at all assessment stages	☒	☐	☐	☐
	Outcome 3	One blinded assessor at all assessment stages	☒	☐	☐	☐
	Outcome 4	One blinded assessor at all assessment stages	☒	☐	☐	☐

	Outcome 5	One blinded assessor at all assessment stages	☒	☐	☐	☐
	Outcome 6	One blinded assessor at all assessment stages	☒	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

Bias related to participant retention

10	**Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	There were dropouts but final analysis included participants who completed the study	☐	☒	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	There were dropouts but final analysis included participants who completed the study	☐	☒	☐	☐
	Result 2		☐	☐	☐	☐

Result 3		☐	☐	☐	☐
Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	There were dropouts but final analysis included participants who completed the study	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	There were dropouts but final analysis included participants who completed the study	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1	There were dropouts but final analysis included participants who completed the study	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**

	Result 1	There were dropouts but final analysis included participants who completed the study	☐	☒	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

Statistical Conclusion Validity

11	**Were participants analysed in the groups to which they were randomized?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**

Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**

	Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
12	**Was appropriate statistical analysis used?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Repeated-measures ANOVA with two factors (group and assessment number) and their interaction was performed on the continuous response variables.	☒	☐	☐	☐
	Result 2	Wilcoxon signed ranks test was carried out on the difference between change following whole body vibration and exercise and change following exercise alone.	☒	☐	☐	☐

Result 3	Categorical tests such as McNemar's test were considered for the variables Modified Ashworth Scale and Nottingham Sensory Assessment	☒	☐	☐	☐
Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Repeated-measures ANOVA with two factors (group and assessment number) and their interaction was performed on the continuous response variables.	☒	☐	☐	☐
Result 2	Wilcoxon signed ranks test was carried out on the difference between change following whole body vibration and exercise and change following exercise alone.	☒	☐	☐	☐
Result 3	Categorical tests such as McNemar's test were considered for the variables Modified Ashworth Scale and Nottingham Sensory Assessment	☒	☐	☐	☐
Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Repeated-measures ANOVA with two factors (group and assessment number) and their interaction was performed on the continuous response variables.	☒	☐	☐	☐
Result 2	Wilcoxon signed ranks test was carried out on the difference between change following whole body vibration and exercise and change following exercise alone.	☒	☐	☐	☐

Result 3	Categorical tests such as McNemar's test were considered for the variables Modified Ashworth Scale and Nottingham Sensory Assessment	☒	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Repeated-measures ANOVA with two factors (group and assessment number) and their interaction was performed on the continuous response variables.	☒	☐	☐	☐
Result 2	Wilcoxon signed ranks test was carried out on the difference between change following whole body vibration and exercise and change following exercise alone.	☒	☐	☐	☐
Result 3	Categorical tests such as McNemar's test were considered for the variables Modified Ashworth Scale and Nottingham Sensory Assessment	☒	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Repeated-measures ANOVA with two factors (group and assessment number) and their interaction was performed on the continuous response variables.	☒	☐	☒	☐
Result 2	Wilcoxon signed ranks test was carried out on the difference between change following whole body vibration and exercise and change following exercise alone.	☒	☐	☐	☐

Result 3	Categorical tests such as McNemar's test were considered for the variables Modified Ashworth Scale and Nottingham Sensory Assessment	☒	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Repeated-measures ANOVA with two factors (group and assessment number) and their interaction was performed on the continuous response variables.	☒	☐	☐	☐
Result 2	Wilcoxon signed ranks test was carried out on the difference between change following whole body vibration and exercise and change following exercise alone.	☒	☐	☐	☐
Result 3	Categorical tests such as McNemar's test were considered for the variables Modified Ashworth Scale and Nottingham Sensory Assessment	☒	☐	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐

		Yes	**No**	**Unclear**	**N/A**

13	**Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?**		☒	☐	☐	☐

Overall appraisal: **Include: ☐** **Exclude: ☒** **Seek Further Info: ☐**

Comments: Lack of internal validity

Table 3 – The JBI Critical Appraisal Tool for RCTs

Assessor: Bokamoso Mthimkulu	**Date of Appraisal: 4 September 2024**	**Record Number: 05**
Study Author: Tramontano, M; Argento, O; O Bustos, A.S; De Angelis, S; Montemurro Bossa, M; Belluscio, V; Bergamini, E; Vann G; Nocentini, U	**Study Title: Cognitive-motor dual-task training improves dynamic stal during straight and curved gait in patients with multiple sclerosis: a random controlled trial**	**Study Year: 2024**

Internal Validity		Choice - Comments/Justification	Yes	No	Unclear	N/A
Bias related to selection and allocation						
1	**Was true randomization used for assignment of participants to treatment groups?**	Computer generated by an independent researcher not participating in the study	☒	☐	☐	☐
2	**Was allocation to treatment groups concealed?**	Stored by researcher in charge	☒	☐	☐	☐

3	**Were treatment groups similar at the baseline?**	The scores for EDSS, MS duration, sex, age, POMA, and MBI were similar.	☒	☐	☐	☐
Bias related to administration of intervention/exposure						
4	**Were participants blind to treatment assignment?**	Stored by researcher in charge	☒	☐	☐	☐
5	**Were those delivering the treatment blind to treatment assignment?**	No, single blind RCT	☐	☒	☐	☐
6	**Were treatment groups treated identically other than the intervention of interest?**	All treatment groups followed the same study method	☒	☐	☐	☐
Bias related to assessment, detection and measurement of the outcome						
7	**Were outcome assessors blind to treatment assignment?**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	Researcher performing the assessments was blinded to the study	☒	☐	☐	☐
	Outcome 2	Researcher performing the assessments was blinded to the study	☒	☐	☐	☐
	Outcome 3	Researcher performing the assessments was blinded to the study	☒	☐	☐	☐
	Outcome 4	Researcher performing the assessments was blinded to the study	☒	☐	☐	☐
	Outcome 5		☐	☐	☐	☐

	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

8	**Were outcomes measured in the same way for treatment groups?**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	Order of the tests was standardized among patients	☒	☐	☐	☐
	Outcome 2	Order of the tests was standardized among patients	☒	☐	☐	☐
	Outcome 3	Order of the tests was standardized among patients	☒	☐	☐	☐
	Outcome 4	Order of the tests was standardized among patients	☒	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

9	**Were outcomes measured in a reliable way**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	One patient was seen by the experienced assessor at a time	☒	☐	☐	☐

	Outcome 2	One patient was seen by the experienced assessor at a time	☒	☐	☐	☐
	Outcome 3	One patient was seen by the experienced assessor at a time	☒	☐	☐	☐
	Outcome 4	One patient was seen by the experienced assessor at a time	☒	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

Bias related to participant retention

10	**Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Reason for exclusion was noted. Data on both groups state the exclusion during analysis was done.	☐	☒	☐	☐
	Result 2		☐	☐	☐	☐

Result 3		☐	☐	☐	☐
Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Reason for exclusion was noted. Data on both groups state the exclusion during analysis was done.	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Reason for exclusion was noted. Data on both groups state the exclusion during analysis was done.	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Reason for exclusion was noted. Data on both groups state the exclusion during analysis was done.	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**

	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

Statistical Conclusion Validity

11	**Were participants analysed in the groups to which they were randomized?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**

Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐

Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐

12	**Was appropriate statistical analysis used?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Normal distribution of each parameter and each clinical scale was expressed using the Shapiro-Wilk	☒	☐	☐	☐
	Result 2	To evaluate significant differences between the two groups, the Mann-Whitney U-test. For the within-group analysis, a Friedman test was performed, to investigate if there were significant differences for each group across the three temporal evaluations	☒	☐	☐	☐
	Result 3	significant effect was found, a *post-hoc* test with the Wilcoxon rank-sign test with Holm-Bonferroni correction was performed	☒	☐	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Normal distribution of each parameter and each clinical scale was expressed using the Shapiro-Wilk	☒	☐	☐	☐
	Result 2	To evaluate significant differences between the two groups, the Mann-Whitney U-test. For the within-group analysis, a Friedman test was performed, to investigate if there were significant differences for each group across the three temporal evaluations	☒	☐	☐	☐

Result 3	significant effect was found, a *post-hoc* test with the Wilcoxon rank-sign test with Holm-Bonferroni correction was performed	☒	☐	☐	☐
Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Normal distribution of each parameter and each clinical scale was expressed using the Shapiro-Wilk	☒	☐	☐	☐
Result 2	To evaluate significant differences between the two groups, the Mann-Whitney U-test. For the within-group analysis, a Friedman test was performed, to investigate if there were significant differences for each group across the three temporal evaluations	☒	☐	☐	☐
Result 3	significant effect was found, a *post-hoc* test with the Wilcoxon rank-sign test with Holm-Bonferroni correction was performed	☒	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Normal distribution of each parameter and each clinical scale was expressed using the Shapiro-Wilk	☒	☐	☐	☐
Result 2	To evaluate significant differences between the two groups, the Mann-Whitney U-test. For the within-group analysis, a Friedman test was performed, to investigate if there were significant differences for each group across the three temporal evaluations	☒	☐	☐	☐

Result 3	significant effect was found, a *post-hoc* test with the Wilcoxon rank-sign test with Holm-Bonferroni correction was performed	☒	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☒	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐

			Yes	No	Unclear	N/A
13	**Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?**		☒	☐	☐	☐

Overall appraisal: **Include: ☒** **Exclude: ☐** **Seek Further Info: ☐**

Comments:

Table 3 – The JBI Critical Appraisal Tool for RCTs

Assessor: Bokamoso Mthimkulu	**Date of Appraisal: 4 September 2024**	**Record Number: 06**
Study Author: Tosun, A.T; Ipek, Y; Ozdincler, Saip, S	**Study Title: The efficiency of mirror therapy on drop foot in Multiple Sclerosis Patients**	**Study Year: 2020**

Internal Validity		Choice - Comments/Justification	Yes	No	Unclear	N/A
Bias related to selection and allocation						
1	**Was true randomization used for assignment of participants to treatment groups?**	Computer generated completed	☒	☐	☐	☐

2	**Was allocation to treatment groups concealed?**	Assessor did not have access to group allocation	☒	☐	☐	☐
3	**Were treatment groups similar at the baseline?**	The scores for EDSS, MS duration, sex, age, drop foot side, and BMI were similar.	☒	☐	☐	☐
Bias related to administration of intervention/exposure						
4	**Were participants blind to treatment assignment?**	Does not state. Only assessor did not have access to allocation	☐	☐	☒	☐
5	**Were those delivering the treatment blind to treatment assignment?**	Does not state. Only assessor did not have access to allocation	☐	☐	☒	☐
6	**Were treatment groups treated identically other than the intervention of interest?**	All treatment groups followed the same study method	☒	☐	☐	☐
Bias related to assessment, detection and measurement of the outcome						
7	**Were outcome assessors blind to treatment assignment?**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	Researcher performing the assessments was blinded to the study	☒	☐	☐	☐
	Outcome 2	Researcher performing the assessments was blinded to the study	☒	☐	☐	☐
	Outcome 3	Researcher performing the assessments was blinded to the study	☒	☐	☐	☐

	Outcome 4	Researcher performing the assessments was blinded to the study	☒	☐	☐	☐
	Outcome 5	Researcher performing the assessments was blinded to the study	☒	☐	☐	☐
	Outcome 6	Researcher performing the assessments was blinded to the study	☒	☐	☐	☐
	Outcome 7	Researcher performing the assessments was blinded to the study	☒	☐	☐	☐

8	**Were outcomes measured in the same way for treatment groups?**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	Order of the tests was standardized among patients	☒	☐	☐	☐
	Outcome 2	Order of the tests was standardized among patients	☒	☐	☐	☐
	Outcome 3	Order of the tests was standardized among patients	☒	☐	☐	☐
	Outcome 4	Order of the tests was standardized among patients	☒	☐	☐	☐
	Outcome 5	Order of the tests was standardized among patients	☒	☐	☐	☐
	Outcome 6	Order of the tests was standardized among patients	☒	☐	☐	☐
	Outcome 7	Order of the tests was standardized among patients	☒	☐	☐	☐

9	**Were outcomes measured in a reliable way**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	One patient was seen by the experienced assessor at a time	☒	☐	☐	☐
	Outcome 2	One patient was seen by the experienced assessor at a time	☒	☐	☐	☐
	Outcome 3	One patient was seen by the experienced assessor at a time	☒	☐	☐	☐
	Outcome 4	One patient was seen by the experienced assessor at a time	☒	☐	☐	☐
	Outcome 5	One patient was seen by the experienced assessor at a time	☒	☐	☐	☐
	Outcome 6	One patient was seen by the experienced assessor at a time	☒	☐	☐	☐
	Outcome 7	One patient was seen by the experienced assessor at a time	☒	☐	☐	☐

Bias related to participant retention

10	**Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Reason for exclusion was noted. Data on both groups state the exclusion during analysis was done.	☐	☒	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Reason for exclusion was noted. Data on both groups state the exclusion during analysis was done.	☐	☒	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Reason for exclusion was noted. Data on both groups state the exclusion during analysis was done.	☐	☒	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Reason for exclusion was noted. Data on both groups state the exclusion during analysis was done.	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Reason for exclusion was noted. Data on both groups state the exclusion during analysis was done.	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Reason for exclusion was noted. Data on both groups state the exclusion during analysis was done.	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**

	Result 1	Reason for exclusion was noted. Data on both groups state the exclusion during analysis was done.	☐	☒	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

Statistical Conclusion Validity

11	**Were participants analysed in the groups to which they were randomized?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐

	Result 3		☐	☐	☐	☐
	Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
12	**Was appropriate statistical analysis used?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Normal distribution data was expressed using the Shapiro-Wilk. The Pearson chi-square likelihood ratio or Fisher's exact test methods were consulted according to the distribution of the expected values of data in the cross tables while using the Ki-square test in the comparison of the independent qualitative data.	☒	☐	☐	☐
	Result 2	The McNemar Test was used in the comparison of the dependent qualitative data. The qualitative data with two independent groups were evaluated with the Mann–Whitney *U*-test	☒	☐	☐	☐
	Result 3	Effect size analysis not stated	☐	☒	☐	☐

Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Normal distribution data was expressed using the Shapiro-Wilk. The Pearson chi-square likelihood ratio or Fisher's exact test methods were consulted according to the distribution of the expected values of data in the cross tables while using the Ki-square test in the comparison of the independent qualitative data.	☒	☐	☐	☐
Result 2	The McNemar Test was used in the comparison of the dependent qualitative data. The qualitative data with two independent groups were evaluated with the Mann–Whitney *U*-test	☒	☐	☐	☐
Result 3	Effect size analysis not stated	☐	☒	☐	☐
Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Normal distribution data was expressed using the Shapiro-Wilk. The Pearson chi-square likelihood ratio or Fisher's exact test methods were consulted according to the distribution of the expected values of data in the cross tables while using the Ki-square test in the comparison of the independent qualitative data.	☒	☐	☐	☐
Result 2	The McNemar Test was used in the comparison of the dependent qualitative data. The qualitative data with two independent groups were evaluated with the Mann–Whitney *U*-test	☒	☐	☐	☐

Result 3	Effect size analysis not stated	☐	☒	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Normal distribution data was expressed using the Shapiro-Wilk. The Pearson chi-square likelihood ratio or Fisher's exact test methods were consulted according to the distribution of the expected values of data in the cross tables while using the Ki-square test in the comparison of the independent qualitative data.	☒	☐	☐	☐
Result 2	The McNemar Test was used in the comparison of the dependent qualitative data. The qualitative data with two independent groups were evaluated with the Mann–Whitney *U*-test	☒	☐	☐	☐
Result 3	Effect size analysis not stated	☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Normal distribution data was expressed using the Shapiro-Wilk. The Pearson chi-square likelihood ratio or Fisher's exact test methods were consulted according to the distribution of the expected values of data in the cross tables while using the Ki-square test in the comparison of the independent qualitative data.	☒	☐	☒	☐
Result 2	The McNemar Test was used in the comparison of the dependent qualitative data. The qualitative data with two	☒	☐	☐	☐

	independent groups were evaluated with the Mann–Whitney *U*-test				
Result 3	Effect size analysis not stated	☐	☒	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Normal distribution data was expressed using the Shapiro-Wilk. The Pearson chi-square likelihood ratio or Fisher's exact test methods were consulted according to the distribution of the expected values of data in the cross tables while using the Ki-square test in the comparison of the independent qualitative data.	☒	☐	☐	☐
Result 2	The McNemar Test was used in the comparison of the dependent qualitative data. The qualitative data with two independent groups were evaluated with the Mann–Whitney *U*-test	☒	☐	☐	☐
Result 3	Effect size analysis not stated	☐	☒	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Normal distribution data was expressed using the Shapiro-Wilk. The Pearson chi-square likelihood ratio or Fisher's exact test methods were consulted according to the distribution of the expected values of data in the cross tables while using the Ki-square test in the comparison of the independent qualitative data.	☒	☐	☐	☐

	Result 2	The McNemar Test was used in the comparison of the dependent qualitative data. The qualitative data with two independent groups were evaluated with the Mann–Whitney *U*-test	☒	☐	☐	☐
	Result 3	Effect size analysis not stated	☐	☒	☐	☐

			Yes	No	Unclear	N/A
13	**Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?**		☒	☐	☐	☐

Overall appraisal: **Include: ☒** **Exclude: ☐** **Seek Further Info: ☐**

Comments:

Table 3 – The JBI Critical Appraisal Tool for RCTs

Assessor: Bokamoso Mthimkulu	**Date of Appraisal: 9 September 2024**	**Record Number: 08**

Study Author: Gandolfi, M; Munari, D; Geroi Gajofatto, A; Benedetti, M.D; Midiri, A; Carl Picelli, A; Waldner, A; Smania, N	Study Title: Sensory integration balance training in patients with mul sclerosis: A randomized, controlled trial	Study Year: 2015

Internal Validity		Choice - Comments/Justification	Yes	No	Unclear	N/A
Bias related to selection and allocation						
1	**Was true randomization used for assignment of participants to treatment groups?**	Computer generated	☒	☐	☐	☐
2	**Was allocation to treatment groups concealed?**	Does not state, but a blinded physician completed the randomisation	☐	☐	☒	☐
3	**Were treatment groups similar at the baseline?**	Demographically, EDSS, MS duration	☒	☐	☐	☐
Bias related to administration of intervention/exposure						
4	**Were participants blind to treatment assignment?**	All parties were aware of the treatment nature	☐	☒	☐	☐
5	**Were those delivering the treatment blind to treatment assignment?**	All parties aware of treatment nature	☐	☒	☐	☐
6	**Were treatment groups treated identically other than the intervention of interest?**	All treatment groups followed the same study method	☒	☐	☐	☐

Bias related to assessment, detection and measurement of the outcome

7	**Were outcome assessors blind to treatment assignment?**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 2	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 3	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 4	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 5	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 6	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

8	**Were outcomes measured in the same way for treatment groups?**		**Yes**	**No**	**Unclear**	**N/A**

	Outcome 1	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 2	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 3	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 4	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 5	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 6	Same assessor used to do assessments. Was not a part of the study	☒	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

9	**Were outcomes measured in a reliable way**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1	One blinded assessor at all assessment stages	☒	☐	☐	☐
	Outcome 2	One blinded assessor at all assessment stages	☒	☐	☐	☐
	Outcome 3	One blinded assessor at all assessment stages	☒	☐	☐	☐

	Outcome 4	One blinded assessor at all assessment stages	☒	☐	☐	☐
	Outcome 5	One blinded assessor at all assessment stages	☒	☐	☐	☐
	Outcome 6	One blinded assessor at all assessment stages	☒	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

Bias related to participant retention

10	**Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	There were dropouts but final anaylsis included all individuals that were initially allocated to a group (80)	☐	☒	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	There were dropouts but final anaylsis included all individuals that were initially allocated to a group (80)	☐	☒	☐	☐

Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	There were dropouts but final anaylsis included all individuals that were initially allocated to a group (80)	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	There were dropouts but final anaylsis included all individuals that were initially allocated to a group (80)	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1	There were dropouts but final anaylsis included all individuals that were initially allocated to a group (80)	☐	☒	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐

	Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	There were dropouts but final anaylsis included all individuals that were initially allocated to a group (80)	☐	☒	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

Statistical Conclusion Validity

11	**Were participants analysed in the groups to which they were randomized?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
	Result 2		☐	☐	☐	☐

Result 3		☐	☐	☐	☐
Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1	Assessors were blinded to allocation	☒	☐	☐	☐

	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	Assessors were blinded to allocation	☒	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

12	**Was appropriate statistical analysis used?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1	An intention-to-treat analysis was used. The last-observation-carried-forward method was used to handle missing data.	☒	☐	☐	☐

Result 2	Descriptive statistics included mean, median, standard deviation and the calculation of confidence intervals.	☒	☐	☐	☐
Result 3	Pre- and post-treatment scores (T1 and T2) for all outcome measures were assessed using repeated-measure analysis of variance (ANOVA) with Bonferroni adjustments ($p < 0.025$).	☒	☐	☐	☐
Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
Result 1	An intention-to-treat analysis was used. The last-observation-carried-forward method was used to handle missing data.	☒	☐	☐	☐
Result 2	Descriptive statistics included mean, median, standard deviation and the calculation of confidence intervals.	☒	☐	☐	☐
Result 3	Pre- and post-treatment scores (T1 and T2) for all outcome measures were assessed using repeated-measure analysis of variance (ANOVA) with Bonferroni adjustments ($p < 0.025$).	☒	☐	☐	☐
Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
Result 1	An intention-to-treat analysis was used. The last-observation-carried-forward method was used to handle missing data.	☒	☐	☐	☐
Result 2	Descriptive statistics included mean, median, standard deviation and the calculation of confidence intervals.	☒	☐	☐	☐

Result 3	Pre- and post-treatment scores (T1 and T2) for all outcome measures were assessed using repeated-measure analysis of variance (ANOVA) with Bonferroni adjustments ($p < 0.025$).	☒	☐	☐	☐
Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1	An intention-to-treat analysis was used. The last-observation-carried-forward method was used to handle missing data.	☒	☐	☐	☐
Result 2	Descriptive statistics included mean, median, standard deviation and the calculation of confidence intervals.	☒	☐	☐	☐
Result 3	Pre- and post-treatment scores (T1 and T2) for all outcome measures were assessed using repeated-measure analysis of variance (ANOVA) with Bonferroni adjustments ($p < 0.025$).	☒	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1	An intention-to-treat analysis was used. The last-observation-carried-forward method was used to handle missing data.	☒	☐	☐	☐
Result 2	Descriptive statistics included mean, median, standard deviation and the calculation of confidence intervals.	☒	☐	☐	☐
Result 3	Pre- and post-treatment scores (T1 and T2) for all outcome measures were assessed using repeated-measure	☒	☐	☐	☐

	analysis of variance (ANOVA) with Bonferroni adjustments ($p < 0.025$).				
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1	An intention-to-treat analysis was used. The last-observation-carried-forward method was used to handle missing data.	☒	☐	☐	☐
Result 2	Descriptive statistics included mean, median, standard deviation and the calculation of confidence intervals.	☒	☐	☐	☐
Result 3	Pre- and post-treatment scores (T1 and T2) for all outcome measures were assessed using repeated-measure analysis of variance (ANOVA) with Bonferroni adjustments ($p < 0.025$).	☒	☐	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐

		Yes	**No**	**Unclear**	**N/A**

13	**Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?**		☒	☐	☐	☐

Overall appraisal: **Include: ☒** **Exclude: ☐** **Seek Further Info: ☐**

Comments:

Table 3 – The JBI Critical Appraisal Tool for RCTs

Reviewer: Bokamoso mthimkulu Date: 11 September 2024

Title: Visuo-proprioceptive training reduces risk of falls in patients with multiple sclerosis

Author: Prosperini, L; Leonardi, L; De Carli, P; Mannocchi, M.L; Pozzilli, C

Year: 2010

Record Number: 07

	Yes	No	Unclear	Not applicable
Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	x	□	□	□
Were cases and controls matched appropriately?	x	□	□	□
Were the same criteria used for identification of cases and controls?	□	□	x	□
Was exposure measured in a standard, valid and reliable way?	x	□	□	□
Was exposure measured in the same way for cases and controls?	x	□	□	□
Were confounding factors identified?	□	x	□	□
Were strategies to deal with confounding factors stated?	□	x	□	□
Were outcomes assessed in a standard, valid and reliable way for cases and controls?	x	□	□	□
Was the exposure period of interest long enough to be meaningful?	x	□	□	□
Was appropriate statistical analysis used?	x	□	□	□

Overall appraisal: Include x Exclude □ Seek further info □

Comments (Including reason for exclusion)

The study identified the differences between the case and control in a reliable way.

Appendix F: Black’s and Downs Checklist

Study	Comparative Effectiveness of 4 Exercise interventions Followed by 2 Years of Exercise Maintenance in Multiple Sclerosis: A Randomized Controlled Trial	**Author**	Hortobágyi, T; Ács, P; Baumann, P; Borbély, G; Áfra, G; Reichardt-Varga, E; Sántha, G; Tollár, J			
Year	2022	**Reviewer**	Bokamoso Mthimkulu			
	Reporting	**Yes =1**	**No =0**	**Unclear = 0**	**Unable to determine =0**	**Comments**
1	*Is the hypothesis/aim/objective of the study clearly described?*	1				
2	*Are the main outcomes to be measured clearly described in the Introduction or Methods section?* If the main outcomes are first mentioned in the results section, the question should be answered as no.	1				Main outcomes found in the methods section
3	*Are the characteristics of the subjects included in the study clearly described?* In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and source for controls should be given.	1				
4	*Are the interventions of interest clearly described?* Treatments and placebo (where relevant) that are to be compared should be clearly described.	1				
5	*Are the distributions of principal confounders in each group of subjects to be compared clearly described?* A list of principal confounders is provided.		0			Only baseline characteristics have been given based

						on the inclusion criteria
6	*Are the main findings of the study clearly described?* Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical test which are considered below).	1				
7	*Does the study provide estimates of the random variability in the data for the main outcomes?* In non-normally distributed data, the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If distribution data is not described, it must be assumed that the estimates used were appropriate and the question should be answered with yes.	1				

8	*Have all important adverse events that may be a consequence of the intervention been reported?* This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).		0			
9	*Have the characteristics of subjects lost to follow-up been described?* This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no, where a study does not report the number of patients lost to follow-up.	1				
10	*Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*		0			
	External validity					

11	*Were the subjects asked to participate in the study representative of the entire population from which they were recruited?* The study must identify the source population for subjects and describe how the subjects were selected. Subjects would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the subjects are derived, the question should be answered as unable to determine.				o	
12	*Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.				0	

13	*Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?* For the question to be answered yes, the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.				0	
	Internal Validity					
14	*Was an attempt made to blind study subjects to the intervention they have received?* For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.		0			Assessor blind study
15	*Was an attempt made to blind those measuring the main outcomes of the intervention?*	1				
16	*If any of the results of the study were based on "data dredging", was this made clear?* Any analyses that had not been planned at the outset of the study should be clearly	1				

	indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.					
17	*In trials and cohort studies, do the analyses adjust for different lengths of follow-up, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?* Where follow-up was the same for all study subjects the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow up are ignored should be answered no.	1				
18	*Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used must be appropriate to the data. For example, nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.	1				

19	*Was compliance with the intervention/s reliable?* Where there was noncompliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.	1				
20	*Were the main outcome measures used accurate (valid and reliable)?* For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.	1				
	Internal Validity – confounding (selection bias)					
21	*Were the subjects in different intervention groups or were they recruited from the same population?* For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and casecontrol studies where there is no				0	

	information concerning the source of patients included in the study.					
22	*Were study subjects in different intervention groups or were they recruited over the same period of time?* For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.				0	
23	*Were study subjects randomised to intervention groups?* Studies which state that subjects were randomized should be answered yes except where method of randomisation would not ensure random allocation. For example, alternate allocation would score no because it is predictable.	1				
24	*Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?* All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.	1				

25	*Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.		0			
26	*Were losses of subjects to follow-up taken into account?* If the numbers of subjects lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.	1				
	Power					
27	*Did the study have sufficient power to detect a clinically important effect where*	1				

	the probability value for a difference being due to chance is less than 5%? Sample sizes have been calculated to detect a difference of x% and y.					
		17/27				

Study	Effect of Training Exercises Incorporating Mechanical Devices on Fatigue and Gait Pattern in Persons with Relapsing-Remitting Multiple Sclerosis	**Author**	Escudero-Uribe, S; Hochsprung, A; Heredia-Camacho, B; Izquierdo-Ayuso, G			
Year	2017	**Reviewer**	Bokamoso Mthimkulu			
	Reporting	**Yes =1**	**No =0**	**Unclear = 0**	**Unable to determine =0**	**Comments**
1	*Is the hypothesis/aim/objective of the study clearly described?*	1				
2	*Are the main outcomes to be measured clearly described in the Introduction or Methods section?* If the main outcomes are first mentioned in the results section, the question should be answered as no.	1				Main outcomes found in the methods section
3	*Are the characteristics of the subjects included in the study clearly described?* In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and source for controls should be given.	1				Both characteristics mentioned
4	*Are the interventions of interest clearly described?* Treatments and placebo (where relevant) that are to be compared should be clearly described.	1				
5	*Are the distributions of principal confounders in each group of subjects to be compared clearly described?* A list of principal confounders is provided.		0			Only baseline measures given for the study
6	*Are the main findings of the study clearly described?* Simple outcome data (including denominators and numerators) should be reported for all major findings	1				

	so that the reader can check the major analyses and conclusions. (This question does not cover statistical test which are considered below).					
7	*Does the study provide estimates of the random variability in the data for the main outcomes?* In non-normally distributed data, the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If distribution data is not described, it must be assumed that the estimates used were appropriate and the question should be answered with yes.	1				
8	*Have all important adverse events that may be a consequence of the intervention been reported?* This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).		0			
9	*Have the characteristics of subjects lost to follow-up been described?* This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by	1				

	their inclusion. This should be answered no, where a study does not report the number of patients lost to follow-up.					
10	*Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*	1				
	External validity					
11	*Were the subjects asked to participate in the study representative of the entire population from which they were recruited?* The study must identify the source population for subjects and describe how the subjects were selected. Subjects would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the subjects are derived, the question should be answered as unable to determine.				0	
12	*Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* The proportion of those asked who agreed should be stated. Validation that the sample was				0	

	representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.					
13	*Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?* For the question to be answered yes, the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.				0	
	Internal Validity					
14	*Was an attempt made to blind study subjects to the intervention they have received?* For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.				0	
15	*Was an attempt made to blind those measuring the main outcomes of the intervention?*	1				assessor blinded
16	*If any of the results of the study were based on "data dredging", was this made clear?*	1				

	Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.					
17	*In trials and cohort studies, do the analyses adjust for different lengths of follow-up, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?* Where follow-up was the same for all study subjects the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow up are ignored should be answered no.	1				
18	*Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used must be appropriate to the data. For example, nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.	1				

19	*Was compliance with the intervention/s reliable?* Where there was noncompliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.	1				
20	*Were the main outcome measures used accurate (valid and reliable)?* For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.	1				
	Internal Validity – confounding (selection bias)					
21	*Were the subjects in different intervention groups or were they recruited from the same population?* For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and casecontrol studies where there is no information concerning the source of patients included in the study.	1				
22	*Were study subjects in different intervention groups or were they recruited over the same period of time?* For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.				0	

23	*Were study subjects randomised to intervention groups?* Studies which state that subjects were randomized should be answered yes except where method of randomisation would not ensure random allocation. For example, alternate allocation would score no because it is predictable.	1				
24	*Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?* All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.				0	
25	*Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.		0			

26	*Were losses of subjects to follow-up taken into account?* If the numbers of subjects lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow- up was too small to affect the main findings, the question should be answered yes.	1				
	Power					
27	*Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?* Sample sizes have been calculated to detect a difference of x% and y.	1				
		18/27				

Study	Pilot Study to Investigate the Effect of a 10-Week Aquatic Exercise Program on Individuals with High Levels of Disability Due to Multiple Sclerosis	**Author**	Sames, C; DeBlois, A			
Year	2021	**Reviewer**	Bokamoso Mthimkulu			
	Reporting	**Yes =1**	**No =0**	**Unclear = 0**	**Unable to determine =0**	**Comments**
1	*Is the hypothesis/aim/objective of the study clearly described?*	1				
2	*Are the main outcomes to be measured clearly described in the Introduction or Methods section?* If the main outcomes are first mentioned in the results section, the question should be answered as no.	1				Main outcomes found in the methods section
3	*Are the characteristics of the subjects included in the study clearly described?* In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and source for controls should be given.	1				
4	*Are the interventions of interest clearly described?* Treatments and placebo (where relevant) that are to be compared should be clearly described.	1				
5	*Are the distributions of principal confounders in each group of subjects to be compared clearly described?* A list of principal confounders is provided.		0			Only baseline measures given for the study
6	*Are the main findings of the study clearly described?* Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical test which are considered below).	1				

7	*Does the study provide estimates of the random variability in the data for the main outcomes?* In non-normally distributed data, the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If distribution data is not described, it must be assumed that the estimates used were appropriate and the question should be answered with yes.	1				
8	*Have all important adverse events that may be a consequence of the intervention been reported?* This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).		0			
9	*Have the characteristics of subjects lost to follow-up been described?* This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no, where a study does not report the number of patients lost to follow-up.				0	

10	*Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*	1				
	External validity					
11	*Were the subjects asked to participate in the study representative of the entire population from which they were recruited?* The study must identify the source population for subjects and describe how the subjects were selected. Subjects would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the subjects are derived, the question should be answered as unable to determine.				0	
12	*Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.				0	
13	*Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?*	1				

	For the question to be answered yes, the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.					
	Internal Validity					
14	*Was an attempt made to blind study subjects to the intervention they have received?* For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.		0			
15	*Was an attempt made to blind those measuring the main outcomes of the intervention?*		0			
16	*If any of the results of the study were based on "data dredging", was this made clear?* Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.	1				
17	*In trials and cohort studies, do the analyses adjust for different lengths of follow-up, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?* Where follow-up was the same for all study subjects the answer should yes. If different lengths of follow-up were	1				

	adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow up are ignored should be answered no.					
18	*Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used must be appropriate to the data. For example, nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.	1				
19	*Was compliance with the intervention/s reliable?* Where there was noncompliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.	1				
20	*Were the main outcome measures used accurate (valid and reliable)?* For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the	1				

	outcome measures are accurate, the question should be answered as yes.					
	Internal Validity – confounding (selection bias)					
21	*Were the subjects in different intervention groups or were they recruited from the same population?* For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and casecontrol studies where there is no information concerning the source of patients included in the study.	1				
22	*Were study subjects in different intervention groups or were they recruited over the same period of time?* For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.				0	
23	*Were study subjects randomised to intervention groups?* Studies which state that subjects were randomized should be answered yes except where method of randomisation would not ensure random allocation. For example, alternate allocation would score no because it is predictable.		0			
24	*Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?*		0			

	All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.					
25	*Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.		0			
26	*Were losses of subjects to follow-up taken into account?* If the numbers of subjects lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow- up was too small to affect the main findings, the question should be answered yes.	1				
	Power					
27	*Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?* Sample sizes have been calculated to detect a difference of x% and y.		0			
		15/27				

Study	Effect of remote ischaemic preconditioning on walking in people with multiple sclerosis: double-blind randomised controlled trial	**Author**	Chotiyarnwong, C; Nair, K; Angelini, L; Buckley, E; Mazza, C; Heyes, D; Ramiz, R; Baster, K; Ismail, A; Das, J; Ali, A; Lindert, R; Sharrack, B; Price, S; Paling, D			
Year	2020	**Reviewer**	Bokamoso Mthimkulu			
	Reporting	**Yes =1**	**No =0**	**Unclear = 0**	**Unable to determine =0**	**Comments**
1	*Is the hypothesis/aim/objective of the study clearly described?*	1				
2	*Are the main outcomes to be measured clearly described in the Introduction or Methods section?* If the main outcomes are first mentioned in the results section, the question should be answered as no.	1				Main outcomes found in the methods section
3	*Are the characteristics of the subjects included in the study clearly described?* In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and source for controls should be given.	1				
4	*Are the interventions of interest clearly described?* Treatments and placebo (where relevant) that are to be compared should be clearly described.	1				
5	*Are the distributions of principal confounders in each group of subjects to be compared clearly described?* A list of principal confounders is provided.		0			Baseline charactersitics have been given based on the inclusion criteria.

6	*Are the main findings of the study clearly described?* Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical test which are considered below).	1				
7	*Does the study provide estimates of the random variability in the data for the main outcomes?* In non-normally distributed data, the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If distribution data is not described, it must be assumed that the estimates used were appropriate and the question should be answered with yes.	1				
8	*Have all important adverse events that may be a consequence of the intervention been reported?* This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).	1				

9	*Have the characteristics of subjects lost to follow-up been described?* This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no, where a study does not report the number of patients lost to follow-up.	1				
10	*Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*	1				
	External validity					
11	*Were the subjects asked to participate in the study representative of the entire population from which they were recruited?* The study must identify the source population for subjects and describe how the subjects were selected. Subjects would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the subjects are derived, the question should be answered as unable to determine.				0	

12	*Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.				0	
13	*Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?* For the question to be answered yes, the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.				0	
	Internal Validity					
14	*Was an attempt made to blind study subjects to the intervention they have received?* For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.	1				

15	*Was an attempt made to blind those measuring the main outcomes of the intervention?*	1				
16	*If any of the results of the study were based on "data dredging", was this made clear?* Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.	1				
17	*In trials and cohort studies, do the analyses adjust for different lengths of follow-up, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?* Where follow-up was the same for all study subjects the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow up are ignored should be answered no.	1				
18	*Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used must be appropriate to the data. For example, nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not	1				

	described it must be assumed that the estimates used were appropriate and the question should be answered yes.					
19	*Was compliance with the intervention/s reliable?* Where there was noncompliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.	1				
20	*Were the main outcome measures used accurate (valid and reliable)?* For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.	1				
	Internal Validity – confounding (selection bias)					

21	*Were the subjects in different intervention groups or were they recruited from the same population?* For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and casecontrol studies where there is no information concerning the source of patients included in the study.	1				
22	*Were study subjects in different intervention groups or were they recruited over the same period of time?* For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.	1				
23	*Were study subjects randomised to intervention groups?* Studies which state that subjects were randomized should be answered yes except where method of randomisation would not ensure random allocation. For example, alternate allocation would score no because it is predictable.	1				
24	*Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?*	1				

	All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.					
25	*Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.		0			
26	*Were losses of subjects to follow-up taken into account?* If the numbers of subjects lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow- up was too small to affect the main findings, the question should be answered yes.	1				
	Power					

27	*Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?* Sample sizes have been calculated to detect a difference of x% and y.	1				
		22/27				

Study	Cognitive-motor dual-task training improves dynamic stability during straight and curved gait in patients with multiple sclerosis: a randomized controlled trial	**Author**	Tramontano, M; Argento, O; Orejel Bustos, A.S; De Angelis, S; Montemurro, R; Bossa, M; Belluscio, V; Bergamini, E; Vannozzi, G; Nocentini, U			
Year	2024	**Reviewer**	Bokamoso Mthimkulu			
	Reporting	**Yes =1**	**No =0**	**Unclear = 0**	**Unable to determine =0**	**Comments**
1	*Is the hypothesis/aim/objective of the study clearly described?*	1				
2	*Are the main outcomes to be measured clearly described in the Introduction or Methods section?* If the main outcomes are first mentioned in the results section, the question should be answered as no.	1				Main outcomes found in the methods section
3	*Are the characteristics of the subjects included in the study clearly described?* In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and source for controls should be given.	1				
4	*Are the interventions of interest clearly described?* Treatments and placebo (where relevant) that are to be compared should be clearly described.	1				
5	*Are the distributions of principal confounders in each group of subjects to be compared clearly described?* A list of principal confounders is provided.		0			Baseline charactersitics have been given based on the inclusion criteria.
6	*Are the main findings of the study clearly described?* Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and	1				

	conclusions. (This question does not cover statistical test which are considered below).					
7	*Does the study provide estimates of the random variability in the data for the main outcomes?* In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If distribution data is not described, it must be assumed that the estimates used were appropriate and the question should be answered with yes.	1				
8	*Have all important adverse events that may be a consequence of the intervention been reported?* This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).		0			
9	*Have the characteristics of subjects lost to follow-up been described?* This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no, where a	1				

	study does not report the number of patients lost to follow-up.					
10	*Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*	1				
	External validity					
11	*Were the subjects asked to participate in the study representative of the entire population from which they were recruited?* The study must identify the source population for subjects and describe how the subjects were selected. Subjects would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the subjects are derived, the question should be answered as unable to determine.				0	
12	*Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* The proportion of those asked who agreed should be stated. Validation that the sample was representative				0	

	would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.					
13	*Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?* For the question to be answered yes, the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.	1				
	Internal Validity					
14	*Was an attempt made to blind study subjects to the intervention they have received?* For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.	1				assessor blinded study
15	*Was an attempt made to blind those measuring the main outcomes of the intervention?*	1				
16	*If any of the results of the study were based on "data dredging", was this made clear?*	1				

	Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.					
17	*In trials and cohort studies, do the analyses adjust for different lengths of follow-up, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?* Where follow-up was the same for all study subjects the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow up are ignored should be answered no.	1				
18	*Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used must be appropriate to the data. For example, nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.	1				

19	*Was compliance with the intervention/s reliable?* Where there was noncompliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.	1				
20	*Were the main outcome measures used accurate (valid and reliable)?* For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.	1				
	Internal Validity – confounding (selection bias)					
21	*Were the subjects in different intervention groups or were they recruited from the same population?* For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and casecontrol studies where there is no information concerning the source of patients included in the study.	1				
22	*Were study subjects in different intervention groups or were they recruited over the same period of time?* For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.	1				

23	*Were study subjects randomised to intervention groups?* Studies which state that subjects were randomized should be answered yes except where method of randomisation would not ensure random allocation. For example, alternate allocation would score no because it is predictable.	1				
24	*Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?* All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.	1				
25	*Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.		0			

26	*Were losses of subjects to follow-up taken into account?* If the numbers of subjects lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow- up was too small to affect the main findings, the question should be answered yes.	1				
	Power					
27	*Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?* Sample sizes have been calculated to detect a difference of x% and y.	1				
		22/27				

Study	The efficiency of mirror therapy on drop foot in Multiple Sclerosis Patients	**Author**	Tosun, A.T; Ipek, Y; Ozdincler, A.R; Saip, S			
Year	2020	**Reviewer**	Bokamoso Mthimkulu			
	Reporting	**Yes =1**	**No =0**	**Unclear = 0**	**Unable to determine =0**	**Comments**
1	*Is the hypothesis/aim/objective of the study clearly described?*	1				
2	*Are the main outcomes to be measured clearly described in the Introduction or Methods section?* If the main outcomes are first mentioned in the results section, the question should be answered as no.	1				Main outcomes found in the methods section
3	*Are the characteristics of the subjects included in the study clearly described?* In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and source for controls should be given.	1				
4	*Are the interventions of interest clearly described?* Treatments and placebo (where relevant) that are to be compared should be clearly described.	1				
5	*Are the distributions of principal confounders in each group of subjects to be compared clearly described?* A list of principal confounders is provided.		0			Baseline charactersitics have been given based on the inclusion criteria.
6	*Are the main findings of the study clearly described?* Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical test which are considered below).	1				

7	*Does the study provide estimates of the random variability in the data for the main outcomes?* In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If distribution data is not described, it must be assumed that the estimates used were appropriate and the question should be answered with yes.	1				
8	*Have all important adverse events that may be a consequence of the intervention been reported?* This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).		0			
9	*Have the characteristics of subjects lost to follow-up been described?* This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no, where a study does not report the number of patients lost to follow-up.				0	

10	*Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*	1				
	External validity					
11	*Were the subjects asked to participate in the study representative of the entire population from which they were recruited?* The study must identify the source population for subjects and describe how the subjects were selected. Subjects would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the subjects are derived, the question should be answered as unable to determine.				0	
12	*Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.				0	
13	*Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?*		0			

	For the question to be answered yes, the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.					
	Internal Validity					
14	*Was an attempt made to blind study subjects to the intervention they have received?* For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.				0	
15	*Was an attempt made to blind those measuring the main outcomes of the intervention?*	1				
16	*If any of the results of the study were based on "data dredging", was this made clear?* Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.	1				
17	*In trials and cohort studies, do the analyses adjust for different lengths of follow-up, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?* Where follow-up was the same for all study subjects the answer should yes. If different lengths of follow-up were	1				

	adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow up are ignored should be answered no.					
18	*Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used must be appropriate to the data. For example, nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.	1				
19	*Was compliance with the intervention/s reliable?* Where there was noncompliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.	1				
20	*Were the main outcome measures used accurate (valid and reliable)?* For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the	1				

	outcome measures are accurate, the question should be answered as yes.					
	Internal Validity – confounding (selection bias)					
21	*Were the subjects in different intervention groups or were they recruited from the same population?* For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and casecontrol studies where there is no information concerning the source of patients included in the study.	1				
22	*Were study subjects in different intervention groups or were they recruited over the same period of time?* For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.				0	
23	*Were study subjects randomised to intervention groups?* Studies which state that subjects were randomized should be answered yes except where method of randomisation would not ensure random allocation. For example, alternate allocation would score no because it is predictable.	1				
24	*Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?*	1				

	All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.					
25	*Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.		0			
26	*Were losses of subjects to follow-up taken into account?* If the numbers of subjects lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow- up was too small to affect the main findings, the question should be answered yes.	1				
	Power					
27	*Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?* Sample sizes have been calculated to detect a difference of x% and y.	1				
		18/27				

Study	Visuo-proprioceptive training reduces risk of falls in patients with multiple sclerosis	**Author**	Prosperini, L; Leonardi, L; De Carli, P; Mannocchi, M.L; Pozzilli, C			
Year	2010	**Reviewer**	Bokamoso Mthimkulu			
	Reporting	**Yes =1**	**No =0**	**Unclear = 0**	**Unable to determine =0**	**Comments**
1	*Is the hypothesis/aim/objective of the study clearly described?*	1				
2	*Are the main outcomes to be measured clearly described in the Introduction or Methods section?* If the main outcomes are first mentioned in the results section, the question should be answered as no.	1				Main outcomes found in the methods section
3	*Are the characteristics of the subjects included in the study clearly described?* In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and source for controls should be given.	1				
4	*Are the interventions of interest clearly described?* Treatments and placebo (where relevant) that are to be compared should be clearly described.	1				
5	*Are the distributions of principal confounders in each group of subjects to be compared clearly described?* A list of principal confounders is provided.		0			Baseline charactersitics have been given based on the inclusion criteria.
6	*Are the main findings of the study clearly described?* Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical test which are considered below).	1				

7	*Does the study provide estimates of the random variability in the data for the main outcomes?* In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If distribution data is not described, it must be assumed that the estimates used were appropriate and the question should be answered with yes.	1				
8	*Have all important adverse events that may be a consequence of the intervention been reported?* This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).		0			
9	*Have the characteristics of subjects lost to follow-up been described?* This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no, where a study does not report the number of patients lost to follow-up.	1				

10	*Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*	1				
	External validity					
11	*Were the subjects asked to participate in the study representative of the entire population from which they were recruited?* The study must identify the source population for subjects and describe how the subjects were selected. Subjects would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the subjects are derived, the question should be answered as unable to determine.				0	
12	*Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.				0	
13	*Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?*				0	

	For the question to be answered yes, the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.					
	Internal Validity					
14	*Was an attempt made to blind study subjects to the intervention they have received?* For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.		0			Cohort study
15	*Was an attempt made to blind those measuring the main outcomes of the intervention?*				0	
16	*If any of the results of the study were based on "data dredging", was this made clear?* Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.	1				
17	*In trials and cohort studies, do the analyses adjust for different lengths of follow-up, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?*	1				

	Where follow-up was the same for all study subjects the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow up are ignored should be answered no.					
18	*Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used must be appropriate to the data. For example, nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.	1				
19	*Was compliance with the intervention/s reliable?* Where there was noncompliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.	1				
20	*Were the main outcome measures used accurate (valid and reliable)?* For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates	1				

	the outcome measures are accurate, the question should be answered as yes.					
	Internal Validity – confounding (selection bias)					
21	*Were the subjects in different intervention groups or were they recruited from the same population?* For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and casecontrol studies where there is no information concerning the source of patients included in the study.				0	
22	*Were study subjects in different intervention groups or were they recruited over the same period of time?* For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.				0	
23	*Were study subjects randomised to intervention groups?* Studies which state that subjects were randomized should be answered yes except where method of randomisation would not ensure random allocation. For example, alternate allocation would score no because it is predictable.		0			
24	*Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?*		0			

	All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.					
25	*Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.		0			
26	*Were losses of subjects to follow-up taken into account?* If the numbers of subjects lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow- up was too small to affect the main findings, the question should be answered yes.	1				
	Power					
27	*Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?* Sample sizes have been calculated to detect a difference of x% and y.	1				

		15/27				

Study	Sensory integration balance training in patients with multiple sclerosis: A randomized, controlled trial	**Author**	Gandolfi, M; Munari, D; Geroin, C; Gajofatto, A; Benedetti, M.D; Midiri, A; Carla, F; Picelli, A; Waldner, A; Smania, N			
Year	2015	**Reviewer**	Bokamoso Mthimkulu			
	Reporting	**Yes =1**	**No =0**	**Unclear = 0**	**Unable to determine =0**	**Comments**
1	*Is the hypothesis/aim/objective of the study clearly described?*	1				
2	*Are the main outcomes to be measured clearly described in the Introduction or Methods section?* If the main outcomes are first mentioned in the results section, the question should be answered as no.	1				Main outcomes found in the methods section
3	*Are the characteristics of the subjects included in the study clearly described?* In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and source for controls should be given.	1				
4	*Are the interventions of interest clearly described?* Treatments and placebo (where relevant) that are to be compared should be clearly described.	1				
5	*Are the distributions of principal confounders in each group of subjects to be compared clearly described?* A list of principal confounders is provided.		0			Baseline characteristics have been given based on the inclusion criteria.
6	*Are the main findings of the study clearly described?* Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical test which are considered below).	1				

7	*Does the study provide estimates of the random variability in the data for the main outcomes?* In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If distribution data is not described, it must be assumed that the estimates used were appropriate and the question should be answered with yes.	1				
8	*Have all important adverse events that may be a consequence of the intervention been reported?* This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).		0			
9	*Have the characteristics of subjects lost to follow-up been described?* This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no, where a study does not report the number of patients lost to follow-up.	1				
10	*Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*		0			
	External validity					
11	*Were the subjects asked to participate in the study representative of the entire population from which they were recruited?*				0	

	The study must identify the source population for subjects and describe how the subjects were selected. Subjects would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the subjects are derived, the question should be answered as unable to determine.					
12	*Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.				0	
13	*Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?* For the question to be answered yes, the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.	1				
	Internal Validity					
14	*Was an attempt made to blind study subjects to the intervention they have received?* For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.		0			single blinded study

15	*Was an attempt made to blind those measuring the main outcomes of the intervention?*	1				
16	*If any of the results of the study were based on "data dredging", was this made clear?* Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.	1				
17	*In trials and cohort studies, do the analyses adjust for different lengths of follow-up, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?* Where follow-up was the same for all study subjects the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow up are ignored should be answered no.	1				
18	*Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used must be appropriate to the data. For example, nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.	1				
19	*Was compliance with the intervention/s reliable?* Where there was noncompliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any	1				

	misclassification was likely to bias any association to the null, the question should be answered yes.					
20	*Were the main outcome measures used accurate (valid and reliable)?* For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.	1				
	Internal Validity – confounding (selection bias)					
21	*Were the subjects in different intervention groups or were they recruited from the same population?* For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and casecontrol studies where there is no information concerning the source of patients included in the study.	1				
22	*Were study subjects in different intervention groups or were they recruited over the same period of time?* For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.	1				
23	*Were study subjects randomised to intervention groups?* Studies which state that subjects were randomized should be answered yes except where method of randomisation would not ensure random allocation. For example, alternate allocation would score no because it is predictable.	1				

24	*Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?* All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.				0	
25	*Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.		0			
26	*Were losses of subjects to follow-up taken into account?* If the numbers of subjects lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow- up was too small to affect the main findings, the question should be answered yes.	1				
	Power					
27	*Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?* Sample sizes have been calculated to detect a difference of x% and y.	1				

		19/27				

Study	Vibration therapy in multiple sclerosis: a pilot study exploring its effects on tone, muscle force, sensation and functional performance	**Author**	Schyns, F; Paul, L; Finlay, K; Ferguson,C; Noble, E			
Year	2009	**Reviewer**	Bokamoso Mthimkulu			
	Reporting	**Yes =1**	**No =0**	**Unclear = 0**	**Unable to determine =0**	**Comments**
1	*Is the hypothesis/aim/objective of the study clearly described?*	1				
2	*Are the main outcomes to be measured clearly described in the Introduction or Methods section?* If the main outcomes are first mentioned in the results section, the question should be answered as no.	1				Main outcomes found in the methods section
3	*Are the characteristics of the subjects included in the study clearly described?* In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and source for controls should be given.	1				
4	*Are the interventions of interest clearly described?* Treatments and placebo (where relevant) that are to be compared should be clearly described.	1				
5	*Are the distributions of principal confounders in each group of subjects to be compared clearly described?* A list of principal confounders is provided.		0			Baseline charactersitics have been given based on the inclusion criteria.
6	*Are the main findings of the study clearly described?* Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical test which are considered below).	1				

7	*Does the study provide estimates of the random variability in the data for the main outcomes?* In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If distribution data is not described, it must be assumed that the estimates used were appropriate and the question should be answered with yes.	1				
8	*Have all important adverse events that may be a consequence of the intervention been reported?* This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).		0			
9	*Have the characteristics of subjects lost to follow-up been described?* This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no, where a study does not report the number of patients lost to follow-up.				0	

10	*Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*	1				
	External validity					
11	*Were the subjects asked to participate in the study representative of the entire population from which they were recruited?* The study must identify the source population for subjects and describe how the subjects were selected. Subjects would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the subjects are derived, the question should be answered as unable to determine.				0	
12	*Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.				0	
13	*Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?*		0			

	For the question to be answered yes, the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.					
	Internal Validity					
14	*Was an attempt made to blind study subjects to the intervention they have received?* For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.				0	
15	*Was an attempt made to blind those measuring the main outcomes of the intervention?*	1				
16	*If any of the results of the study were based on "data dredging", was this made clear?* Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.		0			
17	*In trials and cohort studies, do the analyses adjust for different lengths of follow-up, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?* Where follow-up was the same for all study subjects the answer should yes. If different lengths of follow-up were	1				

	adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow up are ignored should be answered no.					
18	*Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used must be appropriate to the data. For example, nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.	1				
19	*Was compliance with the intervention/s reliable?* Where there was noncompliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.	1				
20	*Were the main outcome measures used accurate (valid and reliable)?* For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the	1				

	outcome measures are accurate, the question should be answered as yes.					
	Internal Validity – confounding (selection bias)					
21	*Were the subjects in different intervention groups or were they recruited from the same population?* For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and casecontrol studies where there is no information concerning the source of patients included in the study.	1				
22	*Were study subjects in different intervention groups or were they recruited over the same period of time?* For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.				0	
23	*Were study subjects randomised to intervention groups?* Studies which state that subjects were randomized should be answered yes except where method of randomisation would not ensure random allocation. For example, alternate allocation would score no because it is predictable.	1				
24	*Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?*				0	

	All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.					
25	*Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.		0			
26	*Were losses of subjects to follow-up taken into account?* If the numbers of subjects lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow- up was too small to affect the main findings, the question should be answered yes.	1				
	Power					
27	*Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?* Sample sizes have been calculated to detect a difference of x% and y.		0			
		15/27				

Appendix G: Consensus on Exercise Reporting Template Checklist

Study	Comparative Effectiveness of 4 Exercise interventions Followed by 2 Years of Exercise Maintenance in Multiple Sclerosis: A Randomized Controlled Trial		**Author**		Hortobágyi, T; Ács, P; Baumann, P; Borbély, G; Áfra, G; Reichardt-Varga, E; Sántha, G; Tollár, J	
Year	2022		**Reviewer**		Bokamoso Mthimkulu	
Section/topic	**Item**	**Checklist Item**	**Location**			
			Primary paper (page, table, appendix)	Other (paper or protocol, website (URL)	Yes= 1 No=0	'Reasons for rating': eg, 'not reported or not. Item Primary paper Other* clearly described'
What: Materials	**1**	Detailed description of the type of exercise equipment (e.g. weights, exercise equipment such as machines, treadmill, bicycle ergometer etc)			0	States what exercises each group did but not the equipment used
Who: provider	**2**	Detailed description of the qualifications, teaching/supervising expertise, and/or training undertaken by the exercise instructor			0	
How: delivery	**3**	Describe whether exercises are performed individually or in a group			1	Group setting
	4	Describe whether exercises are supervised or unsupervised and how they are delivered			1	Delivered by 1 of 3 therapists supervised
	5	Detailed description of how adherence to exercise is measured and reported			1	
	6	Detailed description of motivation strategies			0	
	7a	Detailed description of the decision rule(s) for determining exercise progression			0	

	7b	Detailed description of how the exercise program was progressed			0	
	8	Detailed description of each exercise to enable replication (e.g. photographs, illustrations , video etc)			0	
	9	Detailed description of any home program component (e.g. other exercises, stretching etc)			0	No home programs
	10	Describe whether there are any non-exercise components (e.g. education, cognitive behavioural therapy, massage etc)			0	
	11	Describe the type and number of adverse events that occurred during exercise			0	
Where: location	**12**	Describe the setting in which the exercises are performed			1	
When, how much: dosage	**13**	Detailed description of the exercise intervention including, but not limited to, number of exercise repetitions/sets/sessions, session duration, intervention/program duration etc			1	
Tailoring: what, how	**14a**	Describe whether the exercises are generic (one size fits all) or tailored whether tailored to the individual			1	
	14b	Detailed description of how exercises are tailored to the individual			0	One size fit all
	15	Describe the decision rule for determining the starting level at which people commence an exercise program (such as beginner, intermediate, advanced etc)			0	
How well: planned actual	**16a**	Describe how adherence or fidelity to the exercise intervention is assessed/measured			0	
	16b	Describe the extent to which the intervention was delivered as planned			0	
					6/19	

Study	Effect of Training Exercises Incorporating Mechanical Devices on Fatigue and Gait Pattern in Persons with Relapsing-Remitting Multiple Sclerosis		**Author**		Escudero-Uribe, S; Hochsprung, A; Heredia-Camacho, B; Izquierdo-Ayuso, G	
Year	2017		**Reviewer**		Bokamoso Mthimkulu	
Section/topic	**Item**	**Checklist Item**	**Location**			
			Primary paper (page, table, appendix)	Other (paper or protocol, website (URL)	Yes= 1 No=0	'Reasons for rating': eg, 'not reported or not. Item Primary paper Other* clearly described'
What: Materials	**1**	Detailed description of the type of exercise equipment (e.g. weights, exercise equipment such as machines, treadmill, bicycle ergometer etc)			1	
Who: provider	**2**	Detailed description of the qualifications, teaching/supervising expertise, and/or training undertaken by the exercise instructor			0	
How: delivery	**3**	Describe whether exercises are performed individually or in a group			1	Group setting
	4	Describe whether exercises are supervised or unsupervised and how they are delivered			1	one therapist
	5	Detailed description of how adherence to exercise is measured and reported			1	
	6	Detailed description of motivation strategies			0	
	7a	Detailed description of the decision rule(s) for determining exercise progression			1	

	7b	Detailed description of how the exercise program was progressed			1	
	8	Detailed description of each exercise to enable replication (e.g. photographs, illustrations , video etc)			1	
	9	Detailed description of any home program component (e.g. other exercises, stretching etc)			0	
	10	Describe whether there are any non-exercise components (e.g. education, cognitive behavioural therapy, massage etc)			1	Relaxation and breathing
	11	Describe the type and number of adverse events that occurred during exercise			0	
Where: location	**12**	Describe the setting in which the exercises are performed			1	
When, how much: dosage	**13**	Detailed description of the exercise intervention including, but not limited to, number of exercise repetitions/sets/sessions, session duration, intervention/program duration etc			1	
Tailoring: what, how	**14a**	Describe whether the exercises are generic (one size fits all) or tailored whether tailored to the individual			1	
	14b	Detailed description of how exercises are tailored to the individual			1	
	15	Describe the decision rule for determining the starting level at which people commence an exercise program (such as beginner, intermediate, advanced etc)			0	
How well: planned actual	**16a**	Describe how adherence or fidelity to the exercise intervention is assessed/measured			1	
	16b	Describe the extent to which the intervention was delivered as planned			1	
					14/19	

Study	Pilot Study to Investigate the Effect of a 10-Week Aquatic Exercise Program on Individuals with High Levels of Disability Due to Multiple Sclerosis		**Author**		Sames, C; DeBlois, A	
Year	2021		**Reviewer**		Bokamoso Mthimkulu	
Section/topic	**Item**	**Checklist Item**	**Location**			
			Primary paper (page, table, appendix)	Other (paper or protocol, website (URL)	Yes= 1 No=0	'Reasons for rating': eg, 'not reported or not. Item Primary paper Other* clearly described'
What: Materials	**1**	Detailed description of the type of exercise equipment (e.g. weights, exercise equipment such as machines, treadmill, bicycle ergometer etc)			0	
Who: provider	**2**	Detailed description of the qualifications, teaching/supervising expertise, and/or training undertaken by the exercise instructor			1	
How: delivery	**3**	Describe whether exercises are performed individually or in a group			1	Group setting
	4	Describe whether exercises are supervised or unsupervised and how they are delivered			1	Supervised by 2 therapists
	5	Detailed description of how adherence to exercise is measured and reported			0	
	6	Detailed description of motivation strategies			1	Noted that it was given
	7a	Detailed description of the decision rule(s) for determining exercise progression			1	
	7b	Detailed description of how the exercise program was progressed			1	

	8	Detailed description of each exercise to enable replication (e.g. photographs, illustrations , video etc)			0	
	9	Detailed description of any home program component (e.g. other exercises, stretching etc)			0	
	10	Describe whether there are any non-exercise components (e.g. education, cognitive behavioural therapy, massage etc)			0	
	11	Describe the type and number of adverse events that occurred during exercise			1	
Where: location	**12**	Describe the setting in which the exercises are performed			1	
When, how much: dosage	**13**	Detailed description of the exercise intervention including, but not limited to, number of exercise repetitions/sets/sessions, session duration, intervention/program duration etc			1	
Tailoring: what, how	**14a**	Describe whether the exercises are generic (one size fits all) or tailored whether tailored to the individual			1	
	14b	Detailed description of how exercises are tailored to the individual			1	
	15	Describe the decision rule for determining the starting level at which people commence an exercise program (such as beginner, intermediate, advanced etc)			0	
How well: planned actual	**16a**	Describe how adherence or fidelity to the exercise intervention is assessed/measured			1	
	16b	Describe the extent to which the intervention was delivered as planned			1	
					13/19	

Study	Effect of remote ischaemic preconditioning on walking in people with multiple sclerosis: double-blind randomised controlled trial		**Author**		Chotiyarnwong, C; Nair, K; Angelini, L; Buckley, E; Mazza, C; Heyes, D; Ramiz, R; Baster, K; Ismail, A; Das, J; Ali, A; Lindert, R; Sharrack, B; Price, S; Paling, D	
Year	2020		**Reviewer**		Bokamoso Mthimkulu	
Section/topic	**Item**	**Checklist Item**	**Location**			
			Primary paper (page, table, appendix)	Other (paper or protocol, website (URL)	Yes= 1 No=0	'Reasons for rating': eg, 'not reported or not. Item Primary paper Other* clearly described'
What: Materials	**1**	Detailed description of the type of exercise equipment (e.g. weights, exercise equipment such as machines, treadmill, bicycle ergometer etc)			0	Main equipment was a manual blood pressure cuff (clinical more than exercise)
Who: provider	**2**	Detailed description of the qualifications, teaching/supervising expertise, and/or training undertaken by the exercise instructor			0	
How: delivery	**3**	Describe whether exercises are performed individually or in a group			0	Does not state directly. But one researcher did the testing at a time.
	4	Describe whether exercises are supervised or unsupervised and how they are delivered			1	Supervised protocol
	5	Detailed description of how adherence to exercise is measured and reported			0	Not reported how it was measured
	6	Detailed description of motivation strategies			0	

	7a	Detailed description of the decision rule(s) for determining exercise progression			0	
	7b	Detailed description of how the exercise program was progressed			0	Exercise intervention was not progressed one day study
	8	Detailed description of each exercise to enable replication (e.g. photographs, illustrations , video etc)			1	Graph explaining the protocol
	9	Detailed description of any home program component (e.g. other exercises, stretching etc)			0	
	10	Describe whether there are any non-exercise components (e.g. education, cognitive behavioural therapy, massage etc)			0	
	11	Describe the type and number of adverse events that occurred during exercise			1	
Where: location	**12**	Describe the setting in which the exercises are performed			0	
When, how much: dosage	**13**	Detailed description of the exercise intervention including, but not limited to, number of exercise repetitions/sets/sessions, session duration, intervention/program duration etc			1	
Tailoring: what, how	**14a**	Describe whether the exercises are generic (one size fits all) or tailored whether tailored to the individual			1	
	14b	Detailed description of how exercises are tailored to the individual			0	One size fits all protocol
	15	Describe the decision rule for determining the starting level at which people commence an exercise program (such as beginner, intermediate, advanced etc)			0	
How well: planned actual	**16a**	Describe how adherence or fidelity to the exercise intervention is assessed/measured			0	

	16b	Describe the extent to which the intervention was delivered as planned			1	
					6/19	

Study	Cognitive-motor dual-task training improves dynamic stability during straight and curved gait in patients with multiple sclerosis: a randomized controlled trial		**Author**		Tramontano, M; Argento, O; Orejel Bustos, A.S; De Angelis, S; Montemurro, R; Bossa, M; Belluscio, V; Bergamini, E; Vannozzi, G; Nocentini, U	
Year	2024		**Reviewer**		Bokamoso Mthimkulu	
Section/topic	**Item**	**Checklist Item**	**Location**			
			Primary paper (page, table, appendix)	Other (paper or protocol, website (URL)	Yes= 1 No=0	'Reasons for rating': eg, 'not reported or not. Item Primary paper Other* clearly described'
What: Materials	**1**	Detailed description of the type of exercise equipment (e.g. weights, exercise equipment such as machines, treadmill, bicycle ergometer etc)			1	
Who: provider	**2**	Detailed description of the qualifications, teaching/supervising expertise, and/or training undertaken by the exercise instructor			0	
How: delivery	**3**	Describe whether exercises are performed individually or in a group			1	
	4	Describe whether exercises are supervised or unsupervised and how they are delivered			1	Supervised intervention

	5	Detailed description of how adherence to exercise is measured and reported			0	Not reported how it was measured
	6	Detailed description of motivation strategies			0	
	7a	Detailed description of the decision rule(s) for determining exercise progression			0	Not reported
	7b	Detailed description of how the exercise program was progressed			0	Not reported
	8	Detailed description of each exercise to enable replication (e.g. photographs, illustrations , video etc)			1	Illustrations given
	9	Detailed description of any home program component (e.g. other exercises, stretching etc)			0	
	10	Describe whether there are any non-exercise components (e.g. education, cognitive behavioural therapy, massage etc)			0	
	11	Describe the type and number of adverse events that occurred during exercise			0	
Where: location	**12**	Describe the setting in which the exercises are performed			1	
When, how much: dosage	**13**	Detailed description of the exercise intervention including, but not limited to, number of exercise repetitions/sets/sessions, session duration, intervention/program duration etc			1	
Tailoring: what, how	**14a**	Describe whether the exercises are generic (one size fits all) or tailored whether tailored to the individual			0	
	14b	Detailed description of how exercises are tailored to the individual			0	Not reported
	15	Describe the decision rule for determining the starting level at which people commence an exercise program (such as beginner, intermediate, advanced etc)			0	

How well: planned actual	**16a**	Describe how adherence or fidelity to the exercise intervention is assessed/measured				
	16b	Describe the extent to which the intervention was delivered as planned			0	
					6/19	

Study	The efficiency of mirror therapy on drop foot in Multiple Sclerosis Patients		**Author**		Tosun, A.T; Ipek, Y; Ozdincler, A.R; Saip, S	
Year	2020		**Reviewer**		Bokamoso Mthimkulu	
Section/topic	**Item**	**Checklist Item**	**Location**			
			Primary paper (page, table, appendix)	Other (paper or protocol, website (URL)	Yes= 1 No=0	'Reasons for rating': eg, 'not reported or not. Item Primary paper Other* clearly described'
What: Materials	**1**	Detailed description of the type of exercise equipment (e.g. weights, exercise equipment such as machines, treadmill, bicycle ergometer etc)			1	Theraband
Who: provider	**2**	Detailed description of the qualifications, teaching/supervising expertise, and/or training undertaken by the exercise instructor			0	
How: delivery	**3**	Describe whether exercises are performed individually or in a group			0	Not reported to be a group setting
	4	Describe whether exercises are supervised or unsupervised and how they are delivered			1	Supervised
	5	Detailed description of how adherence to exercise is measured and reported			0	

	6	Detailed description of motivation strategies			0	
	7a	Detailed description of the decision rule(s) for determining exercise progression			0	
	7b	Detailed description of how the exercise program was progressed			0	
	8	Detailed description of each exercise to enable replication (e.g. photographs, illustrations , video etc)			0	
	9	Detailed description of any home program component (e.g. other exercises, stretching etc)			1	
	10	Describe whether there are any non-exercise components (e.g. education, cognitive behavioural therapy, massage etc)			0	
	11	Describe the type and number of adverse events that occurred during exercise			0	
Where: location	**12**	Describe the setting in which the exercises are performed			1	
When, how much: dosage	**13**	Detailed description of the exercise intervention including, but not limited to, number of exercise repetitions/sets/sessions, session duration, intervention/program duration etc			1	
Tailoring: what, how	**14a**	Describe whether the exercises are generic (one size fits all) or tailored whether tailored to the individual			1	
	14b	Detailed description of how exercises are tailored to the individual			1	
	15	Describe the decision rule for determining the starting level at which people commence an exercise program (such as beginner, intermediate, advanced etc)			0	
How well: planned actual	**16a**	Describe how adherence or fidelity to the exercise intervention is assessed/measured			0	

	16b	Describe the extent to which the intervention was delivered as planned			0	
					7/19	

Study	Visuo-proprioceptive training reduces risk of falls in patients with multiple sclerosis		**Author**		Prosperini, L; Leonardi, L; De Carli, P; Mannocchi, M.L; Pozzilli, C	
Year	2010		**Reviewer**		Bokamoso Mthimkulu	
Section/topic	**Item**	**Checklist Item**	**Location**			
			Primary paper (page, table, appendix)	Other (paper or protocol, website (URL)	Yes= 1 No=0	'Reasons for rating': eg, 'not reported or not. Item Primary paper Other* clearly described'
What: Materials	**1**	Detailed description of the type of exercise equipment (e.g. weights, exercise equipment such as machines, treadmill, bicycle ergometer etc)			0	
Who: provider	**2**	Detailed description of the qualifications, teaching/supervising expertise, and/or training undertaken by the exercise instructor			0	
How: delivery	**3**	Describe whether exercises are performed individually or in a group			0	
	4	Describe whether exercises are supervised or unsupervised and how they are delivered			1	Supervised intervention
	5	Detailed description of how adherence to exercise is measured and reported			0	Not reported how it was measured
	6	Detailed description of motivation strategies			0	

	7a	Detailed description of the decision rule(s) for determining exercise progression			0	
	7b	Detailed description of how the exercise program was progressed			0	
	8	Detailed description of each exercise to enable replication (e.g. photographs, illustrations , video etc)			1	DPA, DEB and DVC photos given
	9	Detailed description of any home program component (e.g. other exercises, stretching etc)			0	
	10	Describe whether there are any non-exercise components (e.g. education, cognitive behavioural therapy, massage etc)			0	
	11	Describe the type and number of adverse events that occurred during exercise			0	Not reported
Where: location	**12**	Describe the setting in which the exercises are performed			0	
When, how much: dosage	**13**	Detailed description of the exercise intervention including, but not limited to, number of exercise repetitions/sets/sessions, session duration, intervention/program duration etc			1	Only duration noted
Tailoring: what, how	**14a**	Describe whether the exercises are generic (one size fits all) or tailored whether tailored to the individual			1	
	14b	Detailed description of how exercises are tailored to the individual			0	
	15	Describe the decision rule for determining the starting level at which people commence an exercise program (such as beginner, intermediate, advanced etc)			0	Not reported
How well: planned actual	**16a**	Describe how adherence or fidelity to the exercise intervention is assessed/measured			0	Not reported

	16b	Describe the extent to which the intervention was delivered as planned			1	
					5/19	

Study	Sensory integration balance training in patients with multiple sclerosis: A randomized, controlled trial		**Author**		Gandolfi, M; Munari, D; Geroin, C; Gajofatto, A; Benedetti, M.D; Midiri, A; Carla, F; Picelli, A; Waldner, A; Smania, N	
Year	2015		**Reviewer**		Bokamoso Mthimkulu	
Section/topic	**Item**	**Checklist Item**	**Location**			
			Primary paper (page, table, appendix)	Other (paper or protocol, website (URL)	Yes= 1 No=0	'Reasons for rating': eg, 'not reported or not. Item Primary paper Other* clearly described'
What: Materials	**1**	Detailed description of the type of exercise equipment (e.g. weights, exercise equipment such as machines, treadmill, bicycle ergometer etc)			1	Therabands, and foam mats
Who: provider	**2**	Detailed description of the qualifications, teaching/supervising expertise, and/or training undertaken by the exercise instructor			0	
How: delivery	**3**	Describe whether exercises are performed individually or in a group			1	
	4	Describe whether exercises are supervised or unsupervised and how they are delivered			1	Supervised intervention
	5	Detailed description of how adherence to exercise is measured and reported			1	

	6	Detailed description of motivation strategies			0	Not reported
	7a	Detailed description of the decision rule(s) for determining exercise progression			0	Program was progressed but does not state how
	7b	Detailed description of how the exercise program was progressed			0	
	8	Detailed description of each exercise to enable replication (e.g. photographs, illustrations , video etc)			0	
	9	Detailed description of any home program component (e.g. other exercises, stretching etc)			0	
	10	Describe whether there are any non-exercise components (e.g. education, cognitive behavioural therapy, massage etc)			0	
	11	Describe the type and number of adverse events that occurred during exercise			0	
Where: location	**12**	Describe the setting in which the exercises are performed			1	
When, how much: dosage	**13**	Detailed description of the exercise intervention including, but not limited to, number of exercise repetitions/sets/sessions, session duration, intervention/program duration etc			1	
Tailoring: what, how	**14a**	Describe whether the exercises are generic (one size fits all) or tailored whether tailored to the individual			1	
	14b	Detailed description of how exercises are tailored to the individual			0	Not reported
	15	Describe the decision rule for determining the starting level at which people commence an exercise program (such as beginner, intermediate, advanced etc)			0	Not reported

How well: planned actual	**16a**	Describe how adherence or fidelity to the exercise intervention is assessed/measured			1	
	16b	Describe the extent to which the intervention was delivered as planned			1	
					9/19	

Study	Vibration therapy in multiple sclerosis: a pilot study exploring its effects on tone, muscle force, sensation and functional performance		**Author**		Schyns, F; Paul, L; Finlay, K; Ferguson,C; Noble, E	
Year	2009		**Reviewer**		Bokamoso Mthimkulu	
Section/topic	**Item**	**Checklist Item**	**Location**			
			Primary paper (page, table, appendix)	Other (paper or protocol, website (URL)	Yes= 1 No=0	'Reasons for rating': eg, 'not reported or not. Item Primary paper Other* clearly described'
What: Materials	**1**	Detailed description of the type of exercise equipment (e.g. weights, exercise equipment such as machines, treadmill, bicycle ergometer etc)			1	
Who: provider	**2**	Detailed description of the qualifications, teaching/supervising expertise, and/or training undertaken by the exercise instructor			0	
How: delivery	**3**	Describe whether exercises are performed individually or in a group			0	
	4	Describe whether exercises are supervised or unsupervised and how they are delivered			0	Not reported

	5	Detailed description of how adherence to exercise is measured and reported			0	
	6	Detailed description of motivation strategies			0	
	7a	Detailed description of the decision rule(s) for determining exercise progression			0	
	7b	Detailed description of how the exercise program was progressed			0	
	8	Detailed description of each exercise to enable replication (e.g. photographs, illustrations , video etc)			0	
	9	Detailed description of any home program component (e.g. other exercises, stretching etc)			0	Not reported
	10	Describe whether there are any non-exercise components (e.g. education, cognitive behavioural therapy, massage etc)			0	
	11	Describe the type and number of adverse events that occurred during exercise			0	States there are adverse events only
Where: location	**12**	Describe the setting in which the exercises are performed			1	
When, how much: dosage	**13**	Detailed description of the exercise intervention including, but not limited to, number of exercise repetitions/sets/sessions, session duration, intervention/program duration etc			1	
Tailoring: what, how	**14a**	Describe whether the exercises are generic (one size fits all) or tailored whether tailored to the individual			0	
	14b	Detailed description of how exercises are tailored to the individual			0	
	15	Describe the decision rule for determining the starting level at which people commence an exercise program (such as beginner, intermediate, advanced etc)			0	Not reported

How well: planned actual	**16a**	Describe how adherence or fidelity to the exercise intervention is assessed/measured			0	
	16b	Describe the extent to which the intervention was delivered as planned			1	
					4/19	

Appendix H: Ethics Waiver

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Innovation)

TO: Ms B Mthimkulu
School: Therapeutic Sciences
Department:
Division:
Exercise Science and Sports Medicine
Medical School
E-mail: 1440864@students.wits.ac.za

CC: Supervisor: Ms M Neophytou, et al Natalia.Neophytou@wits.ac.za
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 18/06/2024

REF: *R14/49*

PROTOCOL NO: W-PR-240618-02 (This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)

PROJECT TITLE: *The efects of exercise therapy on proprioception in patients with multipler sclerosis: a systematic review*

Please find attached the Ethics Waiver Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/ClearScanWaiver.wps

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Innovation)

18/06/2024

Ref: W-PR-240618-02

TO WHOM IT MAY CONCERN

Waiver: This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical)

Investigator: Ms B Mthimkulu
Student No. (if appropriate): 1440864
Staff No. (if appropriate):

Supervisor: Ms M Neophytou, et al

School: Therapeutic Sciences
Department:
Division:
Exercise Science and Sports Medicine
Medical School

Project title: *The efects of exercise therapy on proprioception in patients with multipler sclerosis: a systematic review*

Degree: MSc

Reason: Review of information in the public domain
No human participants will be involved in the study

Professor P Ruff
Chairperson: Human Research Ethics Committee (Medical)

Research Office Secretariat:
Third Floor, Phillip Tobias Building, corner of St Andrews and York Roads, Parktown, Johannesburg 2193
Postal address: Private Bag 3, Wits 2050
Tel Nos: +27 (0)11 717 1234/1252/2656/2700
Office E-mail: HREC-Medical.ResearchOffice@wits.ac.za
Website:
https://www.wits.ac.za/research/researcher-support/research-ethics/ethics-committees/

Appendix I: Turnitin Report

BM Masters final

ORIGINALITY REPORT

8%	6%	4%	2%
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