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Chronic Lower Limb Oedema in a Population of Saudi Arabia Residents with Multiple Sclerosis: An Evaluation of Progressive Resistance Exercise

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AWARDS

- Awarded for best poster in the 7th International Conference & Exhibition on Physiotherapy & Physical Rehabilitation. International conference. Roma, Italy**.**
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List of abbreviations

1-RM	One Repetition Maximum
10MWT	10-Meter Walk Test
2MWT	2-Minute Walking Tests
5STS	5-time Sit to Stand Test
6MWT	6-Minute Walking Tests
ACSM	American College of Sports Medicine
ADL	Activities of Daily Living
BCRL	Breast Cancer Related Lymphoedema
BMI	Body Mass Index
BPI	Brief Pain Inventory
CDT	Complete Decongestive Therapy
CEAP	Clinical-Etiological-Anatomical-Pathophysiological
CF	Consent Form
CG	Control Group
CLLO	Chronic Lower Limb Oedema
CO	Chronic Oedema
CON	Concentric
CRF	Case Report Form
CST	Chair Stand Test
DVT	Deep Vein Thrombosis
ECC	Eccentric
EDSS	Expanded Disability Status Scale
EG	Experimental Group
FOF	Fear of Fall
FSS	Fatigue Severity Scale
GCC	Gulf Cooperation Council
GCP	General Clinical Practice guidelines
GDPR	General Data Protection Regulation
HCPs	Health Care Practitioners
IASP	International Association for the Study of Pain

ILF	International Lymphoedema Framework
JBI	Joanna Briggs Institute
KFSH&RC	King Faisal Specialized Hospital and Research Center
KKUH	King Khalid University Hospital
KSA	Kingdom of Saudi Arabia
KSU	King Saud University
LIMPRINT	Lymphoedema Impact and Prevalence project
Lymph-ICF	Lymphoedema Functioning, Disability, and Health
LYMQOL	Lymphoedema Quality of Life
LyQLI	Lymphoedema Quality of Life Inventory
MDU	Medical Day Unit
MFIS	Modified Fatigue Impact Scale
MLD	Manual Lymphatic Drainage
MOH	Ministry of Health
MPQ	McGill Pain Questionnaire
MS	Multiple Sclerosis
MSC	Multiple Sclerosis Clinics
MSWS-12	Multiple Sclerosis Walking Scale
MVIC	Maximum Voluntary Isometric Contractions
NICE	National Institute for Health and Care Excellence
non-RCTs	Non-Randomized Controlled Trials
NORL	Non-Oncology Related Lymphoedema
NRES	National Research Ethics Service
NSCA	National Strength and Conditioning Association
NTP	National Transformation Program
PI	Principal Investigator
PIS	Patient Information Sheet
PPI	Patients and public involvement
PPMS	Progressive Relapsing Multiple Sclerosis
PRE	Progressive Resistance Exercises
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

pwMS	People with Multiple Sclerosis
QMC	Queens Medical Centre
QoL	Quality of Life
RCTs	Randomized Controlled Trials
REC	Research Ethics Committee
ROM	Range of Motion
RRMS	Relapsing-Remitting Multiple Sclerosis
SACB	Saudi Arabian Cultural Bureau
SCT	Stair Climb Test
SF-36	Short Form-36
SF-MPQ	Short Form of the McGill Pain Questionnaire
SPMS	Secondary Progressive Multiple Sclerosis
T25FWT	Timed 25-Foot Walk Test
UoN	University of Nottingham
VAS	Visual Analogue Scale
VLUs	Venous Leg Ulcers
WCLS	Wesley Clinic Lymphoedema Scale
WHOQOL-BREF	World Health Organization Quality of life scale

Abstract

Introduction: Chronic lower limb oedema (CLLO) is a common but often unrecognised problem amongst people with multiple sclerosis (pwMS), for which treatment is rarely provided. The prevalence of CLLO in pwMS has been examined in some countries such as Italy and the UK, however, due to the scarcity of evidence it is very difficult to approximate how common the problem is in developing countries. Added to this, research conducted to date on the management of chronic oedema and lymphoedema has focussed primarily on patients with cancer. CLLO related to other aetiologies warrants further investigation.

Methodology: This mixed methods study aimed to gain an improved understanding of the prevalence and impact of CLLO in pwMS and the contribution of progressive resistance exercise on its remediation. The study was undertaken in two hospitals in Riyadh city, in the Kingdom of Saudi Arabia.

Phase one of this study aimed to evaluate the prevalence of CLLO in pwMS who are resident in the Kingdom of Saudi Arabia and attends one of the two hospitals and to determine the main characteristics of those at increased risk of developing CLLO. This study screened 269 pwMS for CLLO. Data were analysed using univariate and bivariate analysis using SPSS software version 26. Continuous and categorical variables were examined using the Students t and Chi-square tests.

Phase two of the study aimed to assess the effectiveness of Progressive Resistance Exercise (PRE) in the management of CLLO in pwMS who are resident in the Kingdom of Saudi Arabia and to determine the impact of CLLO on pain and quality of life. Those who were found to have CLLO during phase one screening were invited to participate in phase two. Fifteen participants with bilateral CLLO agreed to participate in this phase. They performed a biweekly PRE programme for 12-weeks. The participants were assessed before and following the intervention to determine if any changes occurred in lower limb circumference, Quality of Life (QoL) or pain. Limb circumference was measured at 4 cm intervals. QoL and pain were measured using the Quality of Life Measure for Limb Lymphoedema (LYMQOL) tool and the Short form of the McGill Pain Questionnaire (SF-MPQ).

Phase three of the study aimed to identify and explore factors that contribute to successful or unsuccessful use of PRE from the perspectives of participants. During this phase, the knowledge and understanding developed by physiotherapists of CLLO in pwMS was explored together with their knowledge of current practice in terms of exercise therapy. Ten pwMS and CLLO and five specialist lymphoedema physiotherapists were interviewed. Data were analysed using the Framework Method.

Results: Out of 269 pwMS screened during phase one, 21 (8%) were found to have bilateral CLLO. The bivariate analysis between two groups (with CLLO and without CLLO) shows statistically significant differences were found in CLLO group for all variables (namely: age, weight, BMI, MS duration, EDSS, categorical: MS type) except for gender. In phase two, fourteen participants completed the intervention with mean age of 44±7.11 years, EDSS 5.6±0.96, BMI 29.08±7.91 and disease onset 12.92±3.7 years. The result shows no statistically significant change in overall legs volume but there was a decrease in some segments. A reduction was reported in the SF-MPQ tool in both visual analog scale (VAS) and present pain intensity (PPI) domains. Moreover, statistical significance increase was found in the LYMQOL tool in the overall QoL domain. Three themes emerged from the CLLO participants' data in phase three: life experience before receiving the PRE intervention; participants' experiences after having PRE intervention, and "*little changes but they matter*". Data from physiotherapists emerged with two themes: awareness about CLLO in pwMS and current lymphoedema practice.

Conclusion: This study concluded that although PRE had no effect on CLLO in pwMS, QoL and pain improved significantly after the intervention. The qualitative data also showed improvements in physical and psychological well-being. There was lack of awareness of CLLO in pwMS among health care providers suggesting that this specific gap in knowledge needs to be addressed in order to provide a meaningful treatment plan.

The twelve-week PRE programme may have a secondary impact on some aspects of life and there is some evidence of changes in the legs. However, limb volume did not change overall.

CHAPTER 1: INTRODUCTION

1.1 Demography of the Kingdom of Saudi Arabia

In the Gulf Cooperation Council (GCC), the Kingdom of Saudi Arabia (KSA) has the largest and fastest growing population (Ram, 2014). According to the KSA General Authority for Statistics in 2019, the total KSA population reached 33,400 million with a 2.52% population growth rate in 2017. More than 55% of the population are under 30 years old ('General Authority for Statistic', 2019). This fast-growing population will place a financial pressure and will increase the demand for many services and supporting infrastructure such as educational and health care services.

As the majority of the population are young, the Ministry of Health (MOH) launched the National Transformation Program (NTP) 2020 and the Saudi Vision 2030 to meet the future needs of the population. In the last year, 14 new hospitals have been built leading to a 3% increase in the number of hospital beds available, with Riyadh city (the capital) and Makkah seeing the largest increase in capacity relative to the population ('Annual Report of the Ministry of Health', 2017). Twenty six percent of MOH hospitals are based in Riyadh city. As few hospital facilities are available in nearby cities, most people with chronic conditions (such as multiple sclerosis [MS]) are referred to Riyadh hospitals.

Multiple sclerosis is an autoimmune long-lasting and recurrent disorder that affects people during their most productive years of their life which results in many physical, psychological and social consequences (Hudaif, Bwardi and Kojan, 2014; Alamri and Al-Busaidi, 2016). This disease group has received attention from health care providers over the last two decades in Saudi Arabia due to the fast-growing number of young people presenting with the condition

and concern about the pressures this will create for the health care system, both now and in the future.

1.2 Multiple Sclerosis in the Kingdom of Saudi Arabia

Around the world, approximately 2.1 million people in 2008 have been diagnosed with MS and by 2013 this number had increased to 2.3 million (Multiple Sclerosis International Federation, 2013). Moreover, according to the Atlas of MS, the global average prevalence of MS has risen from 30 to 33 per 100,000 individuals (ibid). In 1988, the first paper about MS in the kingdom of Saudi Arabia was published by Yaqub and Daif which indicated that there is an increase in the incidence of MS in KSA but that it was still considered an uncommon condition (Yaqub and Daif, 1988). Ten years later, another paper by Daif et al. about the pattern of presentation of MS in KSA, stated that the prevalence rate was 20 per 100,000 individuals and this resembled the Western presentation of the type of MS (Daif *et al.*, 1998). However, with the gradual increase of incidence every year, it is now believed to be a substantial health care problem (Alshanqiti *et al.*, 2016). This point is supported by many studies which show an increase in the number of people with Multiple Sclerosis (pwMS) has doubled that reported two decades previously, when it was reported to affect around 35-40 per 10,000 individuals (Aljumah *et al.*, 2013; Bohlega *et al.*, 2013; Mohammed, 2016). This global increase indicates that there are no signs of levelling off in the prevalence of MS.

In Saudi Arabia, relapsing-remitting MS (RRMS) is the commonest clinical type at the onset of the disease affecting (85%), followed by primary progressive MS (PPMS) affecting 10 to 15% of the cases, then progressive relapsing MS (PRMS) with 5% (Aljumah *et al.*, 2013). Secondary progressive MS (SPMS) represents

a stage following RRMS where people with RRMS convert to SPMS with time and show progressive decline in their neurological condition (ibid). The common primary presenting clinical symptoms in KSA residents is limb weakness (Daif *et al.*, 1998). Other frequent physical deficits can be chronic pain, difficulty in executing activities of daily living (ADL), impaired mobility, fatigue, sensory and visual disorders (Al Wutayd *et al.*, 2018). These types of dysfunctions can be temporary, permanent or progressive for pwMS.

In 2013, a very valuable report from the World Health Organization and Multiple Sclerosis International Federation emphasised the importance of the subject as people can experience the consequences of MS for more than 20 years. The report (Multiple Sclerosis International Federation, 2013, p.3) stated that:

> "Some people with MS experience little disability during their lifetime, as many as 60% may be unable to walk without assistance 20 years after onset. This has major implications for the quality of life of people with MS and their families and friends, and for the cost to society if their condition is not managed adequately."

This point is a significant message and must grab the attention of stakeholders in the health care system globally, as the long period of immobilization could lead to unpleasant and life-threatening consequences.

1.3 Potential Consequences of Immobilization in people with Multiple Sclerosis (pwMS)

The underlying mechanisms of impaired functional capacity in pwMS could be related to neural or muscular deficit or a combination of both (Dalgas *et al.*, 2010). In terms of muscular deficit (irrespective of the type and severity of MS), the muscle fibres characteristics show changes. Some studies have pointed out a

loss in muscle mass along with a shift in the proportion of fibre types from type I to type IIa in the lower limb which is similar to results found in immobilized healthy controls individuals (Kent-Braun *et al.*, 1997; Dalgas *et al.*, 2010; Wens *et al.*, 2014). Furthermore, as reported in the Wens et al cross sectional study, the type IIa muscle fibre not only has a greater proportion in pwMS but also tends to atrophy (Wens *et al.*, 2014). The type IIa muscle fibre is a fast twitch oxidative fibre which is ideal for power activities, but they fatigue easily. This could explain the reduction in muscle strength seen amongst pwMS, since the patient cannot tolerate activity for a long time (Kjolhede, Vissing and Dalgas, 2012) and as a result of these changes, low physical activity may develop over time (Solaro *et al.*, 2006). Therefore, tailoring a rehabilitation program for pwMS must concentrate more on preservation and rebuilding muscle strength and consider the changes that occur in muscle fibres.

On the other hand, up to 80% of pwMS show a degree of somatosensory impairment and proprioception problems in the lower extremities (Jamali *et al.*, 2017). This neural deficit as reported in the Jamali et al. prospective cross-sectional study is associated with limited balance and postural control problems. Furthermore, a reduction in plantar sensation was also reported which leads to a cautious walking pattern in which speed of walking is reduced (ibid). It should also be emphasized that, Fear of Fall (FOF) behaviours can also develop in pwMS which is one of the contributing factors that curtail physical activity. This was spotted in cross-sectional data from telephone interviews with 1064 pwMS which showed that 63.5% of participants reported FOF and 82.6% had curtailed physical activity (Peterson, Cho and Finlayson, 2007).

When the movement capacity of pwMS decreases, the physiological mechanisms of calf muscles will be hindered or absent and, as a result, the pumping pressure of the calf muscles on the veins and lymphatic vessels will also decrease (Faett *et al.*, 2012, 2013). Over time, fluid may accumulate in the interstitial space (Faett *et al.*, 2012) which can lead to an inflammatory response, causing fibrotic changes in the subcutaneous tissue and hypertrophy of adipose tissue (Mayrovitz, 2009). Delays in identifying this issue at an early stage may lead to unpleasant outcomes.

Recent published studies have found a correlation between immobility and chronic oedema (CO). One of these studies, a cross-sectional study of community nursing services by Moffatt et al. (2019a) aimed to determine the number of people with CO and the impact on health services. The study indicated that the prevalence of CO was high amongst people with reduced mobility and obesity (71.6%, 61.9%), respectively. Similar results were found in a point-prevalence study of hospital inpatients by Quéré et al. (2019) which reported that CO is prevalent in less moblile patients (41.5%) compared to those with heart failure (34.7%). Another study in Denmark used the same methods and revealed that 44% of in-patients had secondary lymphoedema as a result of immobility (Nøerregaard *et al.*, 2019).

Given the neurological and muscular changes that can occur in pwMS and their effects on mobility, there is a risk for this population of developing chronic oedema. Limited evidence from the literature has shown the prevalence of CO in pwMs (Solaro *et al.*, 2006; Arpaia *et al.*, 2010; Keeley *et al.*, 2017). More in depth understanding about the prevalence rate and main characteristics of those

at high risk of developing CO in pwMS is systematically reviewed in the next chapter.

1.4 Definition of Chronic Oedema

There is some confusion regarding the terminology used to describe patients with leg swelling. In some instances, the term ‘chronic oedema’ and ‘lymphoedema’ are used interchangeably. Traditionally, the term lymphoedema is a very narrow and limited term that is linked to a specific population. It is called primary lymphoedema when a congenital abnormality has occurred in the lymphatic system but when it is linked to lymphatic damage it is called acquired or secondary lymphoedema. Common causes include treatment for cancer and other diseases or trauma that adversely affect the lymphatics including damage to the venous system through issues such as deep vein thrombosis. Currently professionals knowledge is poor and many do not understand the complex mechanisms that give rise to both primary and secondary lymphoedema (Moffatt, Keeley and Quéré, 2019b).

In recent years, the understanding of the pathophysiology of the venous and lymphatic system has supported the idea that the lymphatics are involved in all forms of chronic oedema (Bianchi, Vowden and Whitaker, 2012). Chronic oedema is the broad term that is used to describe oedema that exists for three months or more. The term incorporates the traditional understanding of lymphoedema and also chronic swelling that arises from another more complex aetiology (Moffatt, Keeley and Quéré, 2019b). It can occur in one or more parts of the body such as: the upper or lower limbs, upper or lower body, neck and face (Moffatt *et al.*, 2003). The causes of chronic oedema are summarized in Table 1.1. Neglecting this condition may lead to fluid imbalance and accumulation of

protein-rich extracellular fluid in the interstitial spaces as a result of damage or failure to lymphatic drainage (Bianchi, Vowden, and Whitaker, 2012; Faett *et al.*, 2013). The term chronic oedema is therefore a public health term not a diagnostic category.

Table 1. 1: Causes of Chronic Oedema

Vascular:
• Severe varicose veins • Trauma • Chronic venous insufficiency • Venous hypertension • History of deep vein thrombosis • Lack of calf muscle and plantar foot pump • Phlebitis
Lymphatic:
• Congenital abnormality (primary lymphoedema) • Burns or orthopaedic surgery (secondary lymphoedema) • Cancer treatment (e.g., Radiotherapy)
Other:
• Renal or cardiac diseases • Obesity • Immobility • Limb dependency • Late stage lipoedema with concurrent lymphoedema • Some medications

Unclear nomenclature can impede recognition of this condition and the development of clinical services. Added to this, it might limit the understanding of the underlying factors that cause the swelling which influence negatively on treatment options. Chronic oedema is a more inclusive term, yet it is not a diagnosis and the underlying causes should be identified (Moffatt, Keeley and Quéré, 2019b). Studies have shown that poor understanding among health care professionals about lymphoedema can delay appropriate treatment and this may

lead to progression of the condition and deterioration of Quality of Life (QoL) (Morgan, Franks and Moffatt, 2005; Bogan, Powell and Dudgeon, 2007).

1.5 Economic and Psychosocial Impact of Chronic Oedema

Chronic oedema and its potential progression to more complicated problems such as lymphovenous oedema or lymphoedema can create enormous pressures for health care system (Lawrance, 2009). In addition, facing life-long physical, psychological and social difficulties generate personal pressures for patients which lead to reductions in QoL (Greene and Meskell, 2017). This condition can debilitate a person if it is combined with another physical illness such as multiple sclerosis (MS).

As disability increases, the cost of health care also increases steeply (Patwardhan, 2005). Treatment that is related to MS cost the US health care system $47,000 and €18,000 to €31,000 in Europe per annum (Beer, Khan and Kesselring, 2012). The one related to chronic oedema cost the health care system in the UK for a mean length of 12 days' hospital stay an estimated mean of £2300 when the patient admitted for intravenous antibiotics as a result of acute infection (cellulitis) in the affected area (Moffatt *et al.*, 2003). Bills for health care systems could increase if pwMS develop chronic lower limb oedema (CLLO) and the scenario can be more damaging if the condition is not recognised and treated early. Unfortunately, undetected and/or untreated CLLO in pwMS and non-oncology related lymphoedema (NORL) is commonly reported in the literature. In the Faett et al (2013) prospective longitudinal single cohort study, the demographic data shows that all the pwMS who have CLLO for 2 to 7 years had not received any treatment for oedema (Faett *et al.*, 2013). Similarly, a Canadian qualitative study of 108 participants identified that limited or no access to

treatment was one of the main issues that face the NORL and children with lymphoedema (Hodgson *et al.*, 2011). Unluckily, the consequence of neglect through non recognition of CLLO will not only affect the patient physically (e.g. Pain, increase swelling and infection, decrease mobility) but it will also affect their quality of life (Keast *et al.*, 2015).

Social isolation, work absenteeism, dependence in activities of daily living (ADL) and low self-esteem relating to body image are all forms of psychosocial disabilities that may have socio-economic implications for patients (Williams, Moffatt and Franks, 2004). In 2003, a study conducted in the UK aimed to determine the magnitude of the problem of chronic oedema in the community, and the likely impact of oedema on use of health resources, employment and patient quality of life by carrying out a questionnaire-based survey supported by clinical evaluation and interview. The study reported that 823 patients had CO and 80% out of them had taken time off work and 8% had given up work. Furthermore, quality of life was reported to below normal and 56% were taking regular prescribed analgesia to control pain. The results of this study reflect the indirect costs of this condition and the consequences if diagnosis and treatment are delayed.

Other associated impairments to patients QoL have been reported in the literature including choosing clothes, footwear, adverse effects on relationships, sexual functioning, anxiety, depression and functional impairment (Atkin, 2014; Mercier *et al.*, 2019). In Greene & Meskell's study, a condition-specific tool was used to explore the impacts of CLLO on QoL. Ninety participants completed the Lymphoedema Quality of Life (LYMQOL) questionnaire and over half of the sample had experienced difficulties in finding clothes, footwear, socks and tights

to fit the oedematous limb and indicated that CLLO affected their ability to engage in leisure activity (Greene and Meskell, 2017).

In the last decade, the focus of the literature on the negative impacts of CO on patients QoL has increased substantially. However, much of the evidence focuses on upper limb oedema or lymphoedema due to breast cancer with scarce attention to lower limb CO and the broad concept of CO (Greene and Meskell, 2017).

1.6 Current Treatments for Chronic Oedema

Some people with Multiple Sclerosis (pwMS) face pain, a reduction in muscle strength, mobility and somatosensory function (Rejdak, Jackson and Giovannoni, 2010; Beer, Khan and Kesselring, 2012) which over a long-term period could promote development of CLLO. However, because the prevalence and impact of the problem for this population remains unclear (Keeley *et al*., 2017) provision of care is rarely considered a priority and services are often limited in whether they exist or the range of treatments that are offered.

Currently, health care delivery is based on controlling, managing and preventing the recurrence of lymphoedema symptoms in those with a cancer related lymphoedema, and those with other causes are denied access to care (Moffatt *et al.*, 2003). As a result, there is poor recognition of chronic condition at an early stage which might aggravate the symptoms and lead to potential consequences such as acute infection in the affected area (Moffatt *et al.*, 2016). Poor understanding about the prevalence of CLLO in pwMS, assessment tools or measurements, treatment and best practice among health care providers generate this lack of knowledge and skills that they need to improve quality of life and better outcomes (Tiwari, Myint and Hamilton, 2006; Keen, 2008).

In the literature, the “gold” standard of treatment for chronic oedema or lymphoedema is a range of components that grouped together under the term complete decongestive therapy (CDT) (Lasinski *et al.*, 2012). The treatment consists of manual lymphatic drainage (MLD), compression therapy with garments or bandages, skin care, exercise, and education in self-care. The treatment is provided in two phases: reductive or intensive CDT (phase 1) and maintenance CDT (phase 2). The aims of CDT are to improve QoL, functioning mobility, control and reduce swelling, prevent infections and reduce risk of recurrence (Rodrick *et al.*, 2014). The success of this treatment is affected by a number of factors, including well-trained and high skilled practitioners (Faett *et al.*, 2013), Insurance providers also need to recognize that compression supplies are required for treatment (Moffatt, Keeley and Quéré, 2019b).

Although compression is considered a standard element of care for lymphoedema, the effectiveness of the CDT is often questioned for a variety of reasons. First, the importance of each individual component is not clear in the literature. It is not known which components of CDT are most effective at reducing oedema and what would be the implications if one component of CDT was not applied. In addition, as the individual components of CDT are delivered in different ways, it is possible this also affects outcomes and interpretation of the results. Second, the focus of this treatment is mainly on breast cancer related lymphoedema (BCRL) and widening the sample to non-oncology related population is not well researched. Third, some components such as exercise and self-care education are not well defined in the literature in terms of their frequency, intensity, and duration.

In 2005, a systematic review by McCallin et al investigated the effectiveness of physical therapy treatment for BCRL. The study appraised 20 studies and sought to evaluate the strength of evidence in support of CDT and its individual components. They found that evidence of the effectiveness of CDT was available but the contribution of each component in limb volume reduction was not clear (McCallin, Johnston and Bassett, 2005). Similar results were found in 2012 by Lasinski et al when they conducted a systematic review of the evidence underpinning CDT and individual components in the treatment of lymphoedema. Twenty-two articles met inclusion criteria and they concluded that CDT is an effective treatment but it was difficult to agree which components were effective as the treatment intervention was often bundled and the interactions between each element were difficult to ascertain (Lasinski *et al.*, 2012).

Although there is an abundance of studies that seek to break down CDT into specific components such as MLD or remedial exercise (Schmitz *et al.*, 2009; Williams, 2010; Brown *et al.*, 2013), compression therapy is always used in conjunction with other treatment regimen. Compression therapy has strong effects on both the lymphatic and venous system (Özdemir et al., 2016). Exertion of pressure prevents capillary filtration and helps moving the fluid centrally and into areas with functioning lymphatics. The overall skin condition can be improved and shape distortion improved allowing increased patient functionality (Lee and Wigg, 2012). However, in order to maintain reduction in limb volume, patients need to wear compression bandaging and garments (or equivalent) on a daily basis and for the rest of their life as rebound oedema forms quickly after removal of compression (Moffatt, 2004; Elwell, 2017). Issues of concordance have not been well researched. Non-concordance with compression methods will have a

negative influence on the effectiveness of the compression and also on wound and could rebound oedema rapidly healing (Moffatt *et al.*, 2009).

The reasons for non-concordance with compression are complex and lie outside the scope of this thesis. It is thought that patients who tend to be less committed to using compression therapy have a lack of awareness that compression therapy is the primary treatment (Hodgson *et al.*, 2011) or they cannot wear garments/bandages because they are uncomfortable or they have acute cellulitis (Brennan and Miller, 1998; Kunimoto *et al.*, 2001). In 2006, a survey study by Lam et al. aimed to obtain an overview of patients' experience with lymphoedema (Lam *et al.*, 2006). From the 1,449 patients who responded they concluded that those with complicated oedema involving more than one limb were less likely to use compression garments. Moreover, pain and discomfort were the main reason for ceasing to wear garments (26%) and 15% experienced a problem with the fitting of garments. Other factors were intolerance to the material, especially in hot weather and swelling around the garment. However, it must be noted that this is a biased sample as they were recruited via a patient support group. Therefore, they may not represent other sub-sets in the wider population of patients.

Bearing in mind the weather while tailoring treatment for pwMS who have CO is very important especially in hot countries such as Saudi Arabia where the temperature can reach 55˚C during the summer months. Clinically, heat sensitivity was reported in pwMS between 60% to 80% and the increasing body temperature found to be in correlated with worsening MS symptoms (Syndulko *et al.*, 1996; Frohman *et al.*, 2011; Beer, Khan and Kesselring, 2012). In agreement with these findings Simmons and colleagues found in a multinational internet-based survey that 70% (n= 2,529) of pwMS reported they were sensitive to heat

and this symptom was correlated with fatigue (Simmons *et al.*, 2004). Together with the fatigue, also muscle weakness, concentration difficulties and pain was correlated with heat sensitivity which reported as predictors of accidental falls (Davis *et al.*, 2010; Flensner *et al.*, 2011).

These physiological changes were reported over 130 years ago, when Professor Wilhelm Uhthoff in 1890s - the founder of neuro-ophthalmology - reported a visual deterioration in pwMS after having a hot bath. His conclusion helped to shape the design of the rehabilitation strategies for the management of MS and restrictions in the use of thermal treatments emerged. Explanations of the "Uhthoff phenomenon" (UP) and the exact mechanisms of temperature dependency and its relationship with worsening the signs and symptoms are complicated and was not well known until 2004. In 2004 Humm et al. sought to evaluate UP for the first time by using motor evoked potentials to evaluate conduction velocity (Humm *et al.,* 2004). The team found that demyelinated nerve fibres have slow nerve conduction velocity which tends to have a negative effect on the duration of action potentials, and this was reported when the temperature is between 36 - 40˚C.

Other possibility that linked to heat sensitivity is the brain lesions as a result of MS that is responsible for controlling core temperature (Frohman *et al.*, 2011) and side effects of some medication such as beta-interferon which produce flu like symptoms (Flensner *et al.*, 2011). Therefore, recommendations for easing the effects of heat include wearing less, lightweight and breathable clothing and to conduct exercise in cool environments (Davis *et al.*, 2010). Despite these recommendations, agreement on wearing compression garments to decrease oedema in pwMS have emerged in literature with a suggested starting pressure between with 8-12 or 15-20mm Hg (Frohman *et al.*, 2011). Precautions while

using compression therapy and starting with light pressure must be considered, as over time pwMS can also develop sensory impairments beside the autonomic dysfunction which occurs with disease progression (Huang, Jay and Davis, 2015). Wheelchair dependency, mobility restrictions and incontinence, are common amongst some pwMS and are factors that should influence garment selection (Elwell, 2017). It is also important that personnel are trained to fit compression garments as pressure sores can develop if garments are poorly fitting. Due to the specific characteristics and complications of MS alternative treatment options may be required for CLLO if compression therapy cannot be applied.

1.7 Exercise Therapy

Although there are some favourable results regrading compression therapy for people with venous leg ulcers (VLUs), cancer related lymphoedema and dependency oedema, there is a scarcity of little literature on those with dependency oedema arising from a neurological disorder. In pwMS the reduction in muscle performance during both isometric strength and dynamic power production occur secondary to low physical activities which make them at an increased risk of developing CLLO (Charles, 2013; Solaro *et al*., 2006). Since the origin of dependency oedema is caused by impairment in the calf muscles pumping mechanism (Faett *et al.*, 2012), wearing compression might not help in preservation and rebuilding muscle strength to overcome the muscle weakness. Therefore, well-designed interventional studies that involve the musculoskeletal system need to be conducted. It is important to evaluate each single treatment modality carefully without adding all the other aspects of treatment that are currently used in combination. This will allow clinicians to understand the relative

contribution that single components of treatment can play and then in further research complex programmes of care involving two or more elements can be evaluated. Studies of exercise interventions alone are needed, as these could provide new treatment strategies for those who cannot wear compression garments or bandages. Exercise may also have beneficial consequences for the condition overall.

Treating CO with exercise has received some attention in the scientific literature during the last two decades and more specifically in BCRL. Prior to that, the use of exercise has been controversial in this area due to the assumption that it may contribute to the development of lymphoedema for those at risk or it could increase limb volume through overexertion for those with established lymphoedema (Cooper, 2016). These claims have been rejected for a wide spectrum of exercise therapies examined since the 1990s. The types of exercise examined are non-specific and have ranged from hydrotherapy, deep breathing exercises and yoga. This leaves clinicians with an extensive and complex evidence base that can be difficult to understand and apply correctly in clinical practice.

Kwan et al have tried to identify the what contributes 'best exercise practice' by conducting a systematic review of studies involving patients with lymphoedema (Kwan *et al.*, 2011). The review included 19 studies, of which seven had examined the impact of resistance exercise, a further seven evaluated aerobic and resistance exercise; and five addressed other exercise modalities. The conclusion indicated that there is a strong evidence base for the safety of resistance exercise without an increased risk of lymphedema for breast cancer patients. Furthermore, they reported that combined aerobic and resistance

exercise appeared safe, but larger and more rigorous studies are required for confirmation of the results. Screening all of the studies included in the Kwan et al review indicated that in each instance compression therapy had been applied in combined with an exercise intervention. Such evidence does not enable substantive conclusions to be drawn about the relative effectiveness of each treatment modality.

Very few studies have examined this question and those that are available are methodologically weak. One study by Johansson and colleagues sought to examine the effects of resistance exercise with and without a compression sleeve on BCRL patients (Johansson *et al.*, 2005). For five days, 31 participants were treated with controlled low intensity arm exercise with weights on two non-consecutive days that were interspersed with one day of rest during one session, the exercise was given with a compression sleeve and on the second session it was provided without a sleeve. Two weeks prior to the exercise intervention commencing all participants were asked to wear a compression sleeve. Water displacement was measured before, directly following and 24 hours after exercise. The results showed that limb volume was increased in both conditions immediately after exercise but after 24 hours there was no increase in limb volume compared to baseline. Perceived exertion when exercising with a sleeve was significantly higher than when exercising without one. Perceived exertion is defined as “the feeling of how heavy, strenuous and laborious exercise is” and is measured using a psychophysical scale (Pageaux, 2016). In this study, the Borg rating scale was used which rates exertion on a scale from 6 (minimum) to 20 (maximum) and every step was provided with verbal statement from “very very light” to “very very Hard”. Although this study is one of a few studies that has

aimed to examine individual components of treatment, the methods are weak. One of these weaknesses concerns the ‘dose of treatment’. One session of exercise is not likely to stimulate the physiological changes that are expected to accompany reductions in limb volume. In addition, wearing a compression sleeve for two weeks prior to the intervention could have an impact on the results.

Another study compared the effectiveness of exercise and compression garments in BCRL patients by conducting a randomized control trial (Irdesel, 2007). Nineteen participants were included, one group with home exercise only and the second group conducted home exercises and wore compression garments. The participants were recruited from outpatient clinics in Uludag University, Turkey. The results show reduction in lymphoedema volume in the second group in compared to the other one after a six-month follow-up period. Although the second group showed a significant improvement, the study methods used to determine efficacy are arguable. The first contention is the credibility and accuracy of self-reported accounts of exercise conducted at home. The therapist relied on participant feedback about home exercise activity and encouraged them to do so if they had not. Secondly, accuracy in performing exercises at home without close supervision may have been limited as understanding and interpretation of the instructions could vary greatly from one person to another which may affect the accuracy and validity of the results. The final contention is the small sample size which make limits the degree to which results can be generalized.

In short, the systematic reviews include studies with mixed interventions where the effects of exercise are eventually not as what have been assumed, either because the compression therapy was used prior to intervention or due to

methodological limitations. To our knowledge, no previous study has been carried out without compression therapy being used in conjunction with exercise at some point which creates an important gap in the evidence that needs to be addressed. Carrying out studies of a single intervention can help to clarify the potential benefits and constraints of the modality providing a solid foundation for delivery and commissioning of clinical services.

The primary objective of this programme of research was to find an intervention that can decrease the volume of CO in neurological patients. It is challenging to tailor interventions that are safe, acceptable, and effective for both MS and CLLO. Until the 1990s, exercises were prescribed with extreme caution for people with MS because it was believed that they may exacerbate symptoms of fatigue and that patients would have less energy available to conduct their activities of daily living (Kjolhede, Vissing and Dalgas 2012). This perception has been challenged during the last two decades and exercise is a well-researched and often favoured intervention in the field of MS. Many effective exercises are described in the literature highlight the importance of tailoring exercise to meet the needs of each patient relative to the type, severity, and nature of the condition. Recommendations from the American College of Sports Medicine (ACSM) on one hand are given toward low (30 – 39% Heart Rate Reserve [HRR]) to moderate (40 – 59% HRR) intensity with progression based on the patient's ability (American College of Sports Medicine, 2018). On the other hand, high intensity exercises (60 – 89% HRR) are not suggested as they can lead exhaustion and reduce the effectiveness of treatment (Dalgas, Stenager and Ingemann-Hansen, 2008; Beer, Khan and Kesselring, 2012; American College of Sports Medicine, 2018). This is related to the Uhthoff's phenomenon where core body temperature

tends to increase during physical training which may interfere with a person's activities of daily living.

Progressive resistance and endurance exercises are two forms of training that are both popular in MS rehabilitation programs. Both are tolerated and effective but in contrast to endurance training, resistance exercise has little impact on core temperature (Dalgas, Stenager and Ingemann-Hansen, 2008). This vital point was a determining factor for the choice of exercise examined in this research, particularly as the participants reside in a country with very hot weather and the issue of not causing their physical health to deteriorate was a critical ethical issue. Added to this, this type of exercise also shows it was safe and effective on CO as highlighted in the previous studies with BCRL group, which added favour to this choice. As this study involved tailoring an intervention for neurological patients, chapter 4 will systematically review the literature on the positive and negative effects of resistance exercise and will outline how this influenced the intervention undertaken in this thesis.

1.8 Thesis Rationale

When the clinical signs of CO become visible, that indicates that the condition may have been present for a long time (Keast *et al.*, 2015). Research conducted to date on the prevalence and nature of risk factors associated with CO and lymphoedema focus on those related to oncology but with different aetiology the needs for further research still remain. However, the new LIMPRINT (Lymphoedema Impact and Prevalence project) epidemiology is seeking to redress this balance and is focussing on those with all forms of Lymphoedema both primary and secondary (Moffatt, Keeley and Quéré, 2019b). This gap must

be addressed in order to recognize those who are not correctly diagnosed and consequently do not receive appropriate care.

As a symptom, CO is frequently recognized, but health care providers must understand the underlying causes of this symptom and treat the oedema from its origin. Management of CO amongst people with MS is challenging as impairments arise in many body systems and are not limited to the vascular or lymphatic system. The evidence underpinning best practice for the treatment CO is amassing especially in oncology related lymphoedema and more specifically breast cancer (Kwan *et al.*, 2011; Chang, 2013; Keilani *et al.*, 2016). Treatment in the form of CDT and compression therapy has been shown to be effective. However, the outcomes do not provide clear conclusions to be reached as in-depth interpretation of each component of treatment in the bundle remain poor (Wigg and Lee, 2014). Therefore, a scientific option appraisal is needed of each therapy to support patients who cannot undertake one component of the CDT such as compression therapy.

The advantages and disadvantages of compression therapy should be considered especially if the target group is having a neurological and autonomic dysfunction issues. Exercise therapy as a treatment option and more specifically resistance exercise shows its effectiveness, safety, and suitability in treating both conditions (chronic oedema and MS) separately. Yet, none had been found in the literature about treat CLLO in pwMS. Consequently, this thesis is a first stage and that the results from this study will be then evaluated within larger randomized controlled trials (RCTs) that will include a control group. In view of limited evidence and the gaps in this area this study is intended:

1. To evaluate the prevalence of Chronic Lower Limb Oedema (CLLO) in people with MS (pwMS) who are resident in the Kingdom of Saudi Arabia and attendees one of the two hospitals.
2. To determine the main characteristics of those at high risk of developing CLLO.
3. To assess the effectiveness of Progressive Resistance Exercise (PRE) in the management of CLLO in pwMS who are resident in the Kingdom of Saudi Arabia.
4. To determine the impact of CLLO on pain and Quality of Life (QoL).
5. To identify and explore the factors that contribute to successful or unsuccessful PRE from the perspectives of the participants.
6. To explore the physiotherapists knowledge and understanding of CLLO in pwMS and the current practice in terms of exercise therapy.

1.9 Organisation of this Thesis

In this chapter, the researcher presented the study's aim and objectives. Potential consequences of immobilisation in pwMS and economic and psychosocial impacts of CO have been provided. Current treatments for CO were explored as well as exercise therapy and the rationale behind this thesis.

Chapter 2 presents the study methods and describe the mixed method approach that was used to collect and analyse the study data. Study ethical approval process, data protection, inclusion and exclusion criteria and study regime also were explained.

In chapter 3, the researcher presents a systematic review related to prevalence rate of CLLO in pwMS. It provides the supporting evidence about the rate of CLLO in pwMS and the common characteristics of those who develop CLLO. Chapter

4 represents a systematic review study related to progressive resistance exercise and determine its effects on pwMS muscle performance and QoL. It highlights the effects of the intervention on disability progression, functional capacity, fatigue and QoL, and muscle performance and endurance.

Chapter 5, 6, and 7 presents phase one, two and three of this study. In Chapter 5, the researcher presents the findings of screening data through t-test (to compare the continuous variables and the Chi-square test for categorical variables) and Logistic regression test (to predicate values of an input and the probability of the variables in developing CLLO). Moreover, the researcher discusses this in relation to the existing literature. In chapter 6, the researcher presents the intervention programme and the findings of the quantitative analysis using Paired t-test to compare between pre and post intervention when the data were normally distributed and with Wilcoxon Signed-Rank test when it is not normally distributed. In chapter 7, she identifies and explores the factors that contribute to the successful or unsuccessful use of PRE from the perspective of pwMS which was obtained through individual interviews and used the framework analysis to identify three themes and seven sub-themes. For the physiotherapists' participants, the individual interviews identified two themes and two sub-themes regarding the type and range of exercise therapies adopted routinely by neuro-physiotherapists who are practising in the KSA.

In the final chapter 8, the researcher presents the overall discussion and conclusion of the thesis from the results of phase one, two and three. Overall strengths and limitations of the thesis as well as the implications to clinical practice and research, and recommendations was discussed.

1.10 Summary

Within chapter 1, an overview introduction to the Kingdom of Saudi Arabia demographic information and the multiple sclerosis disease condition in the area. Explaining the potential consequences of immobilization in pwMS and what economic and psychological impacts could be generating if the patients developed CLLO. This chapter also highlighted the current clinical practice in treating chronic oedema and what other opportunities we do have if this practice is difficult to be delivered in some special cases. Thesis rational have been introduced with the overarching research aim and objectives. Lastly, how this thesis is organised from chapters 1 to 8 was highlighted.

In the next chapter, research design, ethical approvals, data protection, study criteria and study regime will be presented in detail.

CHAPTER 2: METHODS

2.1 Introduction

In this chapter, the primary aims of the research are outlined and the methods adopted in each component of the work are described. The rationale for adopting a mixed methods approach is also explained. The chapter concludes with a description of the procedures followed to ensure ethical and legal requirements were met.

2.2 Research Aims and Objectives

As highlighted in chapter 1, although the effectiveness of treatments for chronic oedema have been examined in many previous studies, there are limitations. Some of the gaps in the literature that remain concern the: (a) limited scope of the targeted group (i.e., the majority of participants are oncology related and more specifically they are breast cancer patients), (b) composition of the treatment intervention (Compression therapy has traditionally been used in conjunction with another component, therefore, it is difficult to define the contribution of each treatment element or combination of treatments, and (c) the robustness of the studies in which a single treatment has been applied.

By bridging some of these gaps in knowledge, this research seeks to provide an improved evidence base for clinical practice and improve patient outcomes. For pwMS who have developed CLLO, to our knowledge this is the first research study that tackles this problem and takes a step forward to help shape improved health services. Identifying the effects of exercise on CLLO for pwMS may identify unmet needs and offer an alternative treatment option treatment if compression therapy cannot be used. Furthermore, exploring the relationship between QoL and limb volume reduction in pwMS undergoing PRE will provide a new and valuable insight on this topic. Ultimately, understanding and

exploring the effects of an intervention from the perspective of both participants and clinicians will help to inform health care services in this field and allow the benefits and limitations of the intervention to be understood from a multi-dimensional perspective.

2.2.1 Research aims

The aim of this programme of work was to gain an improved understanding of the prevalence and impact of CLLO in people with multiple sclerosis and the contribution of progressive resistance exercise on its remediation.

2.2.2 Research objectives

1) To evaluate the prevalence of Chronic Lower Limb Oedema (CLLO) in people with MS (pwMS) who are resident in the Kingdom of Saudi Arabia and attendees one of the two hospitals (Chapter 5).
2) To determine the main characteristics of those at high risk of developing CLLO (Chapter 5).
3) To assess the effectiveness of progressive resistance exercise (PRE) in the management of CLLO) in pwMS who are resident in the Kingdom of Saudi Arabia (Chapter 6).
4) To determine the impact of CLLO on pain and Quality of Life (QoL) (Chapter 6).
5) To identify and explore the factors that contribute to the successful or unsuccessful use of PRE from the perspective of pwMS (Chapter 7).
6) To explore the knowledge and understanding of neuro-physiotherapists practising in the Kingdom of Saudi Arabia of CLLO amongst pwMS (Chapter 7).

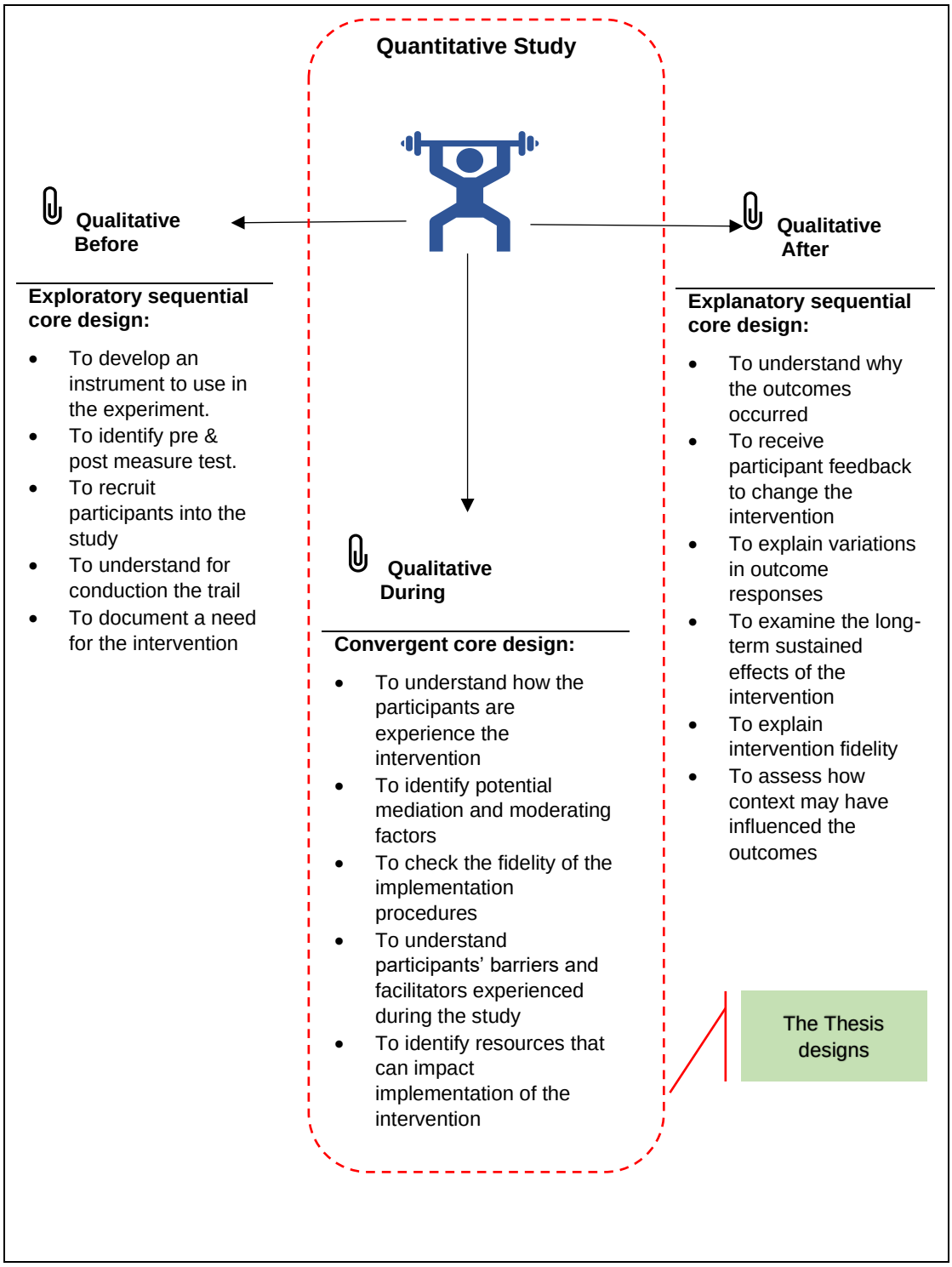
7) To explore the type and range of exercise therapies adopted routinely by neuro-physiotherapists who are practising in the KSA (Chapter 7).

2.3 Research Design

In order to bridge some of the gaps identified in the literature and to deliver the research objectives listed above, a 'mixed methods interventional design' was selected in which both quantitative and qualitative data were gathered (Creswell & Plano Clark, 2017. p.108)

Utilising a mixed methods approach, helps to ensure that the potential limitations of one method can be neutralized by the other (Creswell and Creswell, 2018). The concept of the supplemented qualitative strand occurring during the primary interventional stand was first introduced in 1996 by Sandelowski's paper (Sandelowski, 1996). Implementing a qualitative strand before, during or after a quantitative study is based on the study aims and objectives (see Figure 2.1). By applying a mixed method design the effects of progressive resistance exercise on CLLO in pwMS can then be understood and identified from different aspects and perspectives.

Figure 2. 1: Adding Qualitative Data Into a Study



Source: The contents is adapted from Creswell et al, (2009)

2.4 Mixed Methods Approach

Mixed methods approach is not a new concept of research but which was introduced in the 1980s (Creswell and Creswell, 2018). An early definition of mixed methods was by Greene et al., (1989) when they said:

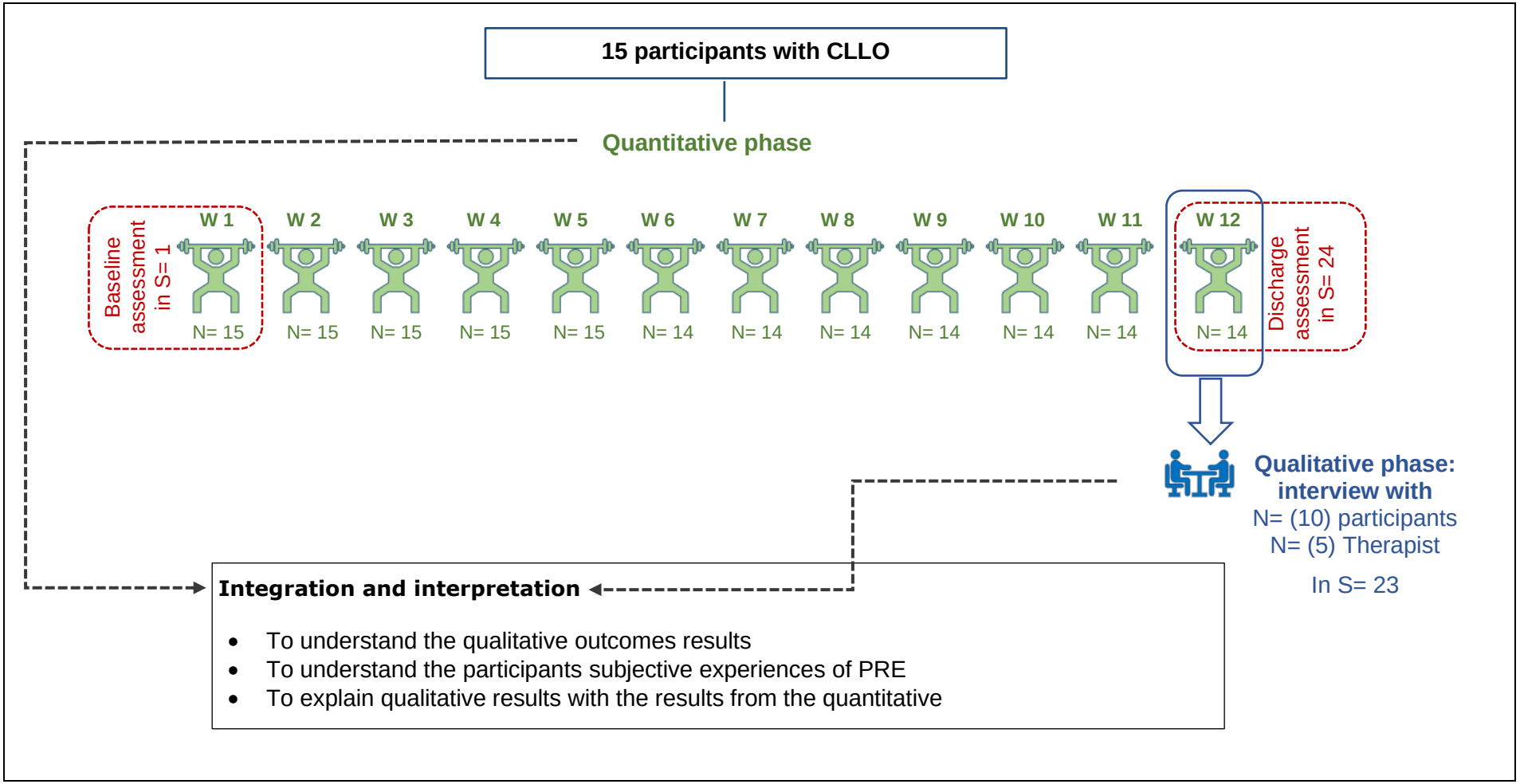
> Mixed method designs as those that include at least one quantitative method (designed to collect number) and one qualitative method (designed to collect words), where neither type of method is inherently linked to any particular inquiry paradigm. (p. 256)

The rationale and purpose of using a mixed methods approach vary from one study to another. Collins et al. in 2006 have reviewed a range of mixed methods studies and identify four broad reasons behind using them, (a) to improve the accuracy of the data, (b) to provide a complete picture of the problem, (c) to avoid biases and weakness in one single method, and (d) to develop the analysis and build on initial findings by using a contrast method (Collins, Onwuegbuzie, and Sutton, 2006). Therefore, expanding the research to include more than one method can make it more comprehensive and help to enhance the information obtained. However, studies which utilise a mixed methods approach can also have limitations since it can be challenging to present and analyse data from convergent methods in a clear way (Creswell and Creswell, 2018).

Within this mixed method, each method functioned in parallel in order to understand and explore the subjective experiences toward the intervention which include barriers and facilitators experiences during the study. This study was conducted in two phases including one quantitative (phase two) and one qualitative (phase three). The primary outcomes of the study were the quantitative (CHAPTER 6: EFFECTS OF PROGRESSIVE RESISTANCE

EXERCISE ON ….) phase where reduction in leg volume and improvements in QoL and pain were the objectives. However, before recruit the participants to phase two, phase one was undertaken to identification and screening for CLLO in pwMS. The objectives of this phase were to measure the prevalence of CLLO in pwMS who are resident in the Kingdom of Saudi Arabia and attendees one of the two hospitals and to determine the main characteristics of those at high risk of developing CLLO. The qualitative phase was used to explore the experiences of the participants. Figure 2.2 demonstrates how and when both phases (two and three) of the mixed methods design were adopted and how the results were analysed and inter-related.

Figure 2. 2: Summary of the Mixed Methods Study Design



2.5 Ethical Approvals and Regulatory Aspects

This study was carried out in accordance with the guidelines determined by the Ministry of Health National Centre in Saudi Arabia (2015) (MOH, 2015) and General Data Protection Regulation (GDPR) (Information Commissioner's Office, 2018). The moral principles have been considered to protect participants' rights and safety, which include justice, autonomy, beneficence and non-maleficence (Ebbesen, 2011). Ethical approval was granted for all phases by the Research Ethics Committee (REC) in King Khaled University Hospital (KKUH) (Reference Number: E-17-2733) on December 2017 (Appendix 1) and King Faisal Specialist Hospital and Research Centre (KFSH&RC) (Reference Number: ORA/0247/39) in March 2018 (Appendix 2).

2.6 Data Protection

Data collection was limited to the minimum required for the purposes of the study (MOH, 2018). Participant details and case report forms (CRFs) were held securely, in a locked room and cupboard. Access to the information was limited to the study staff, principal investigator (PI) and relevant regulatory authorities. Electronic data that included study database for all study phases was held securely by password protected and access was restricted by user identifiers and passwords. Information about the study in the participant's medical records / hospital notes was treated confidentially in the same way as all other confidential medical information. Data confidentiality was ensured by using an identification code numbers in the computer files for each participant. Medical information was shared with the participant's medical team and medical personnel responsible for the participant's health and safety. The PI asked the participants to keep an updated contact details in their study file so that they can be contacted when

needed.

2.7 Record Retention and Archiving

The aim of record-keeping and handling of data is to record, store and transfer the information gathered on each study participant into data that can be used in the report. In the event of electronic data handling, confidentiality of database was secured by safety procedures such as passwords. The PI held overall responsibility for ensuring the accuracy and completeness of data entry.

As required by national regulations and in compliance with the General Clinical Practice (GCP) guidelines, the PI was arranging for the retention of the subject identification codes for a sufficient period of time to permit any medical follow-up which may be warranted, including follow-up for delayed treatment reactions. The sponsors (in this case are the hospitals) made appropriate arrangements for the retention of all other essential documentation pertaining to the clinical trial in a form which can be retrieved for future reference. Archived data was kept on electronic record (e.g., external hard disc) and a hard copy was made available on request. The results of this study can be available for inspection on request by the University of Nottingham (UoN) representatives, the representatives in the King Saud University (KSU) in Riyadh, the KKUH, the KFSH&RC and the participating physicians.

2.8 Informed Consent and Patient Information Sheet

The process for obtaining participant informed consent was in accordance with the KKUH and KFSH&RC guidance. Consent forms (CF) and participant information sheet (PIS) were distributed when patients attended an appointment and all patients who expressed an interest in participating provided informed written consent (Appendix 3 & 4). The PI and participants signed and dated the

CF before any assessments or interventions commenced. The PI explained the purpose of the study and ensured that potential participants had an enough time to consider participating. In Saudi Arabia, there are no written guidelines about the minimum time period required for people to decide if they wish to participate. Therefore, this research study followed the UK National Research Ethical Service (NRES) guideline which stated that there are no fixed guidelines and each study should consider its own merits (National Patient Safety Agency (NHS), 2011). Therefore, this study considered the full understanding of study aims, PIS and given enough time to answer all potential participant's questions as criteria for the time allowed to consider participation. The potential participant was able to ask questions and reflect without rushing into decisions to take part in the study. For those who have decided to take their time to consider participation, 48 hours was given followed by SMS or phone call (based on preference) to have their final decision.

Each participant who returned a signed consent form received a copy of the signed and dated form and a second copy was filed in each participant's medical notes where the original was retained in the study file. A unique study number had been given for each signed consent form to identify all data in the study.

The decision regarding participation in the study was entirely voluntary and the PI emphasized to potential participants that they can withdraw at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which participant is otherwise entitled.

2.9 Study Design and Location

This was a two-centre and one arm mixed methods study managed by the School of Medicine, University of Nottingham. The study was carried out in Riyadh city

(central region of the Kingdom of Saudi Arabia) where around 6 million people reside (*Riyadh Chamber of Commerce*, 2016). Two hospitals were chosen as the setting for this study, namely: King Khaled University Hospital (KKUH) and King Faisal Specialist Hospital and Research Centre (KFSH&RC). The rationale behind choosing these hospitals was based on several factors: first, the availability of a lymphoedema clinic in the hospitals. Second, these hospitals have an advance database system which makes access to patient files relatively easy. Third, those hospitals are at the highest level of specialized medical treatment and technologies available.

2.10 Involvement of People Affected by MS

Patients and public involvement (PPI) in research refers to a partnership between researchers and service users (National Institute for Health Research, 2013). The potential benefit of PPI is to designing relevant intervention that is in favour to patients and/or carers needs (Brett *et al.*, 2014; Bagley *et al.*, 2016). Therefore, in order to have insight that can help in designing applicable intervention, five people with multiple sclerosis (pwMS) had been asked to comment independently on the purpose and methods of this study. The purpose and the methods of the study was written in both Arabic and English language, with a simple and brief texts. People's involvement results had not been used in the study analysis, however, their valuable comments on the study purpose and methods were considered for better study protocol.

2.10.1 PPI method

1) The first step was by identifying which platform can help to reach and involve a wider range of pwMS from different region, gender, and MS type. In the KSA, there are two MS societies: Arfa with 20,000 followers and

Saed with 4,630. These societies are mainly communicating with their audience either by social network platforms or website. According to the GMI (Global Media Insight) organization report in 2019, the total KSA population who are active internet user are 89.39% and 67.95% are active user of social network platform (GMI, 2017). However, from all the social network platform available, twitter is one of the top 5 most used in KSA after YouTube, Facebook, and Instagram, where you can have a formal communication with your audiences. Therefore, to reach people very fast and easily, approval was obtained from both societies to announce in their twitter account about the participating in PPI.

2) After the approval, a message was posted through societies' twitter calling for those who finds themselves interested in giving their feedback about the study purpose and methods.
3) Ultimately, from the replies, five pwMS were selected based on their similarity to study inclusion criteria.
4) A phone call was given for each participant explained their role as a PPI participant and also to arrange for the convenient way of sending PDF files that included the study purpose and methods in simple preferable language (either Arabic or English).
5) Two days after sending the PDF files, the study principal investigator (PI) contacted the participants to have their comments/feedback.
6) The received feedback indicates that people are interested in the project and no amendment was made to the study.

2.10.2 Costs of PPI

Communications between PI and participants were through free call or chat application (WhatsApp or Telegram or Line based on what the participant have). By using this procedure there were no cost to other parties.

2.11 Patients Inclusion and Exclusion Criteria

Inclusion criteria

- Male and female patients in both KKUH and KFS&RC with a confirmed diagnosis of multiple sclerosis (MS)
- Willing and capable of giving informed consent.
- Comprehension of Arabic or English language.
- Patients with an Expanded Disability Status Scale (EDSS) between 3 and 6.5.
- Having chronic lower limb oedema as indicated by a positive pitting oedema test.
- Live in Riyadh city or able to come to treatment sessions if he/she is not living in Riyadh.

Exclusion criteria:

- History of clinical renal, liver or heart condition.
- Participation in any other study which could affect the outcomes of this study.
- Current diagnosis or treatment of cancer.
- Any other condition that could prohibit participation and affects muscle function such as recent lower limb fractures, osteoarthritis or rheumatoid arthritis that limit the normal range of movements in lower extremities.

- Involvement in other structured physical or recreational fitness programs within the last 12 weeks.

2.12 Study Regime

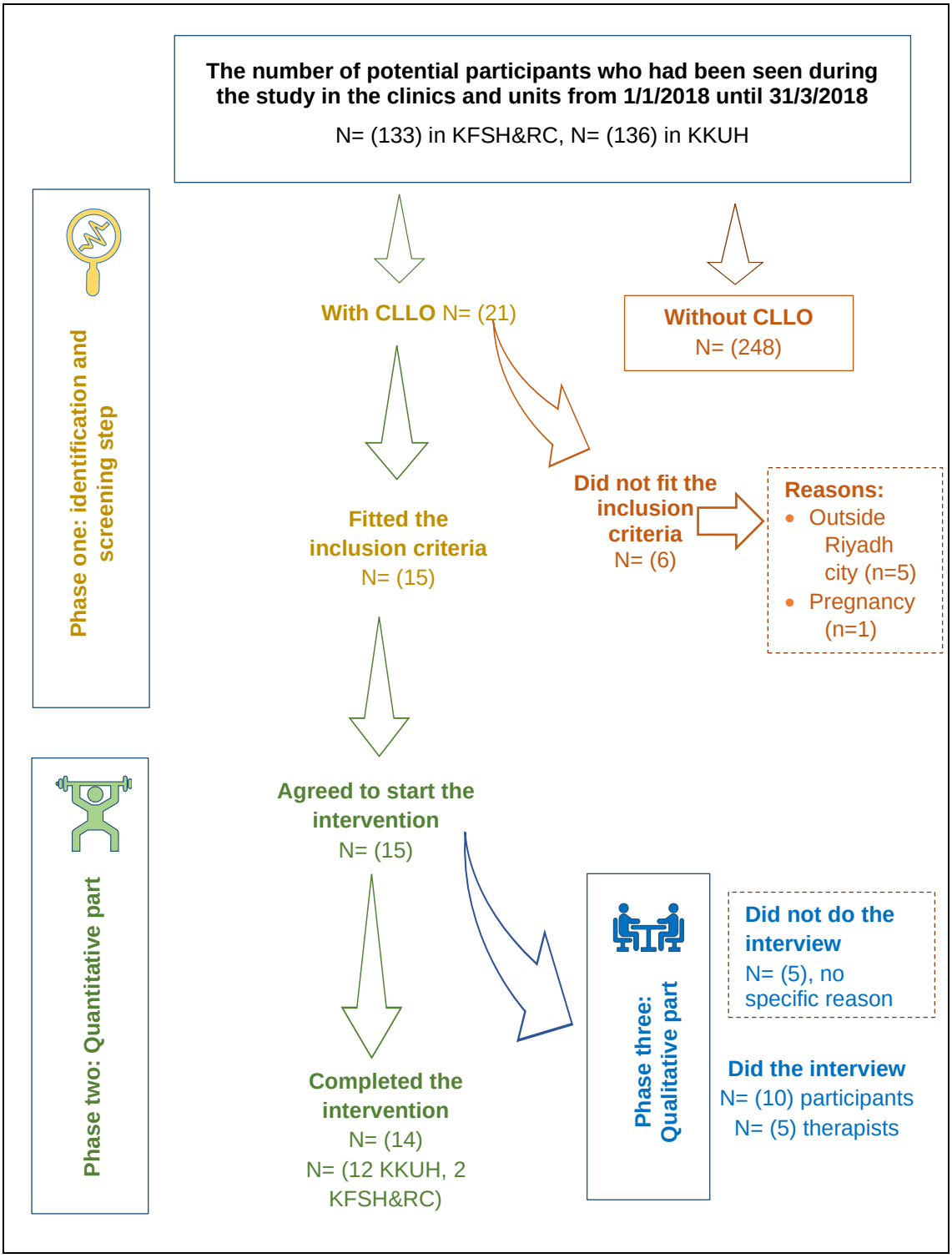
The overall duration of the data collection period from recruitment step to the intervention was 6 months, started from 1st of January 2018 and ended on the 30th of June 2018. Because the researcher had a permission from the SACB to leave the UK for data collection for only 6 months, the recruitment process was taken place from 1st of January 2018 until 31st of March 2018. After this date, no recruitment was undertaken because each participant must participate for 12 weeks (3 months) with two sessions per week (24 sessions) and their participation was commenced upon signing the consent form. Therefore, time management was important to ensure that the research plan is completed and accurate.

The intervention was started for each participant once he/she was recruited. The last session with the last participant was the end of data collection period. During this period, the study was conducted in three phases as can be seen in Figure 2.3:

- Phase one, which was the identification and screening step. The aim of this phase is to provide a preliminary data on the prevalence of CLLO on the pwMS who are residence in Riyadh city, Saudi Arabia. The recruitment of the participants was in this phase and once the participant was agreeing to participate then phase two was started. More in-depth exploration about this phase will be in the chapter 5.
- Phase two, is the quantitative part where the intervention was taken place and chapter 6 will give a comprehensive discussion about this phase.

- Phase three, is the qualitative part where uncovering information that may not been exposed in phase two can be discovered in this phase by interviewing the participants and therapist. Chapter 7 will cover this part.

Figure 2. 3: A Flowchart Shows the Steps from Identification to Recruitment of the Participants



2.13 Summary

In this chapter, the research aims, objectives and methods have been described and the justification for a mixed methods approach has been explained. Lastly, the study setting, PPI procedures and participant selection criteria have been explained.

Available evidence concerning the prevalence rate of CLLO in pwMS are presented in Chapter 3 in which the results of a systematic review are presented.

CHAPTER 3: THE PREVALENCE RATE OF CHRONIC LOWER LIMB OEDEMA IN PEOPLE WITH MULTIPLE SCLEROSIS: A SYSTEMATIC REVIEW

3.1 Introduction

Although chronic oedema (CO) arises in many conditions, (Moffatt *et al.*, 2019a) and has potentially serious consequences, many previous studies have examined the prevalence and impact of CO in specific rather than heterogeneous populations (Quéré *et al.*, 2019). As a result, estimates of the prevalence of CO in the community may not reflect the scale of the problem accurately. The assessment and treatment need of many patients are not identified or underestimated.

One recent cross-sectional study found that the prevalence of CO in community nursing services is high amongst patients with reduced mobility and obesity (71.6%, 61.9% respectively) (Moffatt *et al.*, 2019a). Similarly, a point-prevalence study by Quéré et al. (2019) reported that CO occurred more frequenly in less moblile patients (41.5%) compared to those with heart failure (34.7%) (Quéré *et al.*, 2019). These findings support the idea that immobility can lead to CO and therefore pwMS and other conditions that limit mobility are likely to develop CO.

The aims of this systematic literature review were to:

1. Determine the prevalence rate of CLLO in patients with multiple sclerosis.
2. Identify the main characteristics of those at risk of developing CLLO.

3.2 Methods

3.2.1 Search strategy and data sources

Relevant studies were searched online using the following electronic databases: AMED, BNI, CINAHL, COCHRANE, EMBASE, HBE, HMIC, Medline, PubMed, PsycINFO and Pedro. In addition, searches of grey literature were carried out including: conference proceedings, governmental websites (Saudi Arabian Ministry of Health and the Saudi Arabian General Authority for Statistics), theses

and dissertations. The bibliographies and reference lists of included studies were also examined for potentially relevant studies. Principal authors were also contacted for additional information if it was not possible to evaluate the relevance of study from the abstract or full text. Records of search strategies in the Healthcare Databases Advanced Search (NICE) were saved at each stage detailing when and how the search was undertaken and a monthly alert was set for updates on the search terms used. Saving the results from this platform was helpful in freeing the results from duplication.

The search strategy included a combination of subject terms that were joined with the 'AND' operator. The following search terms were used:

- lower limb oedema AND multiple sclerosis
- chronic lower limb oedema AND multiple sclerosis
- chronic oedema AND multiple sclerosis
- lymphoedema AND multiple sclerosis
- prevalence of lower limb oedema AND multiple sclerosis
- prevalence of chronic lower limb oedema AND multiple sclerosis
- prevalence of chronic oedema AND multiple sclerosis
- prevalence of lymphoedema AND multiple sclerosis

In all search terms, the United States of America (USA) spelling of oedema (edema) and lymphoedema (lymphedema) was searched and the words multiple sclerosis was also searched in its abbreviation (MS) form. The initial search was carried in November 2017 with no restriction on the years included and this was updated in May 2020.

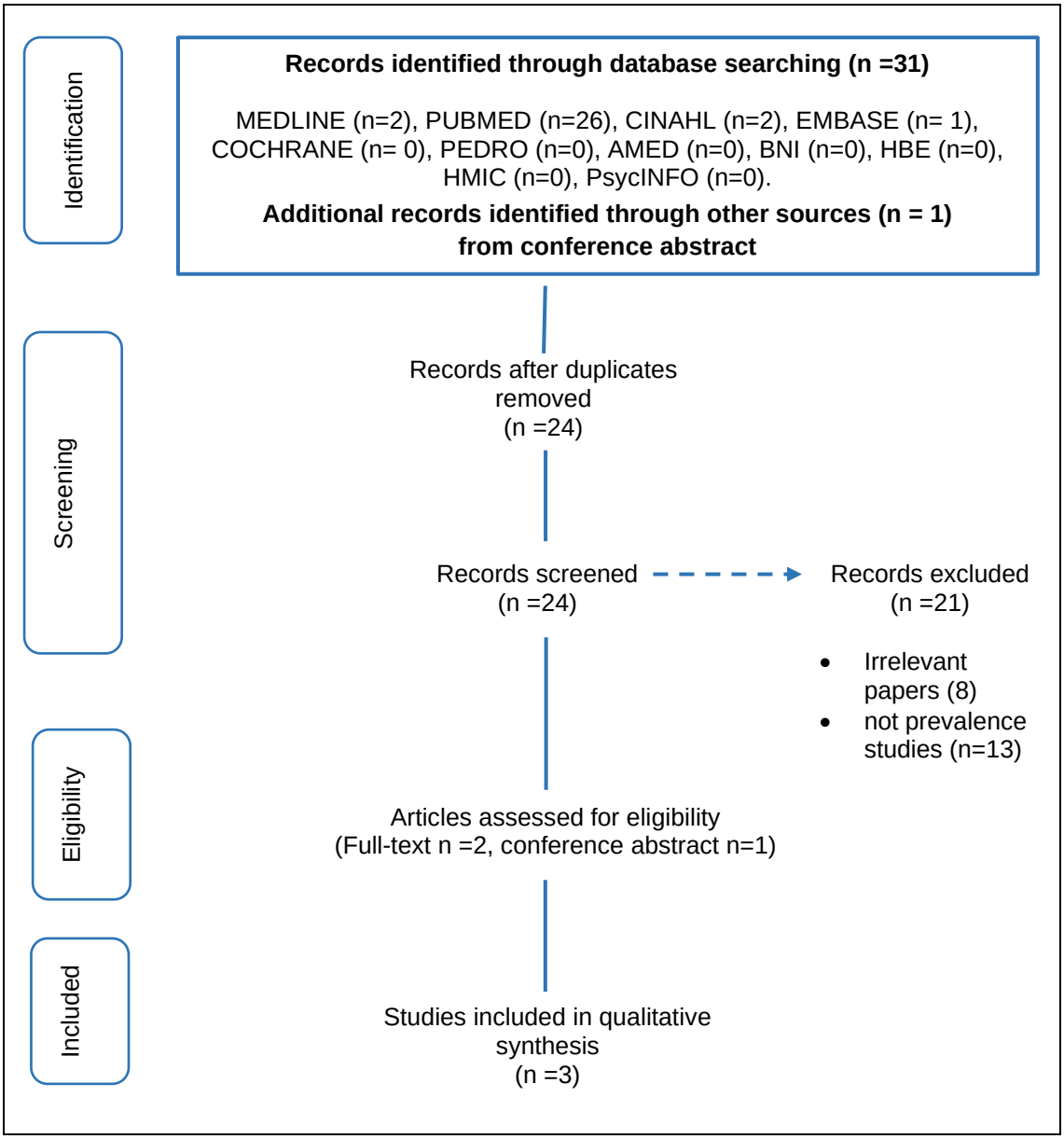
3.2.2 Review criteria

This review is not restricted to a specific clinical study design and all studies were included due to lack of research in this area. However, only studies written in English were included in the review. The studies included participants of either gender, all ages and with a clinical diagnosis of MS (for varying lengths of time). All studies reporting primary and secondary outcomes that measure lower limb oedema were included.

3.2.3 Data acquisition

The results of the search showed the scarcity of studies in this field. Therefore, the reviewer intended to include even not full-text studies (if relevant) and contact the primary author for more details. The reviewer screened studies titles and abstracts that are saved after removed duplication in order to identify relevant publications and to create a list of eligible studies. Studies that did not meet the review criteria were excluded as shown in Appendix 5. The remaining studies were retrieved in full text (if possible) and reviewed. This process was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher *et al.*, 2012) as depicted in Figure 3.1.

Figure 3. 1: PRISMA Flow Chart of Study Selection Process.



A systematic data-extraction form was developed based on this review which aimed to extract data to scrutinise information from the included studies. Information extracted included:

1. Author names and year of publication
2. Study design
3. Study setting and geographic location

4. Sample size
5. Gender
6. CLLO prevalence rate
7. Disease duration (number of years) mean
8. MS course
9. Extended Disability Status Scale score (EDSS) (±SD)
10. Oedema outcome measures.

The data were analysed based on study geographic location and setting, participant characteristics, outcomes measures, and quality. Prevalence in all studies is provided as the number of cases per 100,000 population.

3.3 Quality Assessment and Analysis

In this systematic review, the quality and risk of bias of each study were evaluated in order to report qualifying results, which is a fundamental step in any systematic review study. It is important to determine the quality of published evidence in order to determine the validity, and reliability of the results. Although many tools have been developed to assess the quality of experimental studies, those related to observational studies and estimates of prevalence considered to be unsatisfactory (Mallen, Peat and Croft, 2006) due to limited information about reliability; and internal and external validation (Hoy *et al.*, 2012).

During the last decade, there has been an increase in the number of prevalence related systematic reviews published and it is necessary to identify a suitable critical appraisals checklist. Several critical appraisal tools were identified as shown in Table 3.1. Many of these tools share similar criteria including sample representation, recruitment, and measurement tool reliability.

Table 3. 1: Existing Critical Appraisal Tools on Prevalence Studies

Authors (year of publication)	Tool Name	The number of items included in the tool
Vandenbroucke et al., (2007)	Strengthening the reporting of observational studies in epidemiology (STROBE) checklist	22
Loney et al., (1998)	Critical appraisal tool for prevalence	8
Hoy et al., (2012)	Risk of bias tool	10
JBI (2014)	Joanna Briggs Institute prevalence critical appraisal tool	10

However, Joanna Briggs Institute (JBI) prevalence critical appraisal tool has the advantage of being simple, has clear guidelines and can be administered quickly (Munn *et al.*, 2014).The JBI tool was selected for use in this study based on the simplicity and inclusiveness of the instrument. The JBI tool measures both internal and external validity and has 10 scoring questions:

1. Was the sample representative of the target population?
2. Were study participants recruited appropriately?
3. Was the sample size adequate?
4. Were the study subjects and the setting described in detail?
5. Was the data analysis conducted with sufficient coverage of the identified sample?
6. Were objective, standardised criteria used for the measurement of the condition?

7. Was the condition measured reliably?
8. Was there appropriate statistical analysis?
9. Have all important confounding factors/subgroups/differences been identified and accounted for?
10. Were sub-populations identified using objective criteria?

All questions are scored yes, no, unclear or not applicable according to the information provided, allowing a positive maximum score of 10 points by giving equal weight to all questions (Munn *et al.*, 2014).

The method for analysing the quality of the studies depended on the critical appraisal of each study. When the answer was “Yes”, one point was given and if the answer “No”, “Unclear” or “Not applicable” then no points were given. However, in order to consider the relevance of the study, the JBI guidelines highlight that reviewers can make the decision whether or not to include a study based on meeting a pre-determined proportion of all criteria, or on certain criteria such as sample size or measuring reliability. It is also possible to weigh the different criteria differently (JBI, 2014). The pre-determined proportion or weighting each criterion differently relies on the researcher’s subjective appraisal based on their study aims (ibid).

Therefore, decisions about the scoring system and the cut-off for inclusion of a study were based upon the guidelines, where the question numbers 3, 4, 6, 7 and 8 of the methodological quality score must be rated “Yes” in order for a study to be included in the review.

3.4 Results

Out of the 32 studies identified from the electronic and manual searches, 8 studies were removed due to duplication. The remaining 24 studies were screened for eligibility using the inclusion criteria for titles and abstracts. Out of the 24 studies remaining, the search strategy revealed 3 prevalence related studies (Solaro *et al.*, 2006; Arpaia *et al.*, 2010; Keeley *et al.,* 2017). By manual search in the included studies reference list, no more related data were found. A summary of the data extracted from the included studies is presented in Table 3.2.

Table 3. 2: Study Characteristics

Author (Year)	Study design	Study setting and location	Sample size	Gender	CLLO prevalence rate (%)	Disease duration (year) mean (±SD)	MS course type	EDSS (±SD)	Oedema assessment
3 Solaro, C. (2006)	Cross-sectional study	MS center of the university of Genoa and the regional center of Italian multiple sclerosis society; Italy.	205	F: 130 M: 75	pwO: 93 (45%) pwtO: 112 (55%)	pwO: 20.5 (±11.3) pwtO: 13.7 (±9.2)	RR: 20 pwO, 51 pwtO SP: 49 pwO, 36 pwtO PP: 24 pwO, 25 pwtO	Mean EDSS 5.227 (±2.11)	Instrument evaluation: venous Doppler CW, lymphoscintigraphy (deep & superficial) Classification of oedema: Fovea's sign (+ in venous oedema) & CEAP scale used, Stemmer's sign (+ in lymphatic oedema) & 5-point scale used. Screening assessment: neurologic status & reported presence of oedema.
4 Arpaia, G. (2010)	Prospective cohort study	Don Gnocchi neurological rehabilitation center in Milan; Italy	132	F: 87 M: 45	pwO: 113 (86%), 58 (43.9%) of them had DVT and 40 (69%) out of them	pwO: 18.0 (±8.3) pwtO: 18.5 (±8.0)	Advanced MS (did not specified)	EDSS >6.5	Oedema test was recorded (but not identified how), asked the patient if they had any previous VTE.

					developed CO. 36 (48%) out of 74 of those who did not have DVT, had a CO. pwtO: 19 (14%)				Bilateral compression ultrasonography (CUS) used for DVT diagnosis. Plasma D-dimer test.
5	Keeley, V. (2017) *(unpublished study, only conference abstract)*	Cohort observation and questionnaire study	Derby hospital; UK.	Phase 1: 235 returned questionnaires out of 607. Phase 2: 160 random participants were assessed for CLLO.	F:73.5% M:26.5 %	Phase 1: 101/235 (42.4%) self-reported to have CLLO. Phase 2: 99/160 (62%) have CLLO	Not identified	All MS course was included	EDSS from 3 to 6	Phase 1: self-reporting questionnaire. Phase 2: pitting oedema test, limb circumference measurement, bioimpedance measurement for bilateral oedema, non-invasive moisture meter to assess water content of tissues, Duplex scan for DVT assessment.

Abbreviation: MS= Multiple Sclerosis, CLLO= Chronic Lower Limb Oedema, pwO= patient with Oedema, pwtO= patient without Oedema, RR= Relapsing Remitting, SP= Secondary Progressive, PP= Primary Progressive, EDSS= Expanded Disability Status Scale, DVT= Deep Vein Thrombosis, VTE=Venous Thromboembolism

3.4.1 Description of studies geographic location and setting

All of the included studies were written in English and published between 2006 and 2017. Studies were conducted in different countries: two in Italy (Solaro et al., 2006; Arpaia et al., 2010) and one in the UK (Keeley et al., 2017). One study was a prospective cohort study (Arpaia et al., 2010), one was a cross-sectional study (Solaro et al., 2006) and one was both a cohort observation and questionnaire study (Keeley et al., 2017). One study examined prevalence of CLLO in pwMS in a large geopolitical region in Italy (Milano), one examined in small region in South Italy (Genoa) and regional centre of Italian MS patient society (AISM), and one examined the prevalence in patients recruited from a large hospital in Derbyshire in the UK from rehabilitation and neurological department. Cases were obtained in a similar manner in all included studies which were through MS national society documents, MS clinic checklist and neurology and rehabilitation medicine files. In terms of MS diagnosis, one study (Keeley et al., 2017) was reported that their participants were recruited when they fulfil the 2010 revision to the McDonald criteria of MS, while the other two studies did not define diagnostic criteria.

3.4.2 Participant characteristics

The number of total participants assessed in the included studies ranged from 132 to 235. The presence of CLLO in pwMS has been estimated to be 45%, 85% and 62% respectively (Solaro et al., 2006; Arpaia et al., 2010; Keeley et al., 2017). Patients that were more disabled were found to be more susceptible to CLLO than those who were less disabled.

In the Solaro et al. (2006) study, statistical significance was found between the mean EDSS 5.227 (±2.11) and mean age 55.4 (±2.11), meaning that older

participants who were more disabled were more likely to have oedema. More than 50% (49 out of 93) of patients had the secondary progressive (SP) type of MS with the mean disease duration was 20.5 years (±11.3). Similar findings were reported in Arpaia et al., (2010) as the study shows that less mobile patients with a mean EDSS of 8.1 (±1.15), a mean age of 58 (±11) years old and a mean disease duration 18.7 (±8.4) had developed CLLO. The MS course type was not labelled in the study. In Keeley et al. (2017) study, there was a relationship between Multiple Sclerosis Walking Scale (MSWS-12) and CLLO. The MSWS-12 scores were significantly higher in the CLLO group than in the non-CLLO group which supports the previous results. Moreover, those with CLLO were older with a mean age of 59 years, a mean EDSS of 6.5 and the disease durations were over 10 years. In addition, it was found that the quality of life in the CLLO group was lower than the other group.

3.4.3 Outcome measures

Although these studies measured the same domains (the CLLO), however, different test protocols were used based on study aims. Evaluating the type of oedema was the main aim of the Solaro et al. (2006) study, while the relationship between the presence of CLLO and immobility was the main aim in Keeley et al. (2017) study. In the Arpaia et al., (2010) study, the method used was to assess the frequency of deep vein thrombosis (DVT) in pwMS. However, the procedure to assess the CLLO was not described.

In the Solaro et al. (2006) study, 69 out of 93 oedema participants had vascular examinations. Forty-five participants (65.2%) had a clinical-etiological-anatomical-pathophysiological (CEAP) score of 3 (representing oedema) and 34% had a score of 4 (representing skin changes). According to the 5-point

scale of lymphatic oedema, 73.1% had scores of 1 (no oedema), 13.4% had scores of 2 (persistent oedema) and 13.5% had scores of 3 (ingravescent oedema) (Solaro, 2006). Doppler evaluation was 78 (±4.7) in patients with CEAP stage 4 which indicated vein flow impairment.

In the Keeley et al. (2017) study, the presence of oedema was assessed in two phases. Firstly, by self-report using questionnaires and secondly by clinical examination using the pitting oedema test, Bioimpedance Spectroscopy, Tissue Dielectric constant and ISL classification of stage of lymphoedema. From the first phase, 101 (42%) out of 235 returned questionnaires responded that they have CLLO while from the second phase 99 out of 160 participants (62%) examined clinically were found to have CLLO. In terms of mobility level, MSWS-12 scores were high 77.8 (95% confidence interval (CI) 71.5 84.1) in the CLLO group. A venous duplex scan was used to determine the presence of DVT. Only one participant with CLLO was shown to have deep venous incompetence. This finding does not correspond to the Arpaia et al., (2010) results, where 44% (58) of those who had CLLO were found to have a DVT which was confirmed by Duplex Ultrasonography. However, the participants characteristics were more severe and disabled (EDSS 8.1) than those included in the Keeley et al. (2017) study (EDSS 6.5) and participants were confined to a bed or wheelchair.

3.4.4 Risk of bias in the included studies

The Joanna Briggs Institute (JBI) prevalence critical appraisal tool was used to determine the quality of the studies. Initially, the risk of bias score for the Keeley et al. (2017) study could not be obtained because only an abstract was available however, following a personal communication with the first author, additional information was gathered. The reviewer assessed the risk of bias of the

included studies as presented in Appendix 6. Only one of the studies included (Arpaia *et al.*, 2010) did not fulfil the required criteria (question 4 with answer "NO", 6 & 7 with "Unclear").

Since the findings of this systematic review study were limited (due to the inclusion of only two studies), a meta-analysis was not possible.

3.5 Discussion

This systematic review is presented to determine the prevalence rate of chronic lower limb oedema in patients with MS and the main characteristics of those at high risk of developing CLLO. Published studies on the prevalence rate of CLLO in MS patients up to May 2020 were identified and summarised. The key issue was the lack of relevant studies. Unfortunately, it was not possible to perform a meta-analysis due to different outcome measurements and the small number of studies included. Consequently, a narrative analysis was performed, which showed that the prevalence rate of CLLO was relatively high for some people with MS. The critical appraisal of the included studies was assessed by JBI prevalence tool which was based on the study characteristics, measuring outcomes, quality, and credibility of the results.

With regard to the methodologies used in the studies, employed data were from a single-centre source, except Solaro et al., (2006), which added limitations as the findings cannot be generalised easily or applied to a wider population. In addition, the diversity associated with the participants characteristics such as EDSS, disease duration, age and disease course type may account for the differences observed in prevalence rates i.e., 45%, 85% and 62% respectively (Solaro et al., 2006; Arpaia *et al.*, 2010a; Keeley et al., 2017). For example, the mean EDSS score in Arpaia study was 8.1, whereas in the Keeley study the

mean EDSS score was 6 which indicates that the sample in Arpaia study was more disabled. However, all participants recruited in the studies had a high EDSS score, meaning that their physical activity is limited which effects negatively on the calf muscle pumping mechanism. This suggest that further work is needed to include people with less severe MS to overcome the patient selection bias and to label those who would be at high risk of developing CLLO. The relationship between different characteristics such as disease duration, age, and disease course with the risk of developing CLLO found to be significant in pwMS. The Solaro et al. (2006) study showed a significant relationship between age and the presence of CLLO. Similar findings have been highlighted in Keeley and colleagues (2017) where the prevalence of CLLO was high in older participants and when age was adjusted to the UK MS population, the prevalence of CLLO dropped to 46% instead of 62%. The age, EDSS and MSWS-12 was found to correlate with developing CLLO, indicating that those who are older with more disability were more likely to develop CLLO. Added to this, the disease duration was correlated with EDSS scores which support the results described earlier.

Arpaia (2010) study found that 69% (40 out of 58 participants) of those who had leg oedema had evidence of DVT. In Solaro (2006) study, 24 (34%) out of 69 had a clinical stage CEAP 4 with venous pressure 78 (±4.7) mmHg (normal pressure is 57 mmHg) which flag the need for specialized care. Only one person out of 63 who undertake venous duplex scans in Keeley (2017) study found to have deep venous incompetence. This suggested that future studies to identify the risk factors that place pwMS in high risk of DVT and differentiate lymphoedema from oedema of other origin are needed.

The Keeley study raises a vital point which other studies have not highlighted namely patient self-recognition of CLLO. Around forty-two percent of participants recognized that they have CLLO but when clinical assessments were undertaken 62% were found to have CLLO. This may suggest that with mild/moderate symptoms, patients do not recognise the signs of swelling. This may also apply to health care providers which can result in delays in treatment provision and development of cellulitis. Further research is required to examine the occurrence and implications of poor awareness. Enabling detection of oedema at an early stage could improve clinical outcomes and reduce treatment costs (Stout *et al.*, 2013).

This review is limited by the heterogeneity of the included studies. The variety of outcome measures used also highlights the importance of securing a consensus nationally and internationally about the selection, relative contribution, and importance of alternative measures. Once these agreements are reached, it will be possible to assess and predict the characteristics of CLLO in MS and other patient groups as needed.

3.6 Conclusion

In summary, previous research shows that in some people with MS, the prevalence of CLLO has been confirmed clinically in 45%, 85% and 62% of patients respectively (Solaro *et al.*, 2006; Arpaia *et al.*, 2010; Keeley *et al.*, 2017). The prevalence of CLLO is significant in those who are more disabled (EDSS ≥5.27) and with a disease duration above 10 years. Moreover, a statistical association was found between age and EDSS scores, where older patients with more disability were more likely to have chronic oedema. Increasing awareness of CLLO among pwMS and health care providers can

help to improve identification of the condition and enable provision of treatment at an earlier stage.

However, due to lack of evidence in this area, it is difficult to draw firm conclusions about the prevalence rate of CLLO in pwMS. There is an urgent need for well-designed cross-sectional studies to address this gap in the evidence Studies should not be restricted to a single site or specific course of MS. In addition, an international consensus regarding standard outcome measures of CLLO would enable correct classification and early detection. This could highlight the unrecognized problem that may develop in this group of patients, help improve the efficiency of health care systems and introduce an early intervention for these patients.

3.7 Summary

This chapter examined the literature on the prevalence of CLLO on pwMS. The review aims, search strategy, data analysis and quality assessment have been highlighted. The results found that CLLO in pwMS is a common, un-recognized and under-treated problem. Since autonomic dysfunction, thermal sensitivity, and physical weakness (as discussed in chapter 1) are common impairments in pwMS, developing vascular problems will add challenges when trying to tailor interventions. The next chapter (4) will review the literature concerning the use and effectiveness of resistance exercise. This intervention is thought to be safe and is tolerated by patients.

CHAPTER 4: PROGRESSIVE RESISTANCE EXERCISE AND MULTIPLE SCLEROSIS: A SYSTEMATIC REVIEW

4.1 Introduction

Until the 1990s, exercise was not prescribed for pwMS. Fearing that this would exacerbate fatigue and MS symptoms which might cause deterioration in the patient's general health (Kjolhede, Vissing and Dalgas, 2012). This argument, however, has been challenged in recent years and motor rehabilitation requires the performance of several rehabilitation exercises (White and Dressendorfer, 2004). A large body of research has considered the effects of exercise on MS patients, however, the diversity in the protocols used leaves the health care practitioners confused with what is currently best practice and the clinical protocols they should follow with their patients.

Several reviews have emerged in the literature evaluating the different aspects of exercise in people suffering from MS. In 2008, Dalgas and colleagues reviewed studies on resistance, endurance, and combined training for MS patients. They concluded that resistance training with moderate intensity had beneficial effects on such patients through improvement of the patients' physical activity levels and fatigue, where mood and quality of life diverge. In addition, the interventions were well tolerated by patients. However, because the methodological quality of the resistance training studies included were low, three years later (in 2012) the same group performed another review including new randomised controlled trials (RCTs) and non-RCTs studies (Dalgas, Stenager and Ingemann-Hansen, 2008). The focus of their new study in 2012 was on the literature that evaluates the effects of progressive resistance exercise (PRE) in pwMS up to March 2011. The results consistently reported that PRE has a positive effect on patient's muscle strength and fatigue. Furthermore, mood and quality of life improved but diverse results exist due to

differences in programme protocol, sample size and outcome measures (Kjolhede, Vissing and Dalgas, 2012). However, 50% (8/16) of the studies included were non-RCT, which scored lower (between 3 and 4 of total 11 points) than RCT studies on PEDro methodological quality scale. This suggest that future studies need to consider some aspects such as blinding of assessors, therapist, and participants to improve internal and external validity as well as to evaluate whether sufficient statistical information was introduced to make the results interpretable.

Despite the previous knowledge on PRE in pwMS, an updated systematic review including studies with well defined PRE programme are still warranted. Therefore, this review was intended to include studies regarding pwMS and progressive resistance exercise, published up to August 2020 in order to:

1. Determine the effects of Progressive Resistance Exercise (PRE) on muscle performance (strength, endurance, and fatigue) for patients with multiple sclerosis.
2. Determine the effects of Progressive Resistance Exercise on patients' Quality of Life (QoL).

4.2 Method

4.2.1 Review criteria

I) Types of studies

This review was restricted to English language, in a full text and RCTs study design. The RCT study is defined as a trial in which the study investigators allocate eligible participants to intervention or control groups based on random selection (Kabisch *et al.*, 2011, p.664).

II) Types of participants

Patients of either gender, of all ages and clinically diagnosed of multiple sclerosis (for any length of time) will be included.

III) Types of intervention and outcomes measures

According to the American College of Sports Medicine (ACSM), the progressive resistance training protocols are defined as “dynamic muscle contractions with the use of concentric (CON), eccentric (ECC), and isometric muscle actions against an external load. This load can be increased whenever the subject can perform the required number of repetitions” (American College of Sports Medicine, 2018). Based on this, all papers that fitted this definition were included. Any studies that focused on improving physical function but in association with equipment or body weight such as HIIT or electrical therapy or transcutaneous electrical nerve stimulation (TENS), technology such as visual reality (VR) were excluded.

In terms of outcomes measures, studies that used outcomes to measure aspects of muscle strength, activity limitation, chronic lower limb oedema (CLLO) and patients’ quality of life were included.

4.2.2 Search strategy and data sources

The search strategy identified relevant studies by online literature searches using the following electronic databases: AMED, BNI, CINAHL, COCHRANE, EMBASE, HBE, HMIC, Medline, PubMed, PsycINFO and Pedro. In addition, manual searches were performed. References in relevant publications were examined. MS sociate website and abstracts published in conferences were also searched and personal communication with the principal author was conducted whenever more information was needed. The records of the search

strategy in the Healthcare Databases Advanced Search (NICE) were saved at each stage detailing when and how the search was undertaken and a monthly alert was set for update on the same search terms used.

The search strategy included a combination of subject terms that joint with 'AND' operator. The following search terms were used:

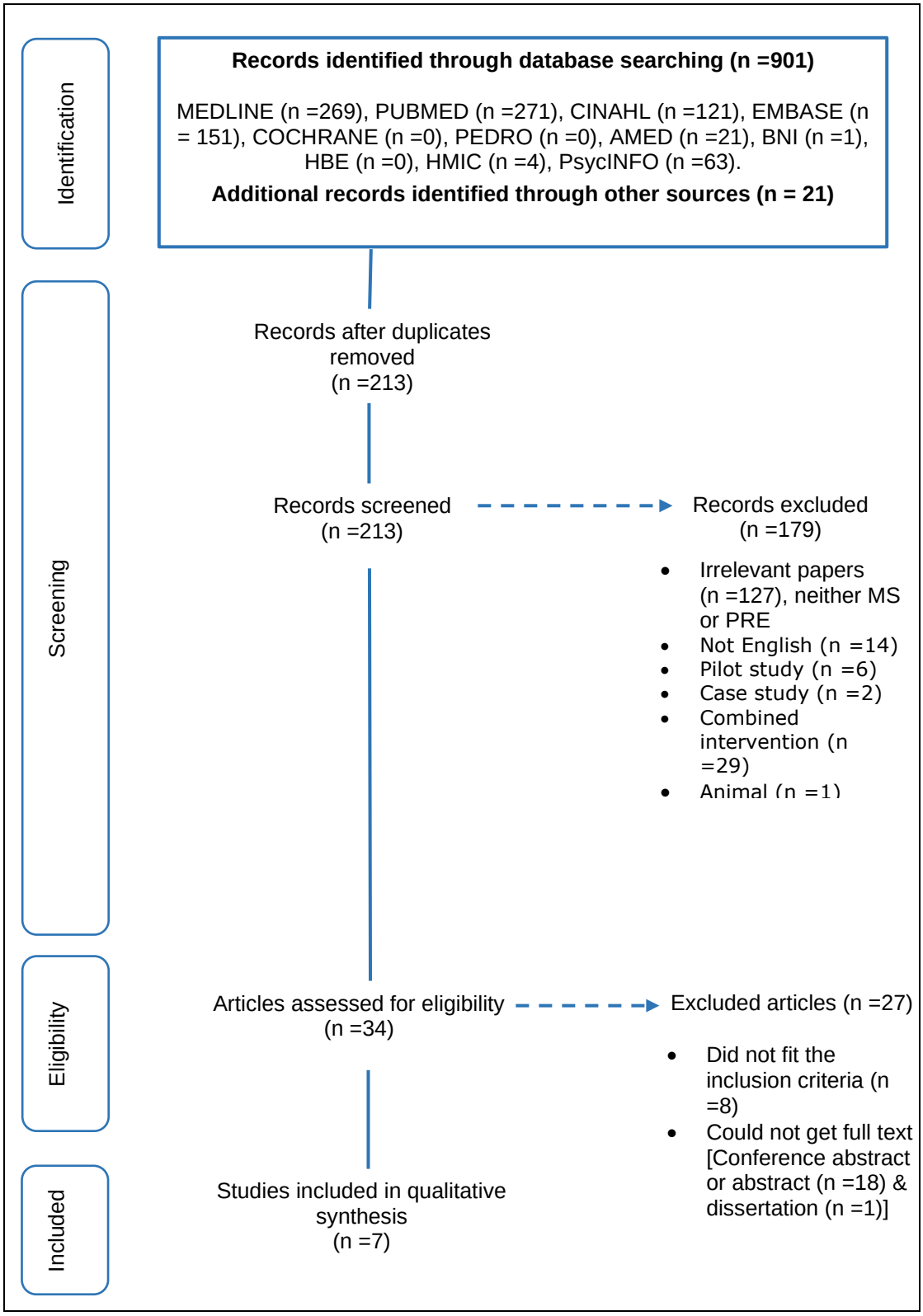
- Multiple sclerosis and progressive resistance exercise
- Multiple sclerosis and resistance exercise
- Multiple sclerosis and resistance training
- Multiple sclerosis resistance training
- Multiple sclerosis and weight training

In all search terms, the words multiple sclerosis was altered to its abbreviation (MS) and plural word of exercise was also searched. The initial search was taken place in December 2017 with no restriction on the years included and this was updated in March 2020.

4.2.3 Data acquisition

All publication results from the search strategy were saved in the Healthcare Databases Advanced Search (NICE) and the duplicate results were removed. The reviewer independently screened the updated list of study titles and abstracts, in order to identify relevant publications and create a list of eligible studies. Studies that did not meet the review criteria were excluded as shown in Appendix 7. The remaining studies were retrieved in full text and reviewed. This process was reported in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009) as can be seen in Figure 4.1.

Figure 4. 1: PRISMA Flow Chart of Study Selection Process.



A systematic data-extraction sheet was developed, and the following characteristics were included:

1. Authors and year of publication
2. Study design and study setting
3. Sample size, dropouts, and adherence
4. Gender
5. EDSS scale and MS disease course
6. Description of study and control protocol
7. Duration and frequency of intervention
8. Outcome measures

For the studies where the required information was missing (for example: the full text was not identified and only the abstract was available), a personal communication with the main author was made.

4.3 Quality Assessment and Analysis

A fundamental step of a systematic review study is to provide the most reliable evidence about the effects of intervention in RCT studies. In order to address this, a risk of bias assessment is used to report qualified results. It is important to consider whether the research has been conducted to the highest possible standards and to determine the extent to which the results can be believed.

Many RCT assessment tools are available, which include scales or checklists. The most widely used scale in systematic reviews of RCT is the Cochrane Collaboration's tool which assesses the risk of bias in such studies (Munn *et al.*, 2014). The tool contains both internal validity and descriptive criteria. Six domains of bias are included in this tool: selection bias, performance bias, detection bias, attrition bias, reporting bias and other sources of bias (Higgins

et al., 2011). Assessment of one or more items can be made within each domain, which may cover various aspects or outcomes of the domain. For each item in the tool, the assessment was in two parts. First part was “reviewer’s judgment”, where three potential answers, “high”, “low” or “unclear” risk of bias, for each item must be given. The second part was “Support for judgment”, in which a descriptive text is provided to ensure transparency in how decisions were made.

The reviewer independently evaluated the quality of included studies by using the following criteria:

1. Checking for selection bias: for each included study, the following was evaluated:
    - Random sequence generation.
        - ❖ Low risk of bias (truly random process). For example: random number table or computer random number generator.
        - ❖ High risk of bias (non-random process). For example: odd, hospital or clinic record numbers.
        - ❖ Unclear.
    - Allocation concealment.
        - ❖ Low risk of bias. For example: telephone randomisation, central randomisation, or sequentially numbered sealed envelopes.
        - ❖ High risk of bias. For example: open random allocation, unsealed envelopes or alternate dates of birth.
        - ❖ Unclear.

2. Checking for performance bias: for each study, blinding of participants and personnel were assessed as the following:
    - ❖ Low risk of bias. For example, the participants and personnel had no knowledge of which intervention was received.
    - ❖ High risk of bias.
    - ❖ Unclear.
3. Checking for detection bias: for each study, blinding for outcome assessment was assessed as the following:
    - ❖ Low risk of bias. For example, the participants and personnel had no knowledge of which outcome assessment was received.
    - ❖ High risk of bias.
    - ❖ Unclear.
4. Checking for attrition bias: for each study, incomplete outcome data such as withdrawals or drop-outs must be explained. For each attrition and exclusion, the reason must be explicit. It should be clear if it was included in the analysis of the study as which of the following:
    - ❖ Low risk of bias: if less than 10% was missing.
    - ❖ High risk of bias: if more than 10% was missing.
    - ❖ Unclear.
5. Checking for reporting bias: for each study, selective reporting must be described as the following:
    - ❖ Low risk of bias: when all of the study's pre-specified outcomes and expected outcomes were reported.
    - ❖ High risk of bias: when not all of the study's pre-specified outcomes were reported.

- ❖ Unclear.

6. Checking for other sources of bias: for each study, other problems, such as: was there any potential source of bias related to specific study design? Was there any bias in the selection of the study participants (for example, only male or female participants were included, only mild cases were included, or a specific type of MS was included).
    - ❖ Low risk of bias: meaning that there are no other problems.
    - ❖ High risk of bias: meaning that there are other problems.
    - ❖ Unclear.

4.3.1 Analysis

The method for analysing the quality of the studies depends on the critical appraisal of each individual study. The answers to the above tool were either low risk of bias, high risk of bias or unclear. The decision about the scoring system and the cut-off for inclusion of a study were based upon the guidelines in the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (2011).

The guidelines highlighted that reviewers could make the decision whether or not to include a study, based on whether the study met key domains. The reviewers should decide which domains are most important in the context, ideally when they are writing the protocol (Higgins *et al.*, 2011, p.3).

In this review, the reviewer considered the potentially included study as "high quality" if all key domains were at low risk of bias. If one or more from the key domains was at high risk of bias, the study was considered as "low quality".

There were four key domains in this review: "selection bias, attrition bias, reporting bias and other sources of bias". In the last domain, study restriction to

one gender were considered as source of bias. Unclear risk of bias was considered when a low or unclear risk of bias was given for all key domains. In addition to the risk of bias evaluation tables for each study included, a summarise judgements figures was used to illustrate the overall analysis (see figure 4.2 and 4.3).

4.4 Results

Out of the 922 studies identified from the electronic and manual searches, 709 studies were removed due to duplication. The remaining 213 studies were screened from titles and abstracts. Out of the 213 studies, 179 were excluded due to: irrelevant titles (not MS patients or not exercise intervention: n=127), written language was not English (n=14), pilot studies (n=6), case studies (n=2), the intervention was combined (n=29), and non-human participants (n= 1). The remaining 34 studies were screened for eligibility using the inclusion criteria for this review. Out of 34, 27 studies were excluded, details are outlined in Appendix 7.

The search strategy revealed seven RCT studies (Dalgas *et al.*, 2009, 2010; Dodd *et al.*, 2011; Medina-Perez *et al.*, 2014, 2016; Kjølhede *et al.*, 2015; Moradi *et al.*, 2015). Details of the seven studies are presented in Table 4.1.

Table 4. 1: Studies' Characteristics

Author (Year)	Study design & setting	Sample size, drop-outs & adherence	Gender	EDSS (±SD) and MS course	Description of study and control protocol	Duration & frequency of intervention	Measuring outcomes	
							After intervention	Follow-up period
1. Dalgas et al. (2009)	RCT in Denmark	SS: 38 (PRT=19, CG=19). Total dropout: 7/38=18% (4RT, 3CG) Adherence: 99%	F=20 M=11 (after drop-out)	EDSS: 3.0-5.5 MS course: RR only	**PRT:** weight machines were used for 5 leg exercises. 3-4 sets, 8-12 rep. at 8-15 RM, 2-3 minutes rest between sets. **CG:** normal physical activity took place. ***Follow-up:** un-supervised training for PRT.	12 weeks 2 sessions/week	Week-12: KE MVC, KF-MVC, 1 RM leg press, FS, SCT, CST, 10-MWT, 6-MWT: all improved in **PRT** but there were no changes in **CG.**	Week-24: In **PRT**: only KE-MVC and FS were maintained. In **CG:** the effects of PRE after the trial were similar to what was gained in the PRT during the trial.
2. Dalgas et al. (2010)	RCT in Denmark	SS: 38 (PRT=19, CG=19). Total dropout: 7/38=18% (4RT, 3CG) Adherence: 99%	F=20 M=11 (after drop-out)	EDSS: 3.0-5.5 MS course: RR only	**PRT:** weight machines were used for 5 leg exercises. 3-4 sets, 8-12 rep. at 8-15 RM, 2-3 minutes rest between sets.	12 weeks 2 sessions/week	Week-12: FSS, MFI-20, MDI, SF-36 (physical & mental): all improved in **PRT** but there were no changes in **CG.**	Week-24: In **PRT:** there were no improvements after week-12 but there were no deteriorations lower than the baseline score.

					CG: normal physical activity took place. ***Follow-up:** un-supervised training for PRT.			In **CG**: there were improvements in fatigue and SF-36 for quality of life (mental component) only.
3. Dodd et al. (2011)	RCT in Australia	SS: 76 (PRT=39, CG=37). Total dropout: 5/76=7% (3PRT, 2CG) Adherence: 92% (22.9±1.5 out of 24)	F & M	Ambulation Index score: 2-4 MS course: RR only	**PRT:** weight machines were used for 5 leg exercises. 2 sets, 10-12 rep. at 10-12 RM, 2 minutes rest between sets. **CG:** normal physical activity habits & social program: 1 hour/week. ***Follow-up:** both groups were advised not to do any PRE, only normal activity.	10 weeks 2 sessions/week	Week-10: MP: **PRT**=increased, **CG**= no changes ME: **PRT**=increased, **CG**= no changes Fatigue: **PRT**=decreased, **CG**= no changes QoL: **PRT**=increased, **CG**= no changes	Week-22: **PRT:** no increase, but the level did not reach baseline level. **CG:** no changes.
4. Kjolhede et al. (2015)	RCT, two centres in Denmark	SS: 35 (PRT=18, CG=17) Total dropouts: 6/35=17% (1 in PRT during intervention period, 5 in	F & M	EDSS: 2.0 to 5.5 (mean of 3) MS course: RR only	**PRT:** weight machines were used for 4 leg exercises & 2 upper limb exercises.	24 weeks 2 sessions/week	Week-24: Functional capacity: all T25FWT, 2MWT, 5STS, MSWS-12, and ascending stairs-climb	Week-48: Functional capacity: all the tests were maintained in follow-up, except MSWS-12 which

		CG=2 during intervention period & 3 at follow-up) Adherence: 93±5% (44.7±2.2 out of 48)			3-5 sets, 6-10 rep. at 6-15 RM, 2-3 minutes rest between sets. **CG:** normal physical activity took place. ***Follow-up:** PRT: continued self-guided training for another 24 weeks. CG: underwent the same PRE for 24 weeks.		improved in the **PRT**. No changes in the **CG**.	declined to baseline level in the **PRT**. In the CG: only T25FWT, 5STS and stair climb were improved.
5. Medina-Perez et al. (2014)	RCT, multi-centre in Spain.	SS: 42 (PRT=30, CG=12). Total dropouts: 0 Adherence: 90% (22.9±1.5 out of 24)	F=23 M=19	EDSS: 1-6 MS course: RR only	**PRT:** weight stack machines were used for bilateral seated knee extensions. 3 sets, 8-12 rep., progressive increased load 35-70% of MVIC, 3 minutes rest between sets. **CG:** normal physical activity took place. ***Follow-up:** both groups were	12 weeks 2 sessions/week	Week-12: MVIC: **PRT=** increased, **CG=** decreased Maximal torque: **PRT=** increased, **CG=** decreased Average muscle power: **PRT=** increased, **CG=** decreased Muscle endurance: **PRT=** increased, **CG=** increased	Week-24 (de-training period): In **PRT:** all variables decreased, except muscle power which was higher than baseline level. In **CG:** all variables decreased.

					advised not to do any PRE, only normal activity.			
6. Medina-Perez et al. (2016)	RCT, multi-centre in Spain.	SS: 77 (PRT=38, CG=39). Final data included and analysed: 40 participants (PRT=20, CG=20) Total dropouts: 37/77=48% Adherence: 95% (22.8 out of 24)	F=20 M=20 (after drop-out)	EDSS: 3-6 MS course: RR only	**PRT:** weight stack machines were used for bilateral knee extensors. 3-4 sets, 4-10 rep., progressive increased load 40-70% of MVIC, 3 minutes rest between sets. **CG:** normal physical activity took place.	12 weeks 2 sessions/week	Week-12: MWIC: **PRT=** increased, **CG=** no changes Maximal torque: **PRT=** increased, **CG=** no changes Peak muscle power: **PRT=** increased, **CG=** no changes	N/A
7. Moradi et al. (2015)	RCT in Iran	SS: 20 (PRT=10, CG=10) Total dropouts: 4/20=20%, (PRT=2/10 & CG=2/10) Adherence: 100%	Only male participants	EDSS: 1.0-6.0 MS course: RR/SP	**PRT:** conventional weight machines were used for seated rowing, chest presses, leg extensions & presses. 1 set, 6-10 rep. at 50% 1-RM & 10-15 rep. at 60-80% 1-RM **CG:** normal physical activity took place.	8 weeks 3 sessions/week	10-metre timed walk test: **PRT=** decreased, **CG=** no changes Three-minute step test: **PRT=** increased, **CG=** decreased Time up & go test: **PRT=** decreased, **CG=** no changes Flamingo stand test: **PRT=** increased, **CG=** no changes	N/A

							Seated rowing, chest presses, leg extensions & presses: **PRT=** increased, **CG=** decreased EDSS: **PRT=** decreased, **CG=** increased	

Abbreviation:

10-MWT= 10 Minute Walking Test
2MWT= Two Minute Walk Test
5STS= 5-Time Sit-To-Stand Test
6-MWT= 6 Minute Walking Test
CG= Control Group
CST= Chair Stand Test
EDSS= Expanded Disability Status Scale
F= Female
FS= Functional System scale
FSS= Fatigue Severity Scale
KE MVC= Knee Extensor Maximum Voluntary Contraction
KF-MVC= Knee Flexor Maximum Voluntary Contraction
M= Male
MDI= Major Depression Inventory
ME= Muscle Endurance
MFI-20= Multidimensional Fatigue Inventory
MP= Muscle Power
MSWS-12= 12-item MS Walking Scale
MVIC= Maximal Voluntary Isometric Contraction
MWIC=
N/A= Not Available
PRE= Progressive Resistance Exercise
PRT= Progressive Resistance Training
QoL= Quality of life
RCT= Randomized Controlled Trials
rep.= repetitions
RM= Repetition Maximum
RR= Relapsing Remitting
SCT= Stair Climbing Test
SF-36= Short Form 36
SP= Secondary Progressive
SS= Sample Size
T25FWT= Time 25 ft Walk Test

4.4.1 Description of studies

All included studies were written in English and published between 2009 and 2016. Moreover, these studies were conducted in different countries: two in Spain (Medina-Perez et al., 2014; Medina-Perez et al., 2016), one in Iran (Moradi et al., 2015), one in Australia (Dodd et al., 2011) and three in Denmark (Dalgas et al., 2009; Dalgas et al., 2010; Kjolhede et al., 2014).

The included studies consisted of 326 participants with 173 enrolled in the interventional group and 153 enrolled in control group (normal physical activities). Two studies contained 76 and 77 participants respectively (Dodd et al., 2011; Medina-Perez et al., 2016), but the rest had between 20 and 42 participants (Medina-Perez et al., 2014; Dalgas et al., 2009; Dalgas et al., 2010; Kjolhede et al., 2014; Moradi et al., 2015).

4.4.2 Risk of bias in included studies

The methodological quality scoring for the included studies was based on the Cochrane Collaboration's tool for RCTs. The reviewer independently assessed the risk of bias in the included studies as presented in Appendix 8. Five studies were classified as high quality studies (Medina-Perez et al., 2014; Dalgas et al., 2009; Dalgas et al., 2010; Kjolhede et al., 2014; Dodd et al., 2011) and two were classified as low quality studies (Moradi et al., 2015; Medina-Perez et al., 2016). As can be seen in Figure 4.2 and Figure 4.3 risk of bias in some individual studies was higher in some domains than others. For all studies, a summary of key domains is highlighted below:

- Random sequence generation and allocation concealment (selection bias): all studies presented some information about the method used for randomisation and the way concealed or randomisation lists were

generated. Three studies (Kjolhede et al., 2014; Dodd et al., 2011; Moradi et al., 2015) provided detailed information about the process.

- Incomplete outcome data (attrition bias): all of the studies, except two (Moradi et al., 2015; Medina-Perez et al., 2016) included all data in the final analysis. In the other two studies, the data from the participants who had dropped-out during the intervention period had not been included in the final analysis and no further information was given about the reasons.
- Selective report (reporting bias): the study protocol was available in most studies; however in three studies (Moradi et al., 2015; Medina-Perez et al., 2016; Medina-Perez et al., 2014), it was difficult to know if there were any deviations from the original protocol or not.
- Restriction to one gender (other bias): one study was found to have a restriction to one gender, male only (Moradi et al., 2015), whereas the rest of the studies included both genders.

All studies provided information about ethical approval and patient consent before the interventions started.

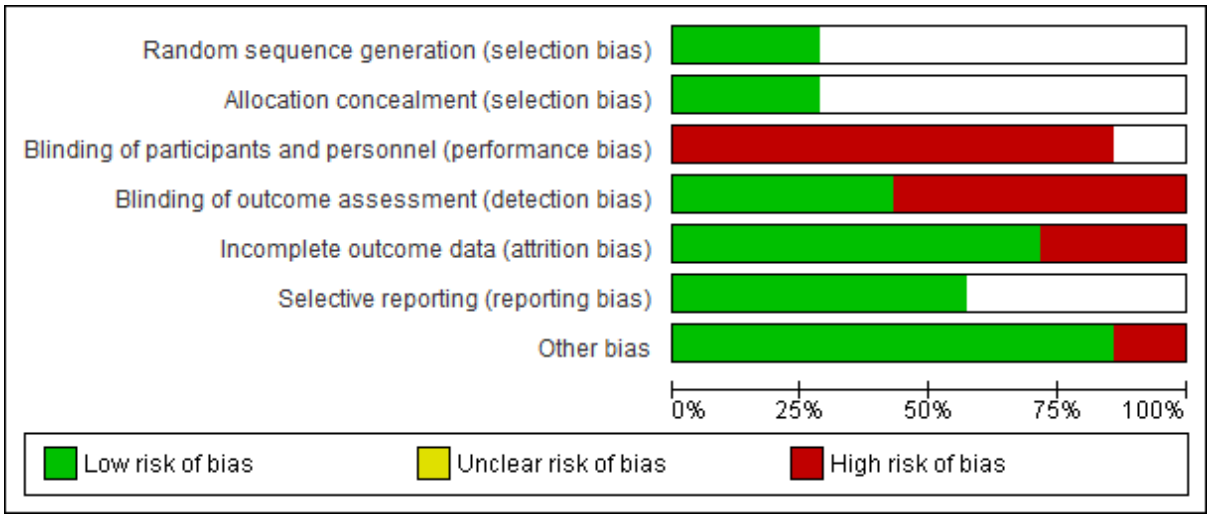


Figure 4. 2: Risk of bias item graph presented as percentages across all included studies.

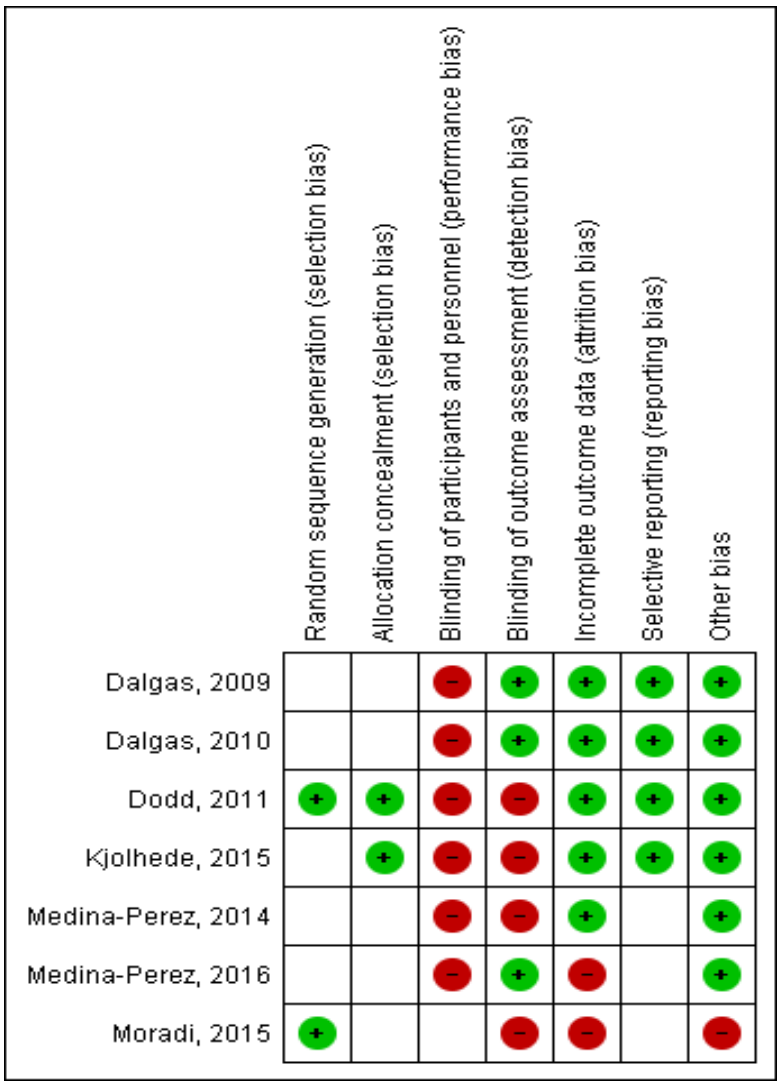


Figure 4. 3: Risk of bias summary: reviewer's judgments about each risk of bias item for each included study.

4.4.3 Effects of intervention

I) Participant characteristics

All participants in the included studies were clinically diagnosed with multiple sclerosis by a neurologist. Between 50% and 62.5% of participants were females. The severity of disease expressed by EDSS ranged between 1 and 6.5 in all studies. All studies only included the relapsing-remitting (RR) MS course, except Moradi et al. (2015) which also included secondary-progressive

(SP). The mean disease duration and participant age group ranged between 5 and 12.2 years, and 34 and 50.4 years, respectively.

II) Disability progression, intervention adherence and drop-out rate

The most common and validated tool to measure the disease progression in the studies was EDSS. In all studies, PRE had no effects on the score except in Moradi et al. (2015), where the score decreased in the exercise group after 8 weeks of intervention. However, no studies reported any deterioration or any symptom exacerbations. The level of adherence in all studies was high (between 90% and 100%), while the drop-out rates ranged between 0% to 20%. Only Medina-Perez et al. (2016) reported a drop-out rate of 48% (37/77 participants).

In summary, as a long-term intervention ranging between 8 and 24 weeks, there was a good adherence to PRE in the experimental group. However, there was no indication about the effects of PRE on disease progression.

III) Muscle performance and endurance

Improvement in muscle strength was consistently reported in the high-quality studies. Lower extremity strength significantly increased in maximum voluntary isometric contractions (MVIC), or isotonic voluntary contractions (which are measured in 1RM, 1 repetition maximum). The MIVC and 1RM of the lower limb at baseline in the experimental group was improve after PRE intervention. The MVIC at the knee extensor, knee flexor and ankle plantar flexion increased between ~7% to 11% (Dalgas et al., 2009; Dalgas et al., 2010; Medina-Perez et al., 2014; Kjolhede et al., 2014) and the 1RM increased 16.8% in leg press and 29.8% in reverse leg press (Dodd et al. 2011). In addition, the peak torque

was measured isokinetically in Medina-Perez et al. (2014) and a slight improvement was found in the knee extension (7.7% increase).

In terms of muscle endurance, the results in the included studies were consistent as well. Slight improvement in muscle endurance was found in Medina-Perez et al. (2014) and Dodd et al. (2011).

In summary, there is strong evidence that PRE can increase MS patients' lower extremity strength. However, no change occurred in the endurance. In general, there is a need for future studies that measure cardiovascular, neural adaptation and morphological and evaluate it relation to different PRE protocol.

IV) Functional capacity

Functional capacity has been measured by different outcome measurements in the included studies. However, the results show consistent improvement in the targeted group. The functional capacity score (FS) in Dalgas et al. (2009 and 2010) improved by 21.5% after 12 weeks of PRE. The patients' ability to walk also showed improvement, the effects of walking performance distance in the 2- or 6-minute walking tests (2MWT, 6MWT) were increase by 3-10% (Dalgas et al., 2009; Kjolhede et al., 2014). The maximum walking velocity, measured by a timed 25-foot walk test (T25FWT) or 10-meter walk test (10MWT) improved by ~12.4% (Dodd et al., 2009; Kjolhede et al., 2014).

Other measurements were also used to evaluate the functional capacity. The stair climb test (SCT), 5-time sit to stand test (5STS) and chair stand test (CST) were all included. In two studies (Dodd et al., 2009; Kjolhede et al., 2014), the SCT improved by 12.3% and 13.5% improvement was reported in the 5STS and CST.

In summary, PRE can improve the functional capacity in the MS patients, along with muscle strength, however more studies are needed to strengthen the recommendations for this intervention.

V) Fatigue and quality of life

Two high quality included studies evaluated the effects of PRE on fatigue and patients' quality of life (Dalgas et al., 2010; Dodd et al., 2011). Dodd et al. (2011) compared the modified fatigue impact scale (MFIS) in experimental (EG) and control groups (CG), finding that all scale categories (physical, cognitive, and psychosocial) improved after 10 weeks in the EG. In addition, the improvement was correlated with their improvement in the 2MWT. Similar findings were reported in Dalgas et al. (2010) by utilizing the fatigue severity scale (FSS) and multidimensional fatigue inventory (MFI-20) to quantify fatigue. In the last scale, different components were measured, and the improvement was significant overall, with the highest scores reported in the physical fatigue and reduced activity components.

In terms of QoL in MS patients, the results of the above studies were in agreement with each other. In Dodd et al. (2011), the World Health Organization Quality of life scale (WHOQOL-BREF) did not show any significant difference between the EG and CG in the overall score after 10 weeks, but there was a difference observed in the physical health component. Likewise, in Dalgas et al, the physical component score of the Short Form-36 (SF-36) questionnaire was improved but no significant difference was reported in the mental component.

In summary, the effects of PRE on fatigue show improvements during the interventional period, whereas findings regarding QoL diverge in the same scale as the improvements reported in the physical component.

VI) Effects of intervention on CLLO

There were no studies highlighted the effects of progressive resistance exercise on CLLO which indicates the need to carry out more studies the overcome this limitation.

VII) Effects of progressive resistance exercise at the follow-up period

After a few weeks of intervention, all variables were reassessed in order to evaluate how PRE effects were maintained after the training period. In the included studies, the follow-up period was divided into two protocols. One advised their participants not to continue with any PRE and only to conduct normal activity (Dodd et al., 2011; Medina-Perez et al., 2014). The other advised their participants to continue unsupervised PRE training during the follow-up period (Dalgas et al., 2009; Dalgas et al., 2010; Kjolhede et al., 2014).

In the first protocol, the studies reported that the participants could not maintain the improvements they gained during the interventional period. However, the deterioration did not exceed the baseline level. In Medina-Perez et al. (2014), the only variable that was maintained was muscle power (see Appendix 8). Conversely, the second protocol showed no significant deterioration after the intervention period.

In summary, MS patients who continued unsupervised PRE training after the intervention period maintained their muscle performance, fatigue, endurance and high scores in the physical QoL component of SF-36, compared to those with normal physical activity without ongoing PRE. These findings are important outcomes but may also indicate a more robust quality of life and coping ability that allows the continued adherence to treatment rather than giving up.

4.5 Discussion

This systematic review aimed to investigate the effects of PRE on MS patients in terms of muscle performance and QoL. The literature revealed seven related studies and five of them have been classified as high-quality studies based on Cochrane Collaboration's tool for RCTs. There was strong evidence in favour of PRE compared to no exercise in terms of muscle performance, functional capacity, fatigue, and physical quality of life for MS patients.

No evidence was found to be superior in terms of exercise duration, intensity, and frequency. However, the studies with durations of 12 weeks and 24 weeks of intervention have had sustainable outcomes when patients continued self-training after the intervention period.

Regarding participants' disability, the EDSS scores between 1 and 6.5 showed an excellent tolerance level, which rejects the myth that exercise therapy may increase fatigue level in MS patients. Furthermore, the adherence to the exercise was high (between 90 - 100%) in all the studies, which reflects the participants' acceptance of such intervention. Although most of the studies reported a drop-out rate between 0% and 20%, with one study having a rate of 48% (Medina-Perez et al., 2016), some of the studies stated that this had started before the intervention (during pre-assessment) (Dodd et al., 2011; Medina-Perez et al., 2016) or the reasons were not related to the intervention (Dalgas et al., 2009; Dalgas et al., 2010; Kjolhede et al., 2014).

Participants

All participants in this review fulfilled the clinical diagnosis of multiple sclerosis. However, in regard to patients' characteristics in the included studies, the disease severity was limited to only one type of MS, which was RR, and

disability ranged between 1 and 6.5 in EDSS scores. Only one study (Moradi et al., 2015), classified as low quality, included both RR and SP types of MS patients. However, it was not clear which type of MS advanced the most in terms of outcomes.

PRE has contributed to the improvement of MS patients in many aspects, however the sample size in the included studies were small in general (mean of 22 [10-38] participants in the experimental group). This could introduce a type II error, which can be avoided by increasing the sample size.

Exercise protocol

The dose (intensity, duration, and frequency) of the intervention is an important factor to determine the effectiveness of this regime. However, the diversity of the "dose" in the included studies made it very difficult to decide which one was the most effective.

Despite this diversity, all the studies reported a positive progression in MS patients in different aspects. Explanations were given in the studies regarding the reasons for choosing their protocol, nothing more than they were following the guidelines in the American College of Sports Medicine. The intensity, duration and frequency of the treatment sessions all need further future studies to guide the health care practitioners in providing the best evidence-based practice for their patients.

Methodological quality

Randomised controlled trials (RCTs) are classified as the best paradigm of interventional studies. Systematic review studies evaluate the effectiveness of the therapeutic intervention in these studies by using a checklist or score tool. In this review, five out of seven studies fulfilled the key domains in the Cochrane

Collaboration's tool for RCTs. However, the other domains, such as blindness of participants and therapists/assessors to the intervention (performance bias) or outcome assessments (detection bias) were generally at a high risk of bias. This gives important points to consider in future studies: the blinding of assessors and participants (if possible) to improve the quality of the studies.

Outcome measures

Although most of the studies measured the same outcomes, different tests were used, which made combining data difficult. The large varieties of measurement outcomes confirm the need for a general agreement about the most valid, reliable, and important measures to assess the effects of therapeutic intervention. In addition, this would enable a comparison to be made of the effects of different intervention protocols.

4.6 Conclusion

Even though there is a plethora of research on the effects of PRE in MS patients, the majority are non-RCTs or conference papers. This systematic review, based on high quality studies, suggests that PRE can be beneficial in terms of muscle strength, endurance, fatigue and walking distance in patients with MS. Weak evidence was found regarding overall improvement in quality of life, except for the physical component which showed significant progress. Finally, no evidence was found that one interventional protocol was superior to another. However, the protocols of 12 weeks and 24 weeks' duration showed that participants maintained the outcomes after the interventional period when they continued with self-training exercise. It is not enough to just consider the optimal intervention outcomes. The patients' adherence to the intervention and any dropouts to the study, which can weaken or strengthen the result regarding

intervention effects, needs to be considered. PRE shows a high level of adherence and low level of dropping out, which reflects the participants' favour to practice such exercises.

CHAPTER 5: THE PREVALENCE RATE AND THE CHARACTERSITICS OF CHRONIC LOWER LIMB OEDEMA IN PATIENTS WITH MULTIPLE SCLEROSIS WHO ARE RESIDENT IN SAUDI ARABIA: A PRELIMINARY STUDY

5.1 Introduction

Data about prevalence of CLLO in pwMS has been reported in some countries such as Italy and the UK (reviewed in Chapter 3) but the number of studies in this area are still small and have different inclusion criteria. Added to this, in developing countries, particularly in the Kingdom of Saudi Arabia, it is very difficult to approximate how common the problem is due to the scarcity of research evidence. By increased recognition of the problem and training of health professionals within health care services it will be possible to provide appropriate care and target specialist interventions for specific patient groups. Data obtained from different geographical and cultural backgrounds, allows for exploration of specific elements of the population such as EDSS, BMI and disease course and compare it with the previous studies. Therefore, this chapter will mainly focus on the first phase of the study which was about identification and screening for CLLO in pwMS. The aim of this phase is to report preliminary data of the prevalence of CLLO in people with MS (pwMS) who are resident in Riyadh city, in the Kingdom of Saudi Arabia. Based on the limited previous evidence examined, the study had two hypotheses:

1) A high prevalence rate of CLLO would be found in pwMS
2) CLLO in pwMS would be associated with high disability, advanced age, and weight.

As highlighted in Chapter 2 (2.5 Ethical Approvals and Regulatory Aspects), ethical approval was obtained before any element of the study was commenced and complied with international standards of research (Ebbesen, 2011; MOH, 2015; Information Commissioner's Office, 2018).

5.2 Objectives of Phase One

1) To evaluate the prevalence of Chronic Lower Limb Oedema (CLLO) in people with MS (pwMS) who are resident in the Kingdom of Saudi Arabia and attendees of one of the two hospitals.
2) To determine the main characteristics of those at high risk of developing CLLO

5.3 Specific Research Questions

1) What is the prevalence rate of CLLO in pwMS who are resident in the Kingdom of Saudi Arabia and attendees one of the two hospitals?
2) To examine whether EDSS, body mass index (BMI), body weight, age, MS type and disease duration have an influence on the developing CLLO in pwMS?

5.4 Methods

5.4.1 Phase one setting and duration

As defined in chapter 2, this study was carried out in two hospitals, King Khaled University Hospital (KKUH) and King Faisal Specialist Hospital and Research Centre (KFSH&RC). In this study patients attending a number of clinics and units (see Table 5.1) were screened for CLLO. Selection of these units was based on feedback received from consultants in neuro-immunology in both hospitals about where to screen for CLLO in pwMS.

Table 5. 1: Phase one setting
Out-patient clinics:
• Multiple Sclerosis Clinics (MSC) (specialized neuro-immunology clinics) • Neuro-rehabilitation clinics, which is under rehabilitation department • Lymphoedema clinic, which is under rehabilitation department but run by physiotherapist(s) only
In-patient unite:
• Medical Day Unit (MDU), which is one-day in-patient unit for some pwMS who are not responding to other MS drugs and they go once a month to this unit to have Natalizumab (Tysabri) injection by IV infusion.

Duration of This Phase

The overall duration of phase one was three months started on the 1st of January 2018 and ended on the 31st of March 2018. The reason behind ending phase one on this date was because the approval for data collection leave was for 6 months only from the 1st of January 2018 until the 30th of June 2018 and by assuming that last participant will be recruited on the 31st of March for 12 weeks that means the last session will be on the last week of data collection period. The restriction to 6 months' time frame was explained in chapter 2 (2.12 Study Regime). Reaching the required sample size would not have succeeded without having in advance planning and good time management.

5.4.2 The identification and screening step

Time management and cooperation with the clinics' head nurses made this process runs smoothly. Every day, the principal investigator (PI) attended 30-40 minutes before the clinic started to screen the patient list and access files thereby saving time by gathering some information about the patient's past-

history.

The Patient information sheet (PIS) and consent form (CF) were given to patients while they were waiting for their appointment in the waiting room. When the patient came to register her/his presence to the appointment, the head nurse handed them the PIS and CF and asked them to take their time to read it. In terms of any question(s) or enquiries related to the study, they were advised to ask the PI when they entered the clinic but after they had completed their time with their doctor. In Appendix 9, the first table shows the number of clinics that were running in each hospital during the data collection period, the average of patient flows each week and the patient characteristics. The second table shows how the researcher managed to cover recruitment within the clinics during each week.

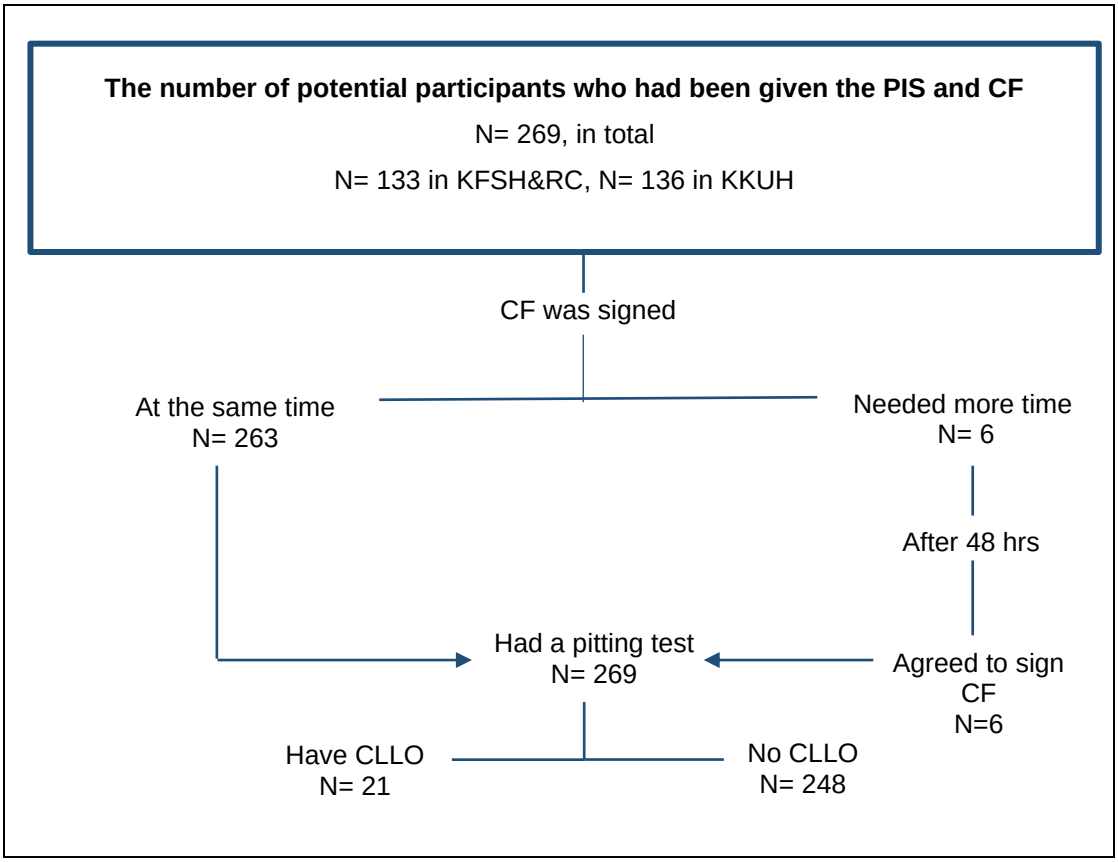
Informed consent given on the day of appointment

For those who provided informed consent on the same day of their appointment, they were undertaken a screening assessment (pitting test) immediately once they finished with their doctor (in the last few minutes of the appointment) and this was taken place in the same clinic.

Later informed consent

Potential participants (n= 6) who decided to have an extra time to consider their participation, a follow-up text or call was made after 48 hours. Then, for those who showed interest to participate (n= 6), a convenient appointment was organized in order for the CF to be signed. After this, the screening assessment was undertaken and if the participant was found to have CO, they were able to proceed with the intervention. The entire process of identification, screening and recruitment is described in Figure 5.1 below.

Figure 5. 1: The process of phase one



5.5 Screening Assessment

The screening assessment was conducted in order to confirm the presence or absence of CLLO, two factors were assessed:

5.5.1 The chronicity of the oedema

Chronic oedema is classed as persistent when swelling is present for more than 3 months (Atkin, 2014). In the study, this was judged based on patient's or carer's feedback. If the oedema presents more than three months, then the oedema was considered as a chronic. In some cases, where the participant could not give an answer, the second factor was considered the main indicator for the screening assessment.

5.5.2 The existence of oedema

The existence of oedema can be assessed by an observational pitting oedema test. This test is clinically considered as a fast and easy method by applying a pressure by one or more fingers to different locations in the participant's skin in the clinical setting (Dai *et al.*, 2015). In research setting, the presence or absent of oedema is depending on the pressure applied by the examiner and the length of application to the area to be examined. However, differences in applying this method may generate poor data if the test are not controlled.

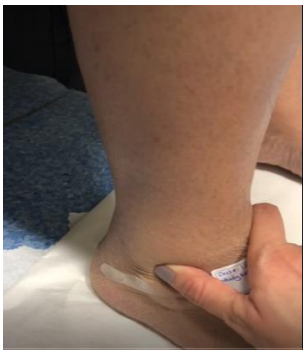
The reliability of the pitting test was examined in 2015 by Dai et al. as a first stage study of an international epidemiological study of chronic oedema (Dai *et al.*, 2015). The AFTD-pitting test was developed as a standard protocol in order to evaluate oedema. The AFTD is an abbreviation derived from the four factors: the A which indicates the Anatomical locations of oedema assessment; F is the Force required to pit; T is the amount of Time; and D is the Definition of oedema. The results showed high agreement between rater (n= 4) (> 0.85) on average of 5 to 6 oedema patients, and the kappa coefficient showed fair agreement which represent the AFTD as a useful method to assess chronic oedema in whole body.

Therefore, this study adopted the AFTD pitting test protocol to assess the CO to assure good quality of data. The procedure was applied as shown in Table 5.2 below:

Table 5. 2: AFTD procedure

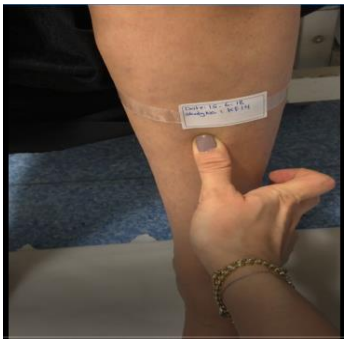
A	Anatomical location was at the following area in both side: **Foot:** behind medial malleolus, front to the lateral malleolus; and in the dorsum area at the metatarsal bone. **Leg:** was in two random locations around the shin bone, one dorsal and one proximal **Thigh:** was also random, one distal and proximal.
F	The examiner was using the thumb to apply the test and the force was strong, fixed and stable every time.
T	10 second for each location measured by mobile timer.
D	Either pitting or non-pitting.

Example of the pitting text with different participants:



Lateral malleolus

Metatarsal bone



Shin bone

This test should be pain less and any tenderness during the test should be further examined to eliminate any association with Deep Venous Thrombosis (DVT). The PI was trained to do this test in the lymphoedema clinic in the Queens Medical Centre (QMC) hospital in Nottingham for one day with a specialized nurse in the clinic. This screening test during this phase was just a quick initial assessment to determine if the potential participant has a CLLO or not but further assessment and investigation was carried out in the second

phase during the first session. When the potential participant did have a positive test, they were asked if they would like to continue and start the intervention. Positive pitting test means that when the PI applied the pressure and removed it after 10 second, the skin did not rebound back to its original position. Non pitting on the other hand, occurs due to changes in tissue composition such as fibrosis and adipose tissue and does not cause any lasting indentation. Non pitting oedema is a sign of an advanced stage of lymphoedema (Moffatt, Keeley and Quéré, 2019b) where the limb has increased in its size but when the pitting test is performed there will be a lack of bounce back.

5.6 Statistical Analysis

Univariate and bivariate analysis was run using SPSS software version 26. For continues variables (age, weight, EDSS, BMI and MS duration), the mean ± standard deviation (SD) was calculated while distribution as percentages was done for categorical variables (gender and MS type). The distribution of the data was normal; therefore, a t-test was used to compare the continuous variables and the Chi-square test for categorical variables. In addition, a Logistic regression test was undertaken to predicate values of an input and the probability of the variables in developing CLLO. Because the outcome of the study is categorical (with or without CLLO), the logistic regression test model was used.

5.7 Results

During the screening phase, 269 pwMS were screened in two hospitals for CLLO. Of these 269, 190 (71%) were women and 79 (29%) were men. Table 5.3 shows the sample characteristics of pwMS, of whom 21 (8%) were suffering from CLLO in both legs and 248 (92%) were not affected. The mean age for

participants with CLLO was 45 (SD±7.6) with a mean MS duration of 12 years and 5 months (150.6 months). The weights, BMI and EDSS were higher in the population with CLLO (mean was 75.9 kg, 28.8 kg/m^2 and 5.4 respectively) in comparison to those without CLLO (mean was 62.9 kg, 23.9 kg/m^2 and 2.4 respectively). From the 21 who presented with CLLO, only 4 (19%) had already recognized the swelling and mentioned it to their doctor.

Most of the sample (with and without CLLO) were suffering from RRMS type (n= 255) (94.7%), with PPMS affecting (n= 10) (3.71%) and SPMS (n= 4) (1.478%) were less common. Of those with RRMS, 6.3% (16 out of 255) had developed CLLO, where 3 out of 4 SPMS and 2 out of 10 in the PPMS had CLLO.

Table 5. 3: Characteristics of pwMS with and without CLLO

Variable	Chronic edema		Mean difference
	Yes N= 21 (±SD)	No N= 248 (±SD)	
Age	Mean= 45 (±7.6)	Mean= 32 (±9.6)	*12.89*
Weight (kg)	Mean= 75.9 (±18.0)	Mean= 62.9 (±26.4)	13.12
BMI (kg/m^2)	Mean= 28.8 (±13.0)	Mean= 23.9 (±10.31)	4.84
MS duration (month)	Mean= 150.6 (±66.0)	Mean= 77.67 (±59.4)	73.00
EDSS	Mean= 5.4 (±1.0)	Mean= 2.4 (±2.0)	2.98
Gender			
Female (%)	18 (9.5)	172 (90.5)	-
Male (%)	3 (3.8)	76 (96.2)	
MS type			
RRMS (%)	16 (6.3)	239 (93.7)	
SPMS (%)	3 (75.0)	1 (25.0)	-
PPMS (%)	2 (20.0)	8 (80.0)	

The bivariate analysis between two groups in Table 5.4 shows that the t-test and chi-square was statistically significant for all variables (continuous: age, weight, BMI, MS duration, EDSS; categorical: MS type) except for gender. This means that when the age or weight or BMI or MS duration or EDSS or MS type increase, the chance to develop CLLO increase as well.

Table 5. 4: Bivariate analysis

Variable	Test	P value	95% CI
Age	t-test= 6.001***	p=0.000	8.6, 17.1
Weight (kg)	t-test= 2.230*	p=0.027	1.5, 24.7
BMI (kg/m^2)	t-test=2.02*	p=0.044	0.1, 9.5
MS duration (month)	t-test=5.35***	p=0.000	46.1, 99.8
EDSS	t-test= 11.415***	p=0.000	2.4, 3.5
Gender	x^2= 2.498	p=0.114	-
MS type	x^2= 27.990***	p=0.000	-
*P<0.05, **P<0.01, ***P<0.001			

To examine the relationship between the presence of CLLO and the significant variables from the bivariate analysis (age, weight, BMI, MS duration, EDSS, MS type), a multivariable analysis by using logistic regression was undertaken as shown in Table 5.5. By running first, a univariate (Crude OR) logistic regression, a statistical significance (p= <0.05) was found between dependent CLLO and the following independent variables (age, weight, BMI, MS duration, EDSS, MS type). A multivariate analysis was undertaken by placing the statistically significant variables found in the univariate analysis.

The analysis showed that (Adjusted OR) logistic regression, 61.8% of the variation in the outcome is influenced by the variables in the logistic regression

model based on negelkereke r-square (the equivalent of adjusted r2 for binary outcomes). A statistical significance (p= <0.05) was found for age, weight and EDSS only compared to the parameters found in the univariate analysis

This indicates that pwMS who are of an advanced age are 1.093(OR) (CI 1.013, 1.179) times more likely to have CLLO than those with younger age. In terms of weight and EDSS, those who have high weight and more disabled are 1.047(OR) (CI 1.006, 1,089) and 2.735 (OR) (CI 1.684, 4.441) time higher odds respectively of developing CLLO than those with low weigh and less disabled.

Table 5. 5: Logistic regression analysis of pwMS developing CLLO (first model)
Outcomes: developing CLLO (Yes/No)
Negelkerke R Square = 0.618, Chi-square= 2.248, p=0.972

Independent variable	Univariate OR (Crude)			Multivariate OR (Adjusted)		
	OR	p value	95% CI	OR	p value	95% CI
Age	1.131***	p=0.000	1.077, 1.188	1.093*	p=0.022	1.013, 1.179
Weight (kg)	1.023*	p=0.025	1.003, 1.043	1.047*	p= 0.024	1.006, 1,089
BMI (kg/m^2)	1.050*	p=0.043	1.002, 1.101	1.046	p=0.311	0.959, 1.141
MS duration (months)	1.015***	p=0.000	1.009, 1.022	1.009	p= 0.140	0.997, 1.021
EDSS	1.815***	p=0 .000	1.448, 2.275	2.735***	p= 0.000	1.684, 4.441
MS type (Reference= RRMS)						
Type 1= SPMS	44.81**	p=0.001		27.696	p=0.061	0.862, 890.348
Type 2= PPMS	3.73	p=0.113		1.180	p= 0.909	0.070, 20.003
*P<0.05, **P<0.01, ***P<0.001						

Abbreviations: OR= odds ratio. **Note:** the dependent variable in this analysis is pwMS developed CLLO coded so that yes CLLO =1 and No CLLO =0

A final logistic regression model (Table 5.6) was created after testing multiple models while removing and adding variables and testing their significance and their effect. The final model appeared significant with 57% negelkereke r-square. This means that pwMS who are more disabled, with more weight and in advance age are 1.111, 1.056 and 2.871 (respectively) higher odds to develop CLLO.

Table 5. 6: Logistic regression analysis of pwMS developing CLLO (final model)
Outcomes: developing CLLO (Yes/No)
Negelkerke R Square = 0.571, Chi-square= 1.713, p= 0.989

Independent Variable	OR	P value	95% CI
Age	1.111**	P=0.002	1.040, 1.187
Weight (kg)	1.056***	P=0.000	1.029, 1.084
EDSS	2.871***	P=0.000	1.845, 4.468
*P<0.05, **P<0.01, ***P<0.001			

Abbreviation: OR= odds ratio. **Note:** the dependent variable in this analysis is pwMS developed CLLO coded so that yes CLLO = 1 and No CLLO=0

5.8 Discussion

The purpose of this phase was to assess the frequency of chronic lower limb oedema in people with MS who are resident in the Kingdom of Saudi Arabia and determine the main characteristics of those at high risk of developing it. The results support what has been identified by other studies (reviewed in chapter 3) that the CLLO in pwMS is a common problem, however, the prevalence in this study was lower (8%) than what have been reported in others. As predicted, our analysis showed that those who are more disabled, with more advanced age and increased weight were more likely to develop CLLO.

The low frequency of CLLO in this study could be related to the sample characteristics in comparison to the previous studies that highlighted in chapter 3. The possible reasons for this include that the majority (95%) of screened sample in our study were RRMS (255/269). In those, 173 (68%) were with EDSS <3.0 and 82 (32%) with EDSS 3.0 and more. None of the 173 have oedema, however, 17 (21%) out of 82 found to be positive. This point was the point of difference between our results and other studies, as in our study fewer physically disabled people were included compared to Solaro et al. (2006), Arpaia et al. (2010) and Keeley et al. (2017). Since, for example, data in Arpaia et al. (2010) study concerning developing CLLO in pwMS was limited to advanced MS who are bedridden or wheelchair bound, this reflects on the results which found that 85% of pwMS have CLLO. As agreed in all studies that those more disabled are more likely to have lower limb oedema.

Another possibility is the obesity. Our study indicates that people with higher weight are more likely to develop CLLO. The BMI recognized to be statistically significant and high in the group with CLLO but not in the other group, which

was similarly reported by Keeley et al. (2017) study. In this respect it is important to note patients' nutrition and raise the awareness among healthcare provider to discuss this point during patients' visit. Further research is recommended about the possibility of preventing CLLO by adopting a healthy lifestyle that includes exercise and good nutrition at the same time.

The role of self-report has not been examined in previous studies of CO in pwMS except in Keeley et al (2017). The study indicates that 38% of the cases did not recognize that they suffered with CLLO. Our study results in this respect were much higher, as 81% of the screened people who have CLLO were not recognized that they have CO and only 19% reported it to their neurologist. Detecting and recognizing the oedema is often difficult especially when the symptoms are mild. Added to this, low level of awareness among pwMS and their health care provider could impact negatively on identifying and receiving treatment at early stage of the problem developing. Although those who recognized their oedema in our study did inform their neurologist, however, under-estimating the problem by their health care provider led to anxiety and discomfort which will be discussed in chapter 7.

Mention should also be made to patients' age. Multivariate analysis in this study demonstrated that older subjects with advanced disability and weight are more likely to have CLLO, this conclusion is in line with the results of other previous studies. It would seem appropriate from a theoretical point of view that measuring indicators that detect CO at early stage can be added during a routine visit to neurological clinic, but challenges would be associated with the time required to be undertaken and skills health care provider to apply it. Further feasible studies are therefore recommended.

Some limitation of this study must be considered. This was a preliminary study and findings cannot be generalized easily. In addition, results of CLLO prevalence in pwMS in this study might under rather than over-estimate the true rate as the majority of screened sample were less disabled. Although this was limited to one city with two centres included, it's a foundation for future research tackling the same issue. The majority of studies that have been undertaken so far have been in Western health care countries, particularly in Europe, and the results may reflect the level of healthcare system available that specializes in the assessment of lymphoedema and the awareness of the healthcare provider in diagnosing and assessing the oedema.

Obviously, the field would benefit from more rigorous epidemiological studies that acknowledge current challenges and changes in identifying chronic oedema earlier in pwMS and including different locations worldwide to compare outcomes. In addition, neurologist should add some simple questions during visit to screen for the risk of chronic oedema and add simple pitting test to the neurological assessment.

5.9 Conclusion

The main strength of this study is the fact that this is the first preliminary study to evaluate and critically assess the frequency of CLLO in pwMS in Saudi Arabia. The CLLO in pwMS is undeniably a common problem, which is unrecognized, under-estimated and undertreated. By raising awareness about CLLO among health care providers and patients, result in early detecting and treatment of the problem can avoid the consequences of which may be the development of serious illness such as cellulitis. Epidemiological Studies in this

area are still limited and further research in other countries including low resource income countries is required to compare the outcomes.

5.10 Summary

Within this chapter, phase one objectives, specific research questions, methods and results have been described. The next chapter will present the quantitative phase, where those who agreed to participate from phase one started their intervention which will be described in detail.

CHAPTER 6: EFFECTS OF PROGRESSIVE RESISTANCE EXERCISE ON CHRONIC LOWER LIMB OEDEMA IN PEOPLE WITH MULTIPLE SCLEROSIS

6.1 Introduction

Focusing on treating the symptom (chronic oedema) and forgetting about the origin of this symptom will not help in solving the problem. Furthermore, addressing the underlying cause may achieve better outcomes. The CLLO in pwMS occurs because of the disease itself. CO is often caused by patient's limited physical activity, especially by the insufficient or incorrect use of the calf muscle pumping mechanism (Arpaia *et al.*, 2010). Therefore, phase two of this thesis is focused on how to treat the problem from its origin by prescribing a progressive resistance exercise that is found to be safe and tolerable for pwMS as well as for lymphoedema patients, as research described in chapter 1 and 4 shows. However, the effects of progressive resistance exercise on patients with both neurological and lymphatic problems are unknown. This PhD study is the first study that focuses on treating CLLO in pwMS. Progressive resistance exercise as highlighted in chapter 1 (1.7 Exercise Therapy and 1.8 Thesis Rationale) has a low effect on Uhthoff's phenomenon, which was the vital point behind selecting this exercise for this study.

This chapter discusses the quantitative method stage of phase two that focused on the objectives relating to pwMS treated for CLLO. Ethical approval, informed consent, patient information sheet, data production and archiving were described in chapter 2.

6.2 Objectives of Phase Two

1) To assess the effectiveness of Progressive Resistance Exercise (PRE) in the management of Chronic Lower Limb Oedema (CLLO) in people with MS who are resident in the Kingdom of Saudi Arabia.
2) To determine the impact of CLLO on pain and quality of life.

6.3 Methods

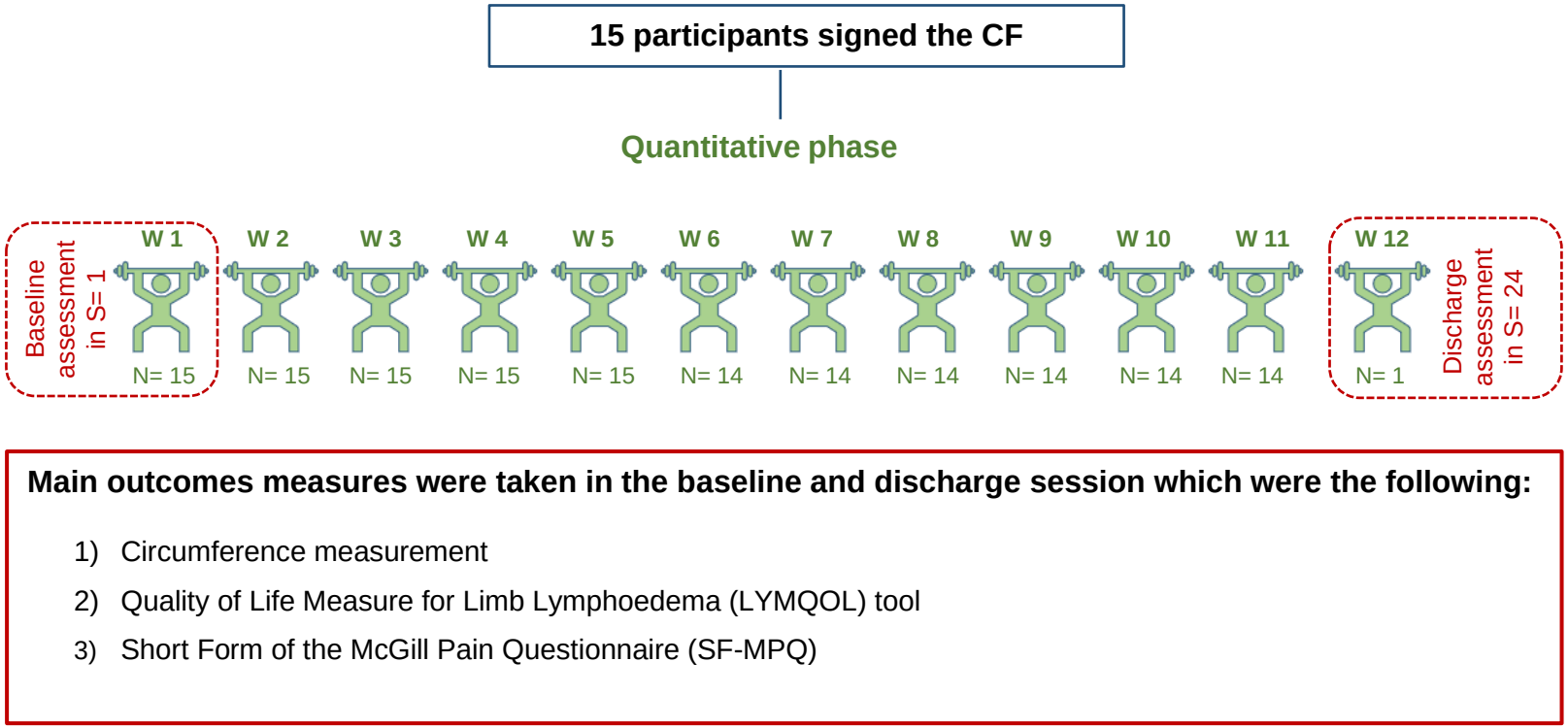
6.3.1 Phase two setting and duration

Phase two was undertaken in the rehabilitation department in both hospitals. The overall duration of the data collection was 6 months starting from 1st of January 2018 and ending on the 30th of June 2018. As highlighted in the previous chapter, the first phase (screening) took place between January 2018 until March 2018, however, once a participant was recruited from phase one, the intervention was implemented after a few days and this where phase two started. Each participant took part in the study for 12 weeks with two sessions per week. The study ended with the last contact with the last participant.

6.3.2 Recruitment of participants

Based on sample size calculation (6.6.1 Sample size and justification) fifteen pwMS were recruited from the secondary care hospitals with bilateral CLLO. Recruited participants were given a participant sheet with information about the study in advance. Participants were given opportunity to ask questions about the study and assured that their participation is voluntary and their decision not to participate will not affect their access to care. Participants who agreed to participate in the study were asked to sign the consent form. It was also explained that they could withdraw at any time, but attempts were made to minimize participants' withdrawal to improve statistical reliability. In terms of discontinuation, participants were aware that they could withdraw from the study at their request or at the request of principle investigator (PI) (for example, due to changes in the person's health). Phase two, as illustrated in figure 6.1, started with the first session of the first week and ended in session 24 of week 12.

Figure 6. 1: Illustration of phase two process



Abbreviation: CF= consent form, W= week, N= number of participants, S= session

6.3.3 Clinical procedure

Once each participant signed the CF, a convenient schedule of sessions for 12 weeks was arranged. Each week included two sessions with one day rest between the two sessions. For example, if the first session was on Monday then the next session was arranged for Wednesday and each week followed the same order of day and time.

In terms of the duration of each session, the first (baseline T0) and last (discharge T1) session in phase two were the longest. Beside the intervention itself, the pre- assessments in the first session and post-assessments in the last session were undertaken in addition which extended the session's duration from 60 to 70 minutes. While the in-between sessions, from 2nd to 23rd, took between 25 to 30 minutes. Documentation was taken at the beginning of each session by completing the case report form (CRF).

I) General instruction

Pre-sessional instructions were sent to participants via SMS message in order to allow the participants to be prepared for the session in advance. The message included the following:

- Wear comfortable clothes that allow your therapist to assess your lower limb.
- Wear a comfortable training sneaker shoe.
- Sleep well and try not to do any exercise on the day of your appointment.
- On the day of your first appointment, you can bring someone to accompany you in case you develop fatigue by the end of this session.
- You can eat your normal meal or snack before your session.

Participants were given information about what to expect during and after the intervention in the session such as muscular soreness and fatigue.

II) Case report forms (CRFs)

The case report form (CRF) is a printed document designed to record all the required information for the study purposes. Each participant was assigned a study identity code number for use on CRFs. The documents used participant initial of first and last names separated by a hyphen or a middle name initial when available, and date of birth (dd/mm/yy). The same study identity code number was used on the consent form. The CRF was completed in accordance with the principals of Good Clinical Practice (GCP).

CRFs were treated as confidential documents and held securely in accordance with regulations. The PI created a separate confidential record of participants' name, date of birth and a local hospital number to allow for identification of all participants enrolled in the study in accordance with regulatory requirements and for follow-up as required. All paper forms were filled in using a pen. Errors were crossed, no errors were corrected with correction fluid. Any change or correction to a CRF was dated, initialled, and explained (if necessary) while ensuring the original entry remained visible.

The CRF was completed as soon as possible after the scheduled visit and was signed and dated by the person completing the form. For the purpose of this study three versions of the CRF were developed (as described below). Depending on the chosen treatment option the PI decided what CRF template to use. All CRFs templates included header and footer. The header included the CRF template name, participant initials and participant's study code. The footer included study name, date, and page number. The CRFs were piloted

and validated using a sample of patients before recruitment for the PhD study commenced. The three CRFs templates are:

1) Baseline (T0) CRFs template

This template (see Appendix 10) was used in the first session (baseline T0) only and included the following information:

- Cover page (include study title, PI name, name of site, participant initials and participant study code)
- Guidance on how to complete the CRF
- General information (date of assessment, date of signed consent form)
- Demographics data (DOB, gender, weight, and height)
- Medical history
- Physical examination which included the following:
    - ❖ Muscle strength: by using manual muscle testing with grad from 0 to 5 (Table 6.1) (Ciesla *et al.*, 2011).

Table 6. 1: Manual muscle testing grading system

Technique		From sitting position, the PI asked the participant first to perform do a full range of motion (ROM) against gravity for both plantar-flexion and dorsi-flexion. If the participant was able to perform this exercise, then the PI was gradually adding resistance by pushing the participant's foot to the opposite direction of either plantar-flexion or dorsi-flexion. Participants were asked to resist this movement. Based on the participant reaction, the PI was grading the muscle strength based on the following:
0	Trace	No visible or palpable contraction
1		Visible or palpable contraction (No ROM)
2	Poor	2- : Partial ROM, gravity eliminated 2: Full ROM, gravity eliminated 2+: Gravity eliminated/slight resistance

3	Fair	3- : > 1/2 but < Full ROM, against gravity 3: Full ROM against gravity 3+: Full ROM against gravity, slight resistance
4	Good	4- : Full ROM against gravity, mild resistance 4: Full ROM against gravity, moderate resistance 4+: Full ROM against gravity, almost full resistance
5	Normal	5: Normal, maximal resistance

- ❖ Range of motion (ROM) of lower limbs by using goniometer. Normal range for plantar-flexion is (0 – 50) and dorsi-flexion is (0 – 20).
- ❖ Skin condition
- ❖ Pitting oedema test from sitting position (detailed in Table 5. 2: AFTD procedure).
- ❖ Leg circumference measurement by using tape measurements.
- ❖ Calculating the one repetitive maximum (1-RM)

- The Quality of Life Measure for Limb Lymphoedema (LYMQOL) tool (Keeley et al. 2010), the Arabic version
- Short form of the McGill Pain Questionnaire (SF-MPQ), the Arabic version (Abdrabou *et al.*, 2016)
- Progressive resistance exercise checklist (include week number, session number, exercise sets, repetitions, and number of rests between each 2 set, and note)
- The PI name and sign-off

2) Follow up CRF template

This was a checklist template (see Appendix 11) and was used from week 1 (session 2) until week 12 (session 23). The template included:

- Cover page (include study title, PI name, name of site, participant initials and participant study code)
- Date of the session, week number and session number
- Calculated % of 1-RM
- Progressive resistance exercise checklist include: repetitions, sets, and rest between sets
- Note column that include questions about participant's general health and feedback about the previous session
- The PI's sign-off

3) Discharge (T1) CRF template

Information gathered in this template (see Appendix 12) was to some extent similar to the information collected in the baseline template. This template included:

- Cover page (include study title, PI name, name of site, participant initials and participant study code)
- Date of discharge assessment
- Progressive resistance exercise checklist (include week number, session number, exercise sets, repetitions, and number of rests between each 2 set, and note)
- General information (weight and height)
- Physical examination (muscle strength and range of motion (ROM) of lower limbs, skin condition, pitting oedema test and leg circumference measurements)
- Study completion checklist (include questions related to participant completion and withdrawal)

- The Quality of Life Measure for Limb Lymphoedema (LYMQOL) tool
- Short form of the McGill Pain Questionnaire (SF-MPQ), the Arabic version
- The PI's name and sign-off.

III) One repetition maximum (1-RM)

According to the American College of Sport Medicine (ACSM) and the National Strength and Conditioning Association (NSCA) (LeSuer *et al.* 1997; Niewiadomski *et al.*, 2008; Jimenez, 2018), testing the one repetition maximum (1-RM) is important prior to exercise to measure muscle strength. Each individual has a different and unique level of muscle fitness, which needs to be determined to track progress in training. One repetition maximum (1-RM) test is considered as a gold standard for assessing muscle strength (Seo *et al.*, 2012). 1-RM is defined as the maximum weight that can be lifted once through full ROM with correct and controlled lifting technique (American College of Sports Medicine, 2018).

The intensity of training can be reported in two ways. First, as a percentage of 1-RM (%1-RM), i.e., the final weight lifted successfully with one clean repetition is considered as 100% of 1-RM. Second, as a resistance appropriate for a given number of repetitions, for example 10-RM indicates the ability to perform exercise for ten and only ten repetitions (Kjolhede, Vissing and Dalgas, 2012). In clinical practice, 86% of 1-RM is the same as 6-RM, however, a standardized 1-RM test of either way with a short warm up and familiarization found to be a reliable measurement to assess muscle strength regardless of muscles location and gender (Seo *et al.*, 2012). However, in this study we used the 1-RM instead of the number of repetitions (for example 6-RM) because we need to find out

what percentage should be used for sets of 6-RM to estimate the 1-RM for each participant and to have an idea where is the 6 or 8 or even 7 are at (Richens and Cleather, 2014).

Several factors are important to consider for optimizing 1-RM test, which includes selection of starting weight, rest intervals between each attempts and percentage increase in weight (Niewiadomski *et al.*, 2008; Halabchi *et al.*, 2017). By applying the standardized procedure as suggested in the literature, the following steps were performed to identify the muscle strength for both plantar-flexion and dorsi-flexion for each participant, which was undertaken in the first session only to estimate the initial weight that the participant can start with. The steps were as the following:

1) On the first visit, participants warmed up prior to the test by stationary bicycle for 5 minutes followed by 1-minute rest.
2) Participants were familiarized with the device (see section 6.5.2) that they will be using and performed 6 - 8 repetition of light load followed by 1-minute rest.
3) Each participant completed the test within 5 attempts and one minute of rest was given between each attempt.
4) Participants started the first set with a load from their choice at 50% of predicted 1-RM and performed between 5 to 10 repetitions through full ROM.
5) Participants rested for one minute.
6) For the second set, load was progressively increased to approximately 70 – 75% of the anticipated 1-RM and the repetition was decreased to 3 – 5 repetition through full ROM.

7) Participants rested for one minute.
8) Load was increased until failed attempt occurred with 85 – 90% of the anticipated 1-RM.
9) All attempts were performed with the same speed of movement and ROM.
10) The final weight lifted successfully with one clean repetition was recorded as 1-RM.

Example

After warming-up, participant performs a set of 8 plantar-flexion with at load, for example 5 kg with a clean full ROM. The load is then gradually increased, and repetition decreased until one full repetition can be achieved before muscle failure. This last attempt is counted as 100% of 1-RM which is in this scenario for example 15kg (15kg equals 1-RM). If intervention program calls for 40% of 1-RM, this means that 6kg equals 40% of 1-RM (which can be calculated as 0.40x15).

Note: each muscle group has its own 1-RM. Therefore, same processes must be taken for dorsi-flexion.

6.4 Main Outcomes Measures

The pitting oedema test revealed that the participants have bilateral CLLO that involved feet and legs but not thighs. The study results were considered successful after 12 week of intervention that showed improvement readings in primary and secondary outcomes measures between the first session in baseline visit (T0) and the 24th session in week 12 visit (T1).

6.4.1 Primary outcome measure

In literature, there are a number of methods to assess oedema and each has its advantages and disadvantages depending on the method's simplicity, sensitivity, and specificity. These methods are based on metric and volume measurements, and electronic impedance techniques (Tuğral, Virén and Bakar, 2017). In the clinical setting limb circumferential measurements by using tape, water displacement volumetry and perometry are the most commonly used methods (Deltombe *et al.*, 2007). Furthermore, percentage water content by using lymphscanner is also a reliable measurement at early stage of the oedema (Yu *et al.,* 2020). This is because the sensitive probe can only measure accumulation of the fluid in the skin dermis at depth up to 2.5mm. Therefore, if the accumulation extends from the dermis to deep fascia then the device cannot reflect the severity of the oedema stage (Bakar, Tuğral and Üyetürk, 2018).

Water displacement method is considered in many studies as a gold standard for leg volume measurement (Guex and Perrin, 2000; Deltombe *et al.*, 2007; Devoogdt *et al.,* 2019). However, some clinical limitations make this method undesirable as a measurement of limb volume. One of the limitations of water displacement is that the method requires thorough preparation and is therefore time-consuming (Devoogdt *et al.,* 2019). When using this method, it is important to follow safety and hygiene procedures including suitable water temperature. The other limitation of this method is that it is restricted to patients who do not present with wounds or ulcers which can often be the case in patient with chronic oedema.

Contrary to the water displacement method, the limb circumferential measurement has been found to be the most convenient and commonly used

method in clinical practice (Tan, Coutts and Bulley, 2013). Nevertheless, the reliability of the circumferential measurement method depends on the clinician's technique because of the tendency to either overestimate or underestimate the true limb volume depends on the clinician's skills (Deltombe *et al.*, 2007).

Research shows that perometry is a more suitable method while limiting the number of errors (Tan, Coutts and Bulley 2013). This infrared light device is reported to be a reliable and quick method for measuring leg volume. It has been found that the results provided by perometer are very close to those obtained by the water displacement (Tan, Coutts and Bulley 2013, Deltombe *et al.,* 2007) than circumference measurement. In contrast, Czerniec et al. found a high correlation between the circumference measurement method and perometer in the assessment of limb volume (Czerniec *et al.*, 2010). However, Czerniec et al. study was conducted on breast cancer related lymphoedema, therefore, findings cannot be generalized to a lower limb oedema. One of the perometer disadvantages is the high cost of the device, therefore many clinicians prefer to use either the circumferential measurement or water displacement method to calculate limb volume and circumference differences.

Considering the advantages, disadvantages, and availability of the above methods to evaluate oedema, this study used the tape limb circumferential measurement in order to ascertain the effectiveness of the intervention. Changes in the lower limbs circumference after the intervention were considered the primary outcome. In order to further shape our understating and knowledge of differences in changes between different leg segments which can help to improve treatment and outcomes, leg volume was also determined. Using an appropriate mathematical formula, circumference-based volumes

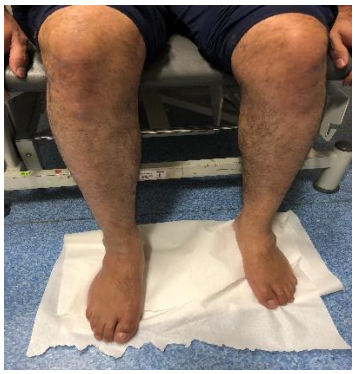
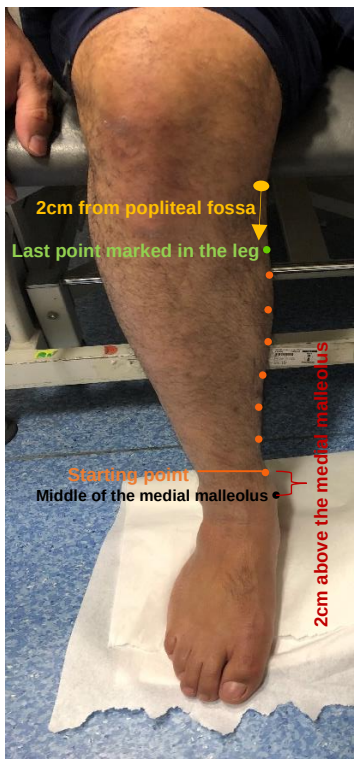
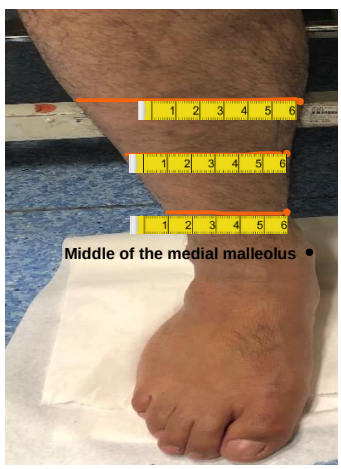
were calculated (subheading 6.4.1 (III) Converting limb circumference to limb volume).

I) Procedure using circumferential limb measurements

Accessibility and reliability of measuring limb circumferential can be easily improved if a standard protocol is strictly followed with a constant tension, limb position and measurements sites (Williams and Whitaker, 2015) . Following the guidelines for circumference measurement from the Best Practice Document for the Management of Lymphoedema, a tape measurement with 4cm intervals mark in the limb was the method used (International Lymphoedema Framework, 2006) but not the foot. Because the size of the foot is limited in length, the circumference measurements were taken at two anatomical landmark points instead of 4cm intervals, which were the great metatarsal phalangeal joints and the ankle by using the figure-of-8 method (Katz *et al.*, 2010).

A non-elastic bendable tape with one-centimetre width was used for leg measurements. Measurements were recorded in centimetres. The tape measure measurement procedure that had been obtained in this study is described in the Table 6.2 below. Measurements were taken during the participant's first and last session with the same experienced certified therapist (researcher). In the first session (T0) the measurements were taken before the intervention whereas in the last session (T1) the measurements were taken after 15 minutes of finishing the exercise (Goto, 2020).

Table 6. 2: Procedure using tape circumferance measurment

	1) Form the sitting position with 90° angle at knee and ankle, the participant was asked to firmly place his/her feet on the ground. 2) The participant's leg can be straight if the participant on the supine position and if the patient in sitting position, his/her bottom was as close to the chair or bed edge as possible.
	3) On the medial aspect of the patient's leg, a starting point was determined by using a ruler and recording the distance from the floor to 2cm above the middle of the medial malleolus. Same procedure was done on the contralateral leg. 4) Then a ruler was placed along the medial aspect of the leg and the limb was marked at 4cm intervals from the starting point to 2cm below the popliteal fossa for swelling below the knee. 5) If swelling extends above the knee, the patient was asked to stand if he/she was in sitting position or to stay in supine position and marking continued at 4cm intervals above the knee to 2cm below the gluteal crease.
	6) After this, with the limb in a relaxed position, the circumference was measured at each mark by placing the top edge of the tape measure just below the mark. 7) The tape was enclosed around the targeted point with the examiner's one hand was holding the zero end of the tape and the second one was holding the other end. 8) Note of the measurements was written in the participant's CRF (the baseline template).

	9) Same process was repeated to take measurements on the other limb.

II) Intra-rater reliability of the circumferential measurement method

For evaluating intra-rater reliability method, the above circumferential measurement method was carried out. Five volunteers above 18 years old (3 female and 2 male) were included with no lower limb deformity, no acute trauma on the lower limb, no history of renal, liver or heart condition. The PI performed the measurements from the reference points described above and again repeated the same measurements after one week at the same time of the day and position. Until the second reading, participants were asked to not enrol in Gym or perform any unusual physical activities other than they normally do and they should report any trauma or changes in their limb to the examiner in the next measurements.

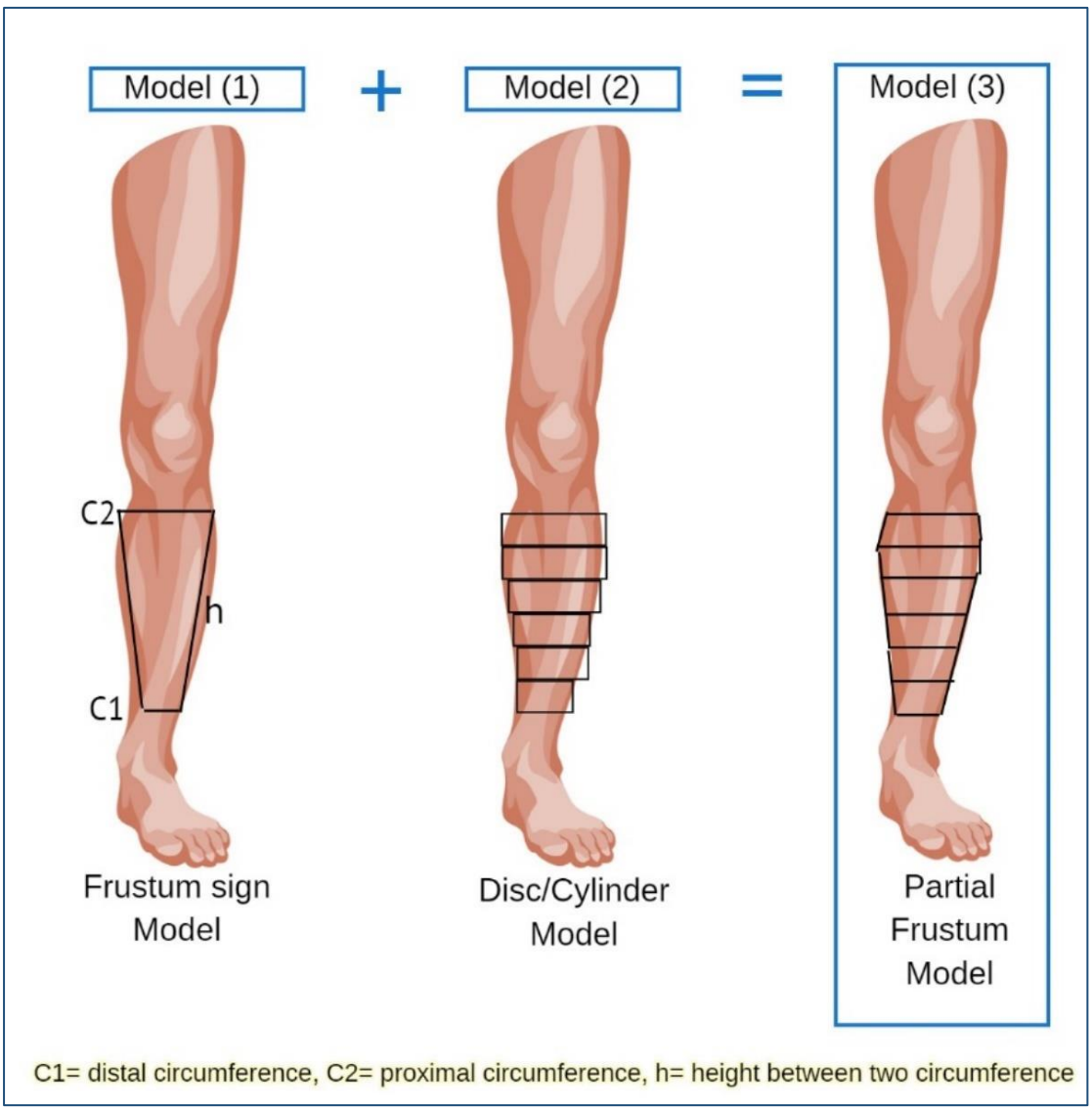
For the statistical analysis, intraclass correlation coefficient (ICC) was used to calculate intra-rater reliability. The ICC range from 0 to 1 and categorized as poor (<0.40), fair to good (0.40 – 0.75) and excellent (>0.75). Results showed that measurements were statistically significant with excellent rate (ICC 0.99, $p<0.001$). This result was consistence with Baker et al. study where the results after first and second week measurements were statistically significant between good and excellent (ICC 0.65 – 0.99, $p<0.001$) (Bakar *et al.*, 2017).

III) Converting limb circumference to limb volume

Determining limb volume and its changes is commonly calculated by using direct methods such as water displacement or indirect methods such as tape measurement (Mayrovitz, 2009). There are different models to calculate limb volume (Figure 6.2), which generally assume that the shape of the limb is

formed from a series of either frustum cones (truncated cones) or cylinders (disc), and the limb volume calculated as the sum of the volumes of these truncated cones or cylinders (Kaulesar *et al.*, 1993; Kazmi *et al.*, 2010). However, foot cannot be calculated in the same way as the leg because it does not have the shape of frustum or cylinder (Sander *et al.*, 2002; Williams and Whitaker, 2015). Therefore, the results of the volume reduction were only presented for the leg.

Figure 6. 2: Difference between the volume calculation of the leg



The first model in the figure is called “Frustum Sign Model” where in the measured region there are only two circumferential measurements taken at two points (distal and proximal of the leg) and the leg volume is calculated by frustum or truncated cone between this area. The advantage of this method is in providing a quick and easy measurements; however, the accuracy has been reported to be low (Chromy *et al.*, 2015). One of the disadvantages of the frustum sign model is the limited number of measurement points that lead to an estimate rather than a precise volume measurement. This is particular important when assessing patients with oedema because the spread of oedema is not homogenous i.e., the affected limb may consist of segments with a high volume and segments with a low volume. The use of this method may therefore provide an inaccurate volume observation albeit quick.

Unlike the Frustum Sign Model, the second “Disc Model” takes into consideration the volume of each segment of the measured leg. The total volume is calculated as the sum of all segments’ volumes. This model is more accurate than the first one in terms of calculating the volumes of segments but the distance between the segments is equidistant (Sander *et al.*, 2002; Chromy *et al.*, 2015). This means that only one circumference from proximal border of segment is calculated, where the distal one is not included. The starting point in this case is not measured and the volume measurement is calculated starting at 4cm above the starting point. This may underestimate the true volume of the leg.

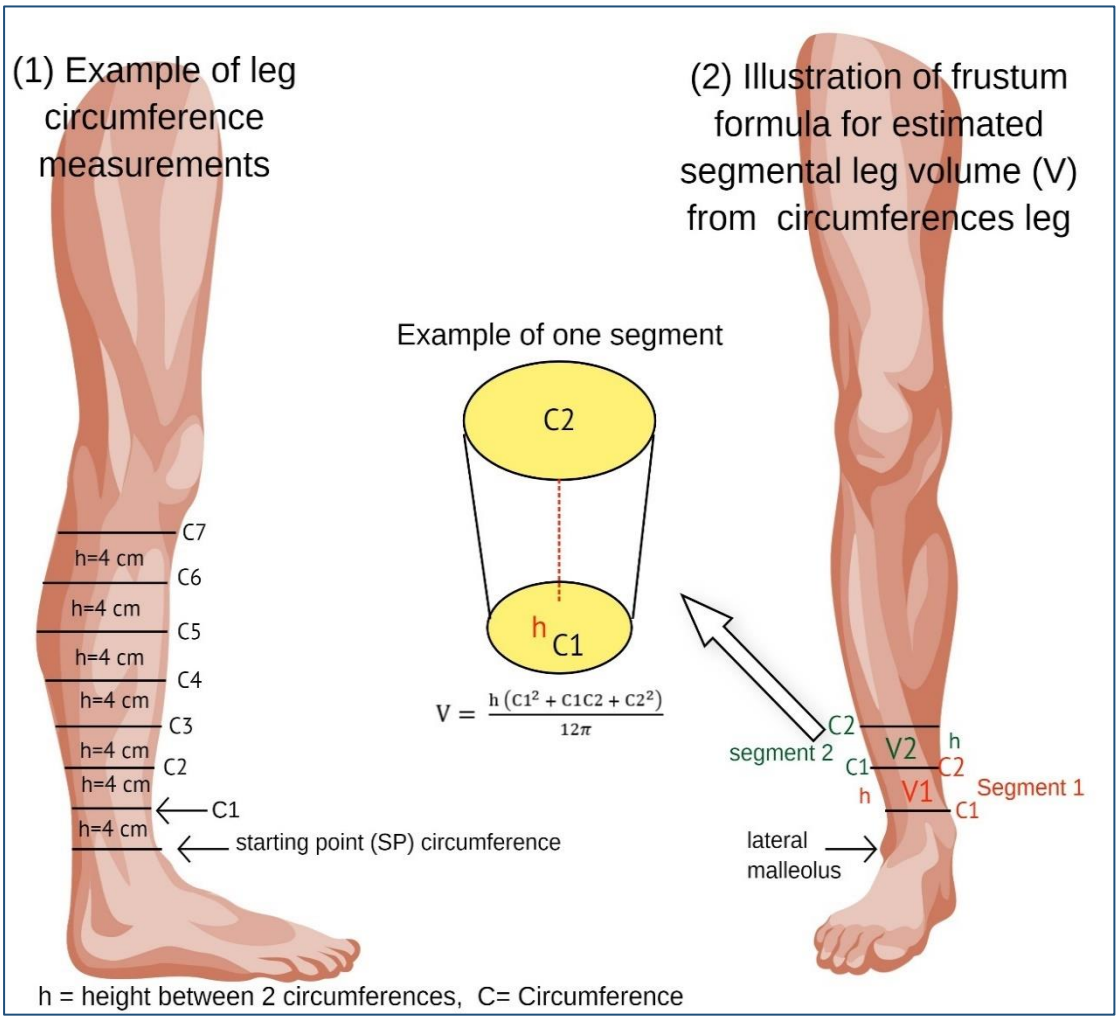
The third “Partial Frustum Model” is a combination of both previous models. It has the advantages of involving 1) the distal and proximal border of the segment as in the first model and 2) dividing the leg into segments and then the sum of

these segments' volumes gives the overall limb volume. This model has been validated by many studies that showed it is an accurate method to calculate limb volume (Katz-Leurer and Bracha, 2012; Chromy *et al.*, 2015). In addition, the Partial Frustrum Model was found to have a strong correlation (r= 0,98) with water displacement (Kazmi *et al.*, 2010). However, one of its disadvantages is that it is a time-consuming measurement method, but this issue can be overcome by computing the data with a software such as Microsoft Excel. Ensuring correct data entry and constant circumference measurements intervals will provide valid outcomes (Williams and Whitaker, 2015). Based on the review of the advantages and disadvantages of all three models, the "Partial Frustum Model" was selected for this PhD study as the method to calculate limb volume based on its inclusiveness and accuracy.

Method

Figure 6.3 illustrates two examples of leg circumference measurements and volume calculations. The first example shows the procedure that was used during this study to take leg measurements. As explained in detail in the previous section (I. Procedure using circumferential limb measurements), measurements at a 4cm interval were taken using a tape measure starting from the ankle up to the proximal end of the leg around 2cm below popliteal fossa. The procedure divided the leg into segments. The number of the segments varied based on the length of participant's leg. The circumferential measurements were then entered into an Excel spreadsheet to calculate leg volume.

Figure 6. 3: Example of leg circumference measurements and volume calculation



The formula used to calculate leg volume in the Excel software was the Frustrum formula as can be seen in example 2 (Figure 6.3):

$$V = \frac{\pi}{3} \times h\,(r^2 + rR + R^2)$$

$$r = \frac{C1}{2\pi} \quad , \qquad R = \frac{C2}{2\pi}$$

or if we proceeded from the circumference:

$$V = \frac{\pi}{3} \times h \left(\left(\frac{C1}{2\pi}\right)^2 + \frac{C1}{2\pi} \cdot \frac{C2}{2\pi} + \left(\frac{C2}{2\pi}\right)^2 \right)$$

$$V = \frac{\pi}{12\pi^2} \times h\,(C1^2 + C1C2 + C2^2)$$

$$V = \frac{h\,(C1^2 + C1C2 + C2^2)}{12\pi}$$

V is the volume, R is the radius of the proximal border of the segment, r is the radius of the distal border of the segment, C1 is the distal circumference, C2 is the proximal circumference and h is the height (h= 4cm).

Each segment has C1 and C2 which represents the distal and proximal border of the segment. However, in the next segment what was C2 in the previous segment is considered as C1 because it is the distal border of this segment. After calculating all the segments, the absolute total leg volume was determined by the sum of these segments. In terms of calculating the percentage of leg volume change, it was calculated as: $\frac{(pot{-}volume - pre{-}volume)}{pre{-}voulme} \times 100$

6.4.2 Secondary outcomes measures

The secondary outcomes measures included instruments that measure pain and quality of life of participants. Those instruments were completed at the following time points: pre-intervention at week1, session 1 (T0) and post-intervention at week12, session 24 (T1). The level of pain was assessed using the Short Form of the McGill Pain Questionnaire (SF-MPQ) and quality of life was assessed using the Quality of Life Measure for Limb Lymphoedema (LYMQOL) tool.

I) Short form of the McGill pain questionnaire (SF-MPQ), the Arabic version

Pain in general has been recognized as a complex, highly personal and subjective phenomenon unique to the individual (Greene and Meskell, 2017). Inadequate assessment of the pain may lead to poor patient outcomes which

cause anxiety, immobility, depression, and most importantly distress and suffering. According to the international association for the study of pain (IASP), chronic pain is considered to be multifactorial in nature with biological, psychological and social factors that contribute to each other (Nicholas *et al.,* 2019).

People who suffer from conditions such as MS may experience a complex pain that is not tied up to one stimulus only. This complex pain compromises patients' quality of life and limit their activities (Fallatah, Fallatah and Zalat, 2019). Various pain tools are available to evaluate individual pain levels such as McGill Pain Questionnaire (MPQ), Visual Analogue Scale (VAS) and Brief Pain Inventory (BIP). However, the McGill Pain Questionnaire (MPQ) is the most widely used, multidimensional instrument for measuring the quality and intensity of pain (Terkawi *et al.,* 2017). The original long form of this questionnaire was introduced by Melzack and Torgerson in 1971 and was modified to a shorter one in 1987 (Short Form of the McGill Pain Questionnaire [(SF-MPQ]) (Melzack, 1987).

The SF_MPQ consists of 15 descriptors, 1-11 represent the sensory and 12-15 represent the affective. Each descriptor is rated on an intensity scale as 0=none, 1=mild, 2=moderate or 3=severe. In total three pain scores are derived:

1) The sum of the sensory words chosen
2) The sum of the affective words chosen
3) The total of all descriptors

The questionnaire also includes the Present Pain Intensity (PPI) index and a Visual Analogue Scale (VAS). The SF-MPQ is a self-reported questionnaire that

is easy to use and usually takes around 5 minutes to complete (Terkawi *et al.,* 2017). Therefore, it was adopted as a pain assessment tool for this study.

Since this study intended to be undertaken in a country with Arabic-speaking community, the SF-MPQ Arabic version was used for participants with Arabic language and the original English version was also provided based on participant language preference. However, all the participants used the Arabic version. The Arabic version of the SF-MPQ was validated and considered reliable by many studies such as in Tashani et al. 2016 (Tashani, Alabas and Johnson, 2016), Abdrabou et al. 2016 (Abdrabou *et al.*, 2016) and Terkawi et al. in 2017 (Terkawi *et al.,* 2017). For this PhD study the version proposed in Terkawi's study was used because their study was conducted in the Kingdom of Saudi Arabia whereas the others were conducted in Libya and Egypt. Although Saudi Arabia, Libya and Egypt are all Arabic-speaking countries they do have different dialects. Therefore, a permission to use this questionnaire was sought and obtained from the author via email and was used with our participants pre and post the intervention (Appendix 10 for the SF-MPQ Arabic version).

II) Quality of life measure for limb lymphoedema (LYMQOL) tool

Chronic oedema and multiple sclerosis are known to significantly impact on persons' quality of life (QoL) (Greene and Meskell, 2017). Quality of life is a very personal matter and is linked to many factors such as culture, belief, social background, age and expectations (Keeley, 2008). In the literature, relevant health related quality of life tools are described as either generic or cancer-specific or lymphoedema-specific (Cornelissen *et al.*, 2018). The generic and condition-specific tools may not be accurate or informative, as it is either very

limited to assess problems experienced by breast cancer patients or very general with no consideration to patient-centred care which may not reflect what matter most to the person (Morgan, Franks and Moffatt, 2005; Keeley, 2008). In addition, some of the tools are not formally validated such as Wesley Clinic Lymphoedema Scale (WCLS) or post mastectomy lymphoedema (Keeley *et al.*, 2010).

A recent review study conducted by Cornelissen aimed to provide an overview of the different questionnaires to assess the most complete and accurate QOL measure (Cornelissen *et al.*, 2018). Out of 15 different questionnaires found, six were lymphoedema-specific questionnaires and the rest were either general (n=6) or cancer-specific (n=3). Among those related to lymphoedema-specific, two were selected as complete and accurate tools (Lymphoedema Quality of Life Inventory [LyQLI] and Lymphoedema Functioning, Disability, and Health [Lymph-ICF]) because they cover the following domains: physical function, mental function, daily activities, hobbies and job, mobility, social activity and sexual function. In contrast the other four tools missed one domain (sexual function). However, among those tools, the Quality of Life Measure for Limb Lymphoedema (LYMQOL) described as a simple and useful instrument that can be used in routine clinical practice (Wedin *et al.*, 2020).

The (LYMQOL) tool is one of the condition specific tools that is commonly used in routine clinical practice. This tool was validated in 2010 by Keeley and colleagues and measures lymphoedema using two separate questionnaires, one for upper and one for lower limb. Another advantage of the LYMQOL tool is that it is not limited to cancer or breast cancer patients. It is a patient-centred tool that assesses the impact of lymphoedema on patient's everyday living and

can be used as an outcome measure (Keeley *et al.,* 2010). The reliability of the tool was tested by test-retest and split-half test for each domain which was good (>0.9) and the internal consistency for each domain was good as well (>0.8). Therefore, this tool was selected to measure the QoL of participants recruited for this study as they are not cancer-related patients.

The tool consists of four domains that assess function, appearance, symptoms, and mood. Participants can rate their overall QoL at the end of the tool on a scale between 0 and 10. The answers to each domain score are: Not at all=1, A little= 2, Quite a bit= 3 and A lot=4. The total score is calculated by adding all scores together and then diving by the total number of questions answered. If one question is not answered a score of 0 is given and if greater than 50% of questions are not answered in one domain, this cannot be calculated and scored as 0 (Keeley *et al.*, 2010). Four domains and its related questions are: Function 1 (a–h), 2, 3; Appearance 4, 5, 6, 7, 8; Symptoms 9, 10, 11, 12, 13, 14; and Mood 15, 16, 17, 18, 19, 20.

Although the LYMQOL tool had been translated into several languages such as Swedish (Wedin *et al.*, 2020), Turkish (Bakar and Tuğral, 2019) and Dutch (van de Pas *et al.*, 2016), it has not yet been translated into the Arabic language. As mentioned previously, the community in the Kingdom of Saudi Arabia consists mainly of Arabic speakers therefore it was of utmost importance to have an Arabic version of LYMQOL -leg for the purpose of this PhD study as this tool is a self-reported tool. Therefore, the questionnaire for the lower limb oedema was translated into Arabic to be used in this study.

The first step in the translation process was to obtain permission from the main author to translate the LYMQOL tool into Arabic. The translation and cultural

adaptation of the tool were carried out in two phases and was conducted as a double-blinded experiment. The first phase comprised of initial translation, when the original English version was sent to an official translation company in Riyadh city and asked them to nominate a person who is a native Arabic speaker to translate the tool. The nominated person was blinded to the study aims. The second phase consisted of backward translation when the Arabic version was sent to the same company but another blinded translator to the original English tool was asked to translate the Arabic version into English. The backward translated English version was then sent to the main author to detect and exclude any discrepancies that could affect the meaning of the original tool. Very few amendments were made by the author related to expression terms such as (verified changed to validated, and edema/chronic lymphoedema to chronic swelling). Piloting of the Arabic version was then conducted on five patients with CLLO. No changes were made to the prefinal version and therefore the final Arabic version of the lower limb LYMQOL was obtained for this study (Appendix 11 for the Arabic version).

6.5 Intervention Protocol and Regimen

After screening for potential participants in phase one (described in detail in chapter 5), those who agreed to participate and signed the CF were invited to phase two that involved the implementation of the intervention. The intervention consisted of 12 weeks of progressive resistance exercise (PRE) performed twice a week. During the session, a recruited participant was using muscle contraction against external load which was calculated according to his/her 1-RM. Intervention parameters such as exercise load, sets and repetitions were progressed based on the intervention programme. The progression model in

this study was derived from both the guideline for multiple sclerosis provided by the American College of Sport Medicine (ACSM) and for advanced breast cancer by the National Institute for Health and Care Excellence (NICE).

Many studies that were highlighted in chapter 4 followed the same moderate resistance training programme for pwMS that the ACSM recommended (Dalgas *et al.*, 2010; Kjolhede, Vissing and Dalgas, 2012; Halabchi *et al.*, 2017). The guideline suggested that people with more disability (EDSS> 2.5) can practice resistance exercise twice a week with intensity between 60% – 80% 1-RM and work up to 2 - 3 sets of 10 – 15 repetitions from 12 to 24 weeks (American College of Sports Medicine, 2018, p.361). However, for beginners, 40% - 50% 1-RM was recommended in the guidelines in terms of initial exercise intensity to avoid injuries and fatigue.

The guidelines for lymphoedema, on the other hand, was not in contrast with the ACSM in terms of time (12 weeks and more) and frequency (2 sessions per week) except for the weight-lifting intensity. In the NICE guidelines, the load intensity is recommended to be low for breast cancer patients but no clear standard of how much the low load is (NICE, 2014). However, some RCT studies (Schmitz *et al.*, 2010; Cormie, Galvão, *et al.*, 2013; Cormie, Pumpa, *et al.*, 2013) and a very recent systematic review (Wanchai and Armer, 2019) about effects of resistance exercise on breast cancer related lymphoedema reported that between 50% to 70% 1-RM was safe load lifting with no increase of lymphoedema. However, consideration must be taken as these studies were for upper limb lymphoedema not lower limb and people can often perform more reps at given intensity (load) with lower body than the upper since there is a greater percentage of type I muscle fibres that has a fatigue resistance

characteristic (Richens and Cleather, 2014). Though, with the scarcity in the studies that is related to resistance exercise for lower limb lymphoedema, we cannot estimate the safe load/intensity. Added to this, as highlighted in chapter 1 (subheading 1.3) the muscle fibres characteristics in pwMS show changes with a shift in the proportion of fibre types from type I to type IIa in the lower limb (Dalgas *et al.,* 2010; Wens *et al.,* 2014) which fatigue easily.

Therefore, considering that participants in this study suffer from both conditions (MS and CLLO) and were beginners, exercise adjustments in terms of intensity (load) to a level that is safe and tolerable were made provided. Table 6.3 shows the intervention programme that involved the load, sets and repetition parameters, which progressed every two weeks. Every two weeks, the exercise programme was adjusted to the next level. Once training adaptation was achieved in one level (for example level 1 which is week 1 – 2), the next level (2, [week 3 – 4]) started with a new load, however, same sets/repetitions of the previous level were maintained in order to prepare the muscles for the new increase in the intensity, until the adaptation was achieved again in this level. Then the level after (3, week 5 - 6), the load was maintained but the increase was in the sets and repetitions.

Table 6. 3: Intervention programme

	Week 1 – 2	Week 3 – 4	Week 5 – 6	Week 7 – 8	Week 9 – 10	Week 11 – 12
Load	40% 1-RM	50% 1-RM	50% 1-RM	60% 1-RM	60% 1-RM	70% 1-RM
Sets	3	3	4	3	4	3
Repetitions	10	10	06	06	04	04
Rest between sets	From 1 to 2 minutes					
Time in each session	**Session 1 and 24:** from 60 to 70 minutes because it did include pre and post assessments alongside with the intervention. **Session 2 to 23:** from 25 to 30 minutes					

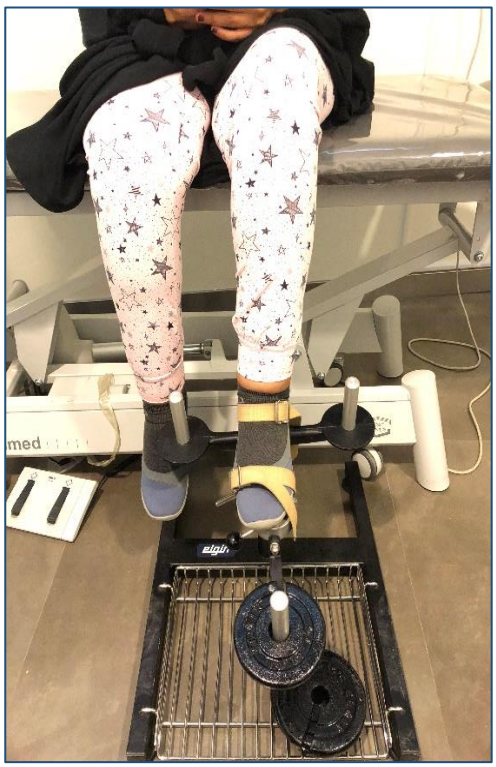
In terms of repetitions as can be seen in the table, the progression decreased as a number but it is actually increasing due to the load/repetitions' inverse relationship (Richens and Cleather, 2014). This was highlighted before in subheading 6.3.3 (III. One repetition maximum (1-RM)), when the 100% of 1-RM is defined as the ability to perform clean and controlled full ROM for one time period (one repetition). Meaning that, if your repetition decrease, the muscle is reaching it full strength which is the 1-RM.

In short, if a new level started with a new load for example as in week 3 -4, the sets/repetitions were maintained from the level before (week 1 -2) and if the load maintained in the next level as in week 5 -6, the sets/repetitions then increased.

6.5.1 Components of the intervention session

All participants had 24 sessions of PRE. Each session included the following phases: warming-up, intervention related exercise and cooling-down (Figure 6.4). In addition to those phases, in the baseline (T0) and discharge (T1) sessions the pre and post intervention assessments were also included.

Figure 6. 4: Intervention methods

Intervention components	Details
1 Warming-up 	**Device:** stationary bicycle. **Device programme:** zero resistance and active mode programme. **Duration:** for 5 minutes. **Participant's position:** sitting, either on an external chair or on participant's wheelchair. The feet were secured with straps in its designated place on the device. **Instructions:** the PI was instructing the participants to not over-speed and exhaust themselves when they cycled. **Safety**: for patient's safety the exercise was performed from sitting position to avoid falling.
2 Intervention related exercise **Image 1: proper position** 	**Device:** Elgin leg and ankle exercise device. N.P.: next subheading 6.5.2 is describing the device in detail. **Device programme:** on plantar-flexion and dorsi-flexion movements and isolate the inversion and eversion movements. **Duration:** for 20 - 25 minutes. **Participant's position:** sitting position with 90° flexion in both knees and the targeted ankle. Participants were sat on a height adjustable bed with both knees at the edge of the bed (image 1). **Foot position:** targeted foot was placed on the designated place and secured with anterior and posterior straps. **Weights position:** for dorsi-flexion movement, the weights were placed on the anterior prong and for plantar-flexion the weights were place in the posterior prong. **Instructions:** the PI was instructing the participants to perform concentric contraction (muscle shortening) as fast as possible while a slow controlled contraction was performed during eccentric contraction (muscle lengthening). **Example:** during dorsi-flexion, the participant was asked to raise her/his foot as fast as possible and lower it with slow and

<table>
<tr>
<td>Image 2: improper position

In both images, participant was in a position to perform a dorsi-flexion movement.</td>
<td>controlled movement. Opposite instructions were given for plantar-flexion movement.

Safety: for patient’s safety, the exercise was performed with training or any closed shoes with socks to avoid injury. Participants were recommended to avoid wearing sandals or high-heel shoes.

During performing the movements, participants were recommended to hold the edge of the bed to support their balance.

Participants were advised to avoid improper position (image 2) while seated to assure the involvement of the targeted muscles.</td>
</tr>
<tr>
<td>3 Cooling-down

  </td>
<td>Device: stationary bicycle

Device programme: zero resistance and active mode programme

Duration: for 5 minutes

Participant’s position: sitting, either on an external chair or on a participant’s wheelchair. Feet were secured with straps in its designated place on the device.

Instructions: the PI was instructing the participants to not over-speed and exhaust themselves when they cycled.

Safety: for patient’s safety the exercise was performed from sitting position to avoid falls.</td>
</tr>
</table>

General considerations:

In terms of safety considerations, worsening of any symptoms related to MS or CO was not expected. However, the PI advised all participants to contact her if any unusual symptoms would appear. In addition, information about expected

signs such as muscular soreness or fatigue especially in the first week was provided and discussed with the participants.

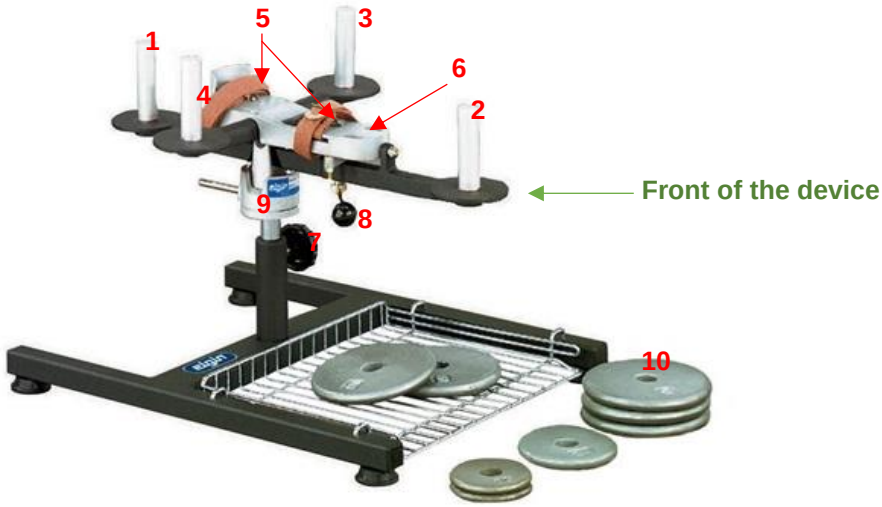
Another consideration was the intervention characteristics in terms of muscle action. Ensuring that the participant was performing the eccentric and concentric action was emphasized in order to gain the benefits of the exercise as the eccentric action is less metabolically demanding, more neuromuscularly efficient and delayed onset muscle soreness (Ratamess *et al.*, 2009; American College of Sports Medicine, 2018).

6.5.2 The intervention device

Targeting the plantar-flexion and dorsi-flexion muscles was obtained by using the “Elgin leg and ankle exercise device” which was used in both hospitals (KKUH and KFSH&RC). This device is designed mainly to provide progressive resistance exercise for inversion, eversion, plantar-flexion, and dorsi-flexion muscles. However, in this study only the plantar and dorsi flexion were involved in order to strength the muscles that are responsible for the pumping mechanism.

This portable device as presented in Figure 6.5 contains two crossed bars with four prongs for loading disk weights. Each prong can be loaded up to 5-disc weights depending on the person 1-RM and the training programme; the disc weights are ranging from 0.5 kg (1.25 lb) to 5 kg (11 lb).

Figure 6. 5: Device description



1 & 2= anterior and posterior prongs: for plantar and dorsi flexion
3 & 4= lateral and medial prongs: for inversion and eversion
5= anterior and posterior straps: to fix the foot in place
6= designated place for foot to be positioned
7= hight adjustment
8= safety lock: to prevent the movements of one bare when the other in use.
9= rest position lock: to prevent the movements in all directions.
10= different size of disk weights

Foot position

Plantar flexion

Dorsi flexion

Inversion

Eversion

Permission to use these images was taken from the mother company through email.

6.6 Statistics

6.6.1 Sample size and justification

The primary outcome measure in the study was the changes in lower limb circumference and volume following the intervention in people with MS who developed CLLO. This was presented by mean circumference averaged over several measurement points in the limb. There has been no previous study, which has assessed the effectiveness of progressive resistance exercise in the management of CLLO in people with MS. The majority of previous evidence about the current clinical practice in treating chronic oedema (as discussed in chapter 2) are relates to upper extremity lymphoedema (breast cancer-related lymphoedema) or the treatment has included compression therapy in combination with exercise which cannot be used as a comparable to our study. The outcome of treatment for lymphoedema is often measured as a change in limb circumference or volume but there is no internationally agreed method nor definition of what constitutes a clinically significant change. Therefore, given the lack of existing data upon which to base a sample size calculation, expert opinion method was used to determine a clinically significant outcome for the study. In the initial step, participants (two expert physiotherapists with mean of 15 years' experience in lymphoedema management) were asked to state a minimum reduction in circumference which was felt to be clinically significant when patients practice PRE without compression therapy. In a second step, two other participants (a nurse and a physician with experience in lymphoedema management more than 30 years) were asked to state a minimum percentage reduction in volume, which would be considered to be clinically significant. Based on their responses, it was proposed that the primary outcome of this

study would be a 1.5 cm reduction (-1.5cm) in the mean circumference in one level with a standard deviation of ±1.5. Using these parameters, it was calculated that 13 participants were required to provide 90% power at the two-sided 5% significance level. To account for a loss-to-follow-up rate of 20% (Kjolhede, Vissing and Dalgas, 2012), a total of 16 participants were required.

In terms of percentage reduction in volume, participants responded that 5% reduction would be considered clinically significant. To make the results comparable, the absolute reduction of 1.5 cm was expressed as a percentage reduction in circumference using the baseline clinical data in the study. By computing this, a 4.8% reduction in circumference and a 5% reduction in volume would be considered to be clinically significant after 12 weeks of PRE.

6.6.2 Methods

The statistical analysis was taken by the study principal investigator (PI) and under statistician consultation. All statistical analysis was performed using IBM SPSS Statistics (Version 26. Armonk, NY: IBM Corp).

For descriptive purposes, continuous data was summarised in terms of mean and standard deviation, while the categorical data was summarised in terms of frequency counts and percentages. The primary and secondary outcomes were presented using a mean, standard deviation and 95% confidence interval. The level of significance was set at 0.05. Variables were tested for normality by assessing the data distribution on a histogram.

For the leg volumes, SF-MPQ and LYMQOL, Paired t-test was used to compare between pre and post intervention when the data were normally distributed. If the data were not normally distributed, the Wilcoxon Signed-Rank test was used.

6.6.3 Procedures for missing, unused and spurious data

Only completed data were used for the analysis.

6.7 Results

Fifteen participants with bilateral CLLO were selected for the second phase of this study. One participant withdrew from the study during the third week of the intervention due to transportation issue and her related data were excluded from the study analysis. Twenty-eight limbs (14 right and 14 left) of 14 participants were analysed. Demographic details of the 14 participants can be seen in Table 6.4. The adherence to the intervention in the study was 97%, with the median number of sessions completed by the participants being 23.21/24 sessions.

Table 6. 4: Demographic data

Variable	N= 14 (±SD)
Gender **Female (%)** **Male (%)**	 11 (78.6%) 3 (21.4%)
Age (years)	Mean= 44 (±7.1)
Weight (kg)	Mean= 71.2 (±15.1)
BMI (kg/m^2)	Mean= 27 (±10.9)
MS duration (years)	Mean= 13 (±3.7)
EDSS	Mean= 5.6 (±1.0)
MS type **RRMS** **SPMS** **PPMS**	 9 4 1

Muscle strength in all participants did improve using the manual muscle testing with grad from 0 to 5 as can be seen in Table 6.5. Moreover, a statistically significant difference was found in the EDSS (p< .009) after the intervention.

Table 6. 5: Changes in muscle strength and EDSS

Variable	Pre-intervention Mean (± SD)	post-intervention Mean (± SD)	P-value
Plantar-flexion (Rt)	4.29 (±0.59)	4.86 (±0.35)	*0.021
Plantar-flexion (Lt)	3.86 (±1.36)	4.14 (±1.41)	NS
Dorsi-flexion (Rt)	4 (±0.93)	4.79 (±0.56)	*0.013
Dorsi-flexion (Lt)	3.50 (±1.55)	4.07 (±1.49)	*0.023
EDSS	5.67 (±0.9)	5.21 (±1.24)	*0.009

*Wilcoxon Signed Ranks Test. **Abbreviation:** Rt= Right side, Lt= Left side, NS= Not significant

6.7.1 Changes in limb circumference and volume

Paired t-test for 14 participants with bilateral CLLO showed no significant difference between pre and post intervention in relation to segmental leg volume in both lower limbs as can be seen in Table 6.6. Although, the reduction is not statistically significant, a trend towards significance (p value 0.06) has been found in the right-side proximal segments (the 8th). The 8th segments here represent the participants (n= 6) with longer legs.

Table 6. 6: Leg volume and changes based on different segments arranging from most distal (1st) to most proximal (8th)

leg segments (n)	Pre-intervention Mean (± SD)		post-intervention Mean (± SD)		Mean difference Post-Pre (95% CI)		Mean % change in limb volume		P-value	
	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt
1st segments (n=14)	203.25 ml (± 88.45)	204.67 (± 95.85)	200.43 ml (± 78.74)	203.78 (± 96.18)	-2.81 ml (-11.33, 5.70)	-0.89 (-6.12, 4.33)	-0.25	-0.35	0.48	0.71
2nd segments (n=14)	228.66 ml (± 119.5)	227.52 ml (± 119.68)	222.46 ml (± 103.75)	223.01 ml (± 113.35)	-6.20 ml (-20.10, 7.70)	-4.51 ml (-11.56, 2.53)	-1.01	-1.35	0.35	0.19
3rd segments (n=14)	278.54 ml (± 135.67)	273.22 ml (± 128.33)	272.91 ml (± 120.22)	267.84 ml (± 120.77)	-5.63 ml (-22.64, 11.38)	-5.37 ml (-14.35, 3.6)	-0.43	-1.37	0.48	0.21

4th segments (n=14)	340.62 ml (± 141.18)	330.17 ml (± 137.83)	332.54 ml (± 125.65)	336.21 ml (± 141.72)	-8.08 ml (-28.9, 12.73)	6.03 ml (-21.12, 33.18)	-1.04	3.04	0.41	0.63
5th segments (n=14)	407.18 ml (± 151.6)	401 ml (± 152.99)	403.45 ml (± 142.73)	411.84 ml (± 154.99)	-3.73 ml (-26.51, 19.05)	10.83 ml (-17.29, 38.96)	-0.10	3.62	0.72	0.42
6th segments (n=14)	461.45 ml (± 171.51)	459.19 ml (± 157.3)	461.51 ml (± 163.27)	462.75 ml (± 149.13)	0.06 ml (-21.68, 21.81)	3.56 ml (-14.07, 21.19)	0.50	1.25	0.99	0.67
7th segments (n=11)	458.85 ml (± 95)	460.52 ml (± 85.21)	450.28 ml (± 94.14)	458.78 ml (± 100.08)	-8.57 ml (-22.24, 5.09)	-1.74 ml (-22.18, 18.68)	-1.83	-0.68	0.19	0.85
8th segments (n=6)	471.51 ml (± 73.04)	467.355 (± 67.66)	449.07 ml (± 63.64)	451.47 (± 74.95)	-22.44 ml (-47.31, 2.42)	-15.88 ml (-36.12, 4.36)	-4.48	-3.54	0.06	0.1

Abbreviations: SD= standard deviation, n= number of participants, Rt= right leg, Lt= left leg. In relation to segmental number, the 7th and 8th segments were lower in the number than the other segments due to variation in leg length in each participant.

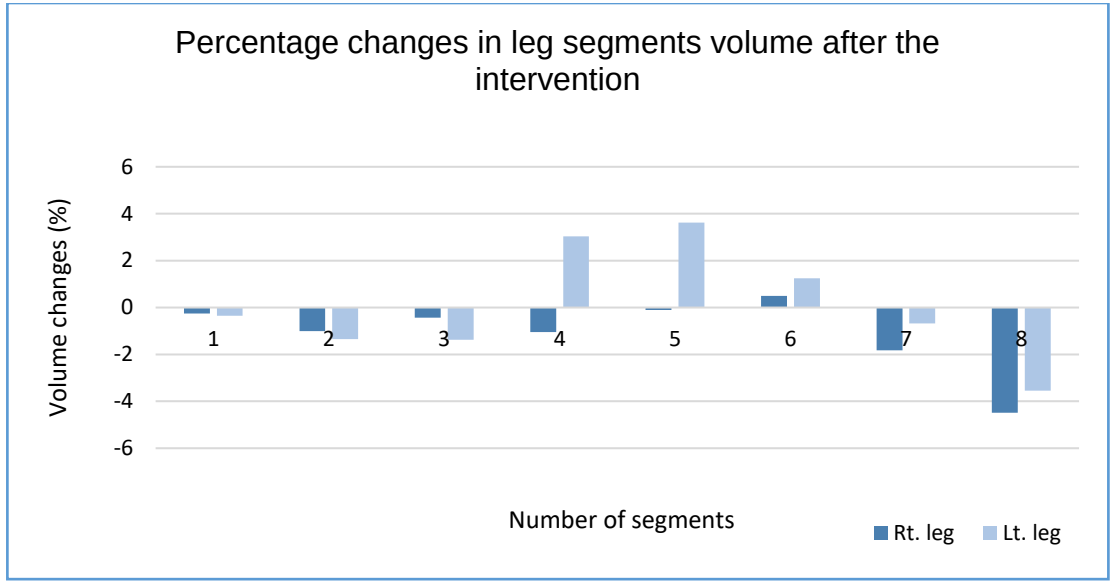


Figure 6. 6: Distribution of mean percentage changes from pre-intervention to post-intervention in each segments. Negative values are decreases.

In terms of leg circumference, a mean reduction in the absolute leg circumference of -0.66% for the right leg and no reduction found in the left side (Table 6.7). In terms of foot, no reduction was found in both side after the intervention (0.95% in the right feet and 0.03% in the left). Comparing this result with what was considered to be, in the experts opinion step, as a minimum reduction in circumference (-4.8%), the percent changes in absolute limb circumferences were not considered clinically significant after a 12 weeks of PRE.

Table 6. 7: Changes in circumference over several measurement points in the leg in each participant

Participant number	Pre-intervention leg circumference (Mean) cm		Post-intervention leg circumference (Mean) cm		Changes in leg circumference (Mean) cm		% change of absolute leg circumference		% change of 1.5 cm reduction of absolute baseline	
	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt
P1	284.5 (30.45)	298.2 (33.13)	278.2 (30.91)	292.1 (32.46)	-6.3 (-0.70)	-6.1 (-0.68)	-2.21	-2.05	-4.75	-4.53
P2	269.9 (29.99)	263.3 (29.26)	266.6 (29.62)	253.1 (28.12)	-3.3 (-0.37)	-10.2 (-1.13)	-1.2	-3.87	-5.00	-5.13
P3	222.6 (27.83)	234.2 (29.28)	222.5 (27.81)	229.3 (28.66)	-0.01 (-0.01)	-4.9 (-0.61)	-0.04	-2.09	-5.39	-5.12
P4	293.2 (32.58)	267.9 (29.77)	288.1 (32.01)	283.5 (31.50)	-5.1 (-0.57)	15.6 (1.73)	-1.74	5.82	-4.60	-5.04

P5	229 (28.63)	226.6 (28.33)	227.2 (28.40)	224.8 (28.10)	-1.8 (-0.23)	-1.8 (-0.23)	-0.79	-0.79	-5.24	-5.30
P6	305.3 (33.92)	303.6 (33.73)	301.9 (33.54)	303.6 (33.73)	-3.4 (-0.38)	0.00 (0.00)	-1.11	0.00	-4.42	-4.45
P7	288.5 (32.06)	278.4 (30.93)	290.5 (32.28)	275.5 (30.61)	2 (0.22)	-2.9 (-0.32)	0.69	-1.31	-4.68	-4.85
P8	181.2 (25.89)	180.6 (25.80)	181.9 (25.99)	180.3 (25.76)	0.7 (0.10)	-0.3 (-0.04)	0.39	-0.17	-5.79	-5.81
P9	235.9 (29.49)	234.2 (29.28)	240.7 (30.09)	238.6 (29.83)	4.8 (0.60)	4.4 (0.55)	2.03	1.88	-5.09	-5.12
P10	215.5 (26.94)	222.7 (27.84)	222.4 (27.80)	224 (28.00)	6.9 (0.86)	1.3 (0.16)	3.20	0.58	-5.57	-5.39
P11	336.4 (37.38)	343 (38.11)	317.9 (35.32)	333.8 (37.09)	-18.5 (-2.06)	-9.2 (-1.02)	-5.50	-2.68	-4.01	-3.94
P12	332 (47.43)	326.8 (46.69)	320.3 (45.76)	325.6 (46.51)	-11.7 (-1.67)	-1.2 (-0.17)	-3.53	-0.37	-3.16	-3.21
P13	284.8 (35.60)	284.7 (35.59)	297.2 (37.15)	293.8 (36.73)	12.4 (1.55)	9.1 (1.14)	4.35	3.20	-4.21	-4.21

P14	198.9 (28.41)	193.6 (27.66)	191.3 (27.33)	197.8 (28.26)	-7.6 (-1.09)	4.2 (0.60)	-3.82	2.17	-5.28	-5.42
Mean	262.69	261.27	260.48	261.13	-2.21	-0.14	-0.66	0.04	-4.80	-4.82

Abbreviation: P= participant, Rt= right leg, Lt= left leg.
Measuring absolute leg circumference changes in 14 participants with bilateral CLLO before and after 12 week of progressive resistance exercise. Absolute leg circumference is the sum of all measurement points in the leg. Mean circumference averaged over several measurement points in the limb was also calculated by adding the measurement points and divided it by the number of measurements points. The last two highlighted columns represent what the percent change is in the 1.5 cm circumference reduction using the pre-intervention data.

In terms of leg volume changes, bilateral CLLO show a mean reduction in the absolute leg volume of -1.72% (range -0.14 to -10.92) for the right leg and no reduction found in the left side (Table 6.8). Some of the participants show increase in the absolute leg volume after 12 weeks of intervention. Comparing this result with what was considered to be, in the experts opinion step, as a minimum reduction in leg volume (5%), findings revealed that the percent changes in absolute leg volume were not clinically significant between pre and post intervention.

Table 6. 8: Measuring leg volume change in fourteen participants with bilateral CLLO

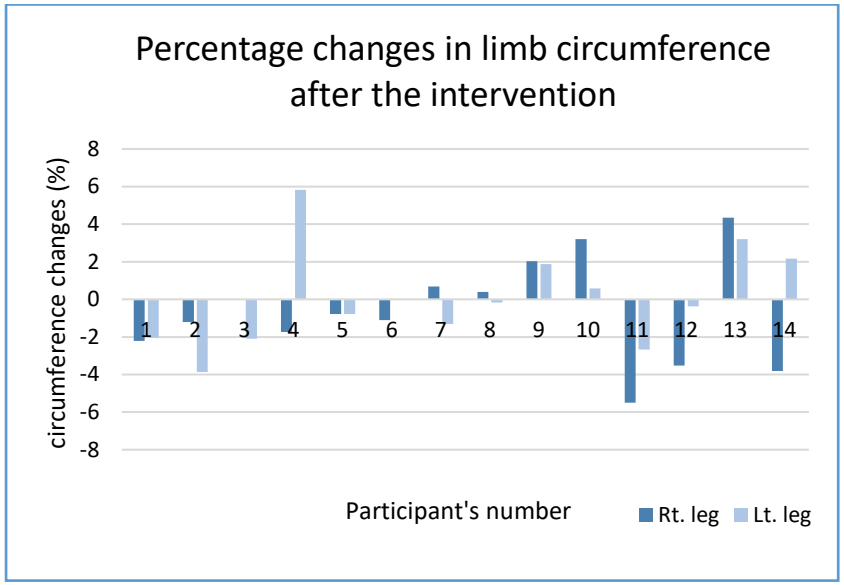
participant number	Pre-intervention absolute leg volume (ml)		post-intervention absolute leg volume (ml)		changes in absolute leg volume (ml)		% change in absolute leg volume	
	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt
P1	2624.02	2912.86	2499.92	2793.11	-124.1	-119.75	-4.73	-4.11
P2	2373.38	2250.94	2296.76	2061.75	-76.62	-189.19	-3.23	-8.40
P3	1784.23	1973.30	1781.66	1900.89	-2.57	-72.41	-0.14	-3.67
P4	2878.10	2373.55	2732.50	2641.35	-145.6	267.8	-5.06	11.28
P5	1882.63	1866.78	1866.18	1840.85	-16.45	-25.93	-0.87	-1.39
P6	2997.41	2977.57	2955.25	2988.65	-42.16	11.08	-1.41	0.37
P7	2686.75	2524.37	2774.15	2486.36	87.4	-38.01	3.25	-1.51

P8	1275.33	1277.63	1284.89	1269.57	9.56	-8.06	0.75	-0.63
P9	1964.05	1940.63	2076.43	2041.04	112.38	100.41	5.72	5.17
P10	1672.67	1785.64	1797.78	1818.30	125.11	32.66	7.48	1.83
P11	3678.44	3828.54	3276.77	3600.69	-401.67	-227.85	-10.92	-5.95
P12	4396.35	4258.12	4086.23	4220.19	-310.12	-37.93	-7.05	-0.89
P13	2939.21	2934.17	3250.54	3147.83	311.33	213.66	10.59	7.28
P14	1599.71	1507.17	1474.96	1621.22	-124.75	114.05	-7.80	7.57
Mean	2482.3057	2457.948	2439.57	2459.41	-42.73	1.47	-1.72	0.060

Abbreviation: P= participant, Rt= right leg, Lt= left leg. Measuring total leg volume changes in 14 participants with bilateral CLLO before and after 12 week of progressive resistance exercise. Total leg volume is the sum of all segments volumes.

Measurements of limb circumference and volume changes as a percentage of the preintervention value (figure 6.1- A & B), which are the primary clinical outcome measure, indicate that there was no significant effect of PRE after 12 weeks in pwMS who have bilateral CLLO and the outcomes of either measurements were quite close to each other.

(A)



(B)

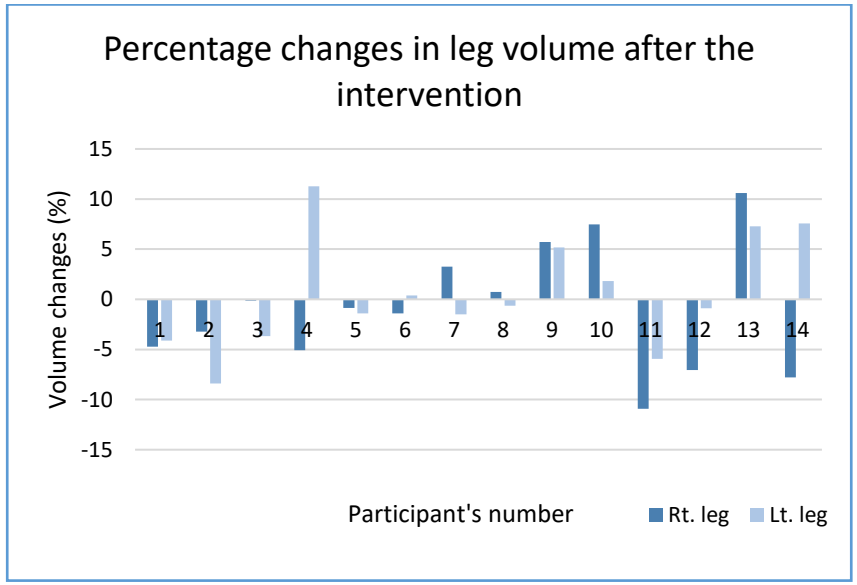


Figure 6. 7: Distribution of percentage changes from pre-intervention to post-intervention: (A) Circumference, (B) volume. Negative values are decreases.

6.7.2 Short form of the McGill pain (SF-MPQ)

Using Paired t-test, there was a significant reduction in pain (as measured by the VAS) following the intervention with moderate effect size (d= -0.4) based on Cohen's convention (Cohen, 1988). However, no significant difference was found between pre and post intervention in sensory, affective, and total description of SF-MPQ questionnaire (Table 6.9).

A Wilcoxon Signed-Rank Test in PPI indicated that the median post-intervention ranks were statistically significantly lower than the median pre-intervention, Z= -2.27, p< .027, meaning that the Present Pain Intensity (PPI) index was improved after the intervention.

Table 6. 9: Paired t-test for SF-MPQ

SF-MPQ description	Pre-intervention Mean (± SD)	post-intervention Mean (± SD)	Mean difference Post-Pre (95% CI)	P-value
Sensory	8.57 (±8.21)	7 (±7.64)	-1.57 (-4.04, 0.90)	0.19
Affective	2.78 (±3.44)	2.78 (±3.35)	0.00 (-0.71, 0.71)	1.00
Total of descriptors	11.35 (±11.35)	9.78 (±10.59)	1.57 (-1.10, 4.24)	0.22
VAS	4.29 (±3.34)	2.55 (±2.69)	-1.73 (-2.98, -0.49)	0.01
***PPI**	1.21 (±1.71)	0.35 (±0.63)	-	0.02

*Wilcoxon Signed-Rank test. **Abbreviation:** PPI= Present Pain Intensity, VAS= Visual Analogue Scale.

6.7.3 Quality of life measure for limb lymphoedema (LYMQOL)

Paired sample t-test was conducted to evaluate the quality of life pre and post the intervention. The results of the test were significant in domain 5 (LYMQOL VAS) as can be seen in the Table 6.10 with moderate effect size (d= -0.4) based on Cohen's convention (Cohen, 1988). However, in the other domains the results were not significant.

Table 6. 10: Paired t-test for LYMQOL

LYMQOL domains	Pre-intervention Mean (± SD)	post-intervention Mean (± SD)	Mean difference Post-Pre (95% CI)	P-value
Domain 1 (function)	2.35 (±0.84)	2.32 (± 0.66)	-.025 (-.51, 0.46)	0.91
Domain 2 (appearance)	2.11 (±0.85)	1.91 (±0.86)	-.20 (-.67, 0.26)	0.36
Domain 3 (symptoms)	2.65 (±0.90)	2.37 (± 1.12)	-.28 (-.75, 0.17)	0.20
Domain 4 (emotions)	1.85 (±0.97)	1.65 (±0.65)	-.20 (-.55, 1.55)	0.24
Domain 5 (LYMQOL VAS)	5.42 (± 1.94)	7.42 (± 1.55)	2 (.69, 3.30)	0.006

Abbreviation: VAS= Visual Analogue Scale.

6.8 Discussion

The purpose of this study was to demonstrate the effectiveness of progressive resistance exercise in the management of chronic lower limb oedema in people with multiple sclerosis and to determine the impact of CLLO on pain and quality of life. Intervention outcomes with respect to changes in oedema were assessed based on limb circumferences, which were used to estimate limb volume changes using a mathematical formula. Circumference-based measurements has been validated as a good estimators of both arm and leg volume in previous studies (Karges *et al.*, 2003; Mayrovitz *et al.*, 2007). The measurements were performed at 4 cm intervals of the leg and at two anatomical landmark points of the feet. Concerning the changes after the intervention, the excess limb volume in patient with bilateral CO cannot be calculated because we do not have a control limb (Katz-Leurer and Bracha, 2012). Therefore, monitoring the changes in the absolute circumference and volume of each limb provides information about intervention outcomes over time, which can be presented as a percentage change from the baseline value (Williams and Whitaker, 2015).

Compared to pre-intervention, no significant reductions in circumference measurements nor volume were observed after the 12 week of PRE. However, it can be seen in Table 6.6 that the segments volumes were responding differently to the intervention with more volume reduction noticed in the proximal part of the leg than the distal, some areas were stable, others increased and more reduction occurred in the right side than left. These findings could be explained by increasing muscle bulk in some parts of the limb and reduced oedema in others. This would require further investigation with appropriate measures which can detect changes in muscle bulk and fluid content.

This idea is supported by Dalgas et al. study which reported that biweekly 12 week of PRE in pwMS (EDSS 3 – 5.5) consisting of 3 – 4 sets of 15 – 8 repetitions of 1-RM did increase participants' thigh volume by 2.9 ± 2.7% which indicated an increase of the muscle mass (Dalgas *et al.*, 2010). Dodd et al. also reported that muscle strength in pwMS increased in average of 16.8% in leg press and 29% in reverse leg press after twice a week of PRE for 10 weeks (Dodd *et al.*, 2011). Likewise, Medina-Perez et al. found that 12 week of PRE significantly improved muscle strength and power ($p=0.004$ and $p<0.001$ respectively) but not endurance and the training adaptation was maintained after 12 weeks of detraining (Medina-Perez *et al.*, 2014). Based on the previous literature, there is no doubt the resistance exercise has a positive effect on improving muscle strength and power. However, the majority of studies that assessed the effects of PRE on pwMS were not designed to assess the factors behind muscle strength and they are often attributed to neural adaptations but not to the muscle mass increase.

To the best of our knowledge, the only study that used very similar protocol to our study was Dalgas et al., where changes in muscle mass was reported after 12 weeks of the PRE in pwMS (Dalgas *et al.*, 2010). This can explain our results, since more volume increase in the middle part of the leg (segments 5 and 6) was found, where the muscle bulk of gastrocnemius, soleus and tibialis anterior are located and the increase was in the left more than right as the participants were having more muscle weakness in the left than the right side. Supporting this, we found also that muscle strength for the participants improved after the intervention in both plantar-flexion and dorsi-flexion movements in the left more than right side which could justify the findings.

On the other hand, a reduction in volume was noticed in the proximal and distal part of the leg. From an anatomical point of view that these parts include the tendons of the anterior and posterior leg muscles which does not have the same biomechanical response to exercise as the muscle. Muscle tissue may hypertrophy following a long period of training, while the tendons are made of collagen which transmit the mechanical force of muscle contraction to the bone and their size may not be affected by exercise (Bordoni and Varacallo, 2018). Conversely, Brumitt et al. reported in their clinical commentary paper that tendons could respond to resistance exercise by increasing total number and diameter of collagen fibrils (Brumitt and Cuddeford, 2015). However, the paper did not clarify under which training parameter the adaptation was happened. Added to this, the paper was undertaken on normal subjects and it is difficult to assume the same tendon adaption could happen in pwMS due to different muscle and tendon physiological characteristics as a result of the disease (highlighted in chapter 1).

Although the reduction was found in areas where the tendons of the muscles are located. However more reduction was notable in the proximal than the distal part of the leg. Considering the normal distribution of lower limb lymphoedema (LLL), Iker et al. study found that the lymphoedema to be more located in the distal part of the extremity (Iker *et al.*, 2019). Similar findings were reported in Mayrovitz et al. retrospective study on 190 patients with unilateral and bilateral limb oedema. The study showed that limb segments were responding differently to the intervention with more reduction noticed in the proximal (mean difference (±SD) 1,248 ±823) than distal (1,204 ±775) (Mayrovitz *et al.*, 2007). This can be linked to the gravity effects and the exercise effects on calf muscle pump and

on venous hemodynamic in the leg which could support the lymphatic flow in the leg more than feet (Keilani *et al.*, 2016). Added to this, the small muscle in the feet that does not have the same pumping mechanism as the calf muscle which could lead to less reduction of the fluid in the distal part of the lower limb (Corley *et al.*, 2010).

Conducting this study on this patients' population was challenging, as the effects of PRE can be interpreted differently when it comes to MS and chronic oedema. Since we aimed to increase calf muscle pumping mechanism to create external compression of lymph vessels in order to push the fluid upward to decrease the oedema, the effects were considered positive when the muscle strength increased. This could be associated with increased mass especially since we were training people complaining of weakness in their lower extremities. At the same time, we were looking for a reduction in the volume due to a reduction in oedema which might be masked by the hypertrophied muscle. However, reading through previous studies on cancer-related lower limb lymphoedema in which their aim was to assess the effects of PRE on developing or aggravating lymphoedema reported that the resistance exercise did not develop lymphoedema in those at high risk to develop it or increase it in those who already have it (Mayrovitz *et al.*, 2007; Katz *et al.*, 2010). This could add to our understanding about the result that the increase could be related to muscle mass not the fluid. Further unmeasured variables such as water content in tissue may account for difference and requires attention in future studies.

Although the circumference and volume reduction were not statistically significant, there were a significant effect found on QoL and pain suggesting that PRE has an impact on a patient's QoL as a result of their chronic condition.

Undoubtedly, the contribution of MS on patient's QoL in this study should not be neglected. The intervention did improve the muscle strength and the EDSS which indicate that the MS has an impact as well on pain and QoL. However, measuring QoL in pwMS was not the scope of this study. Despite the small sample size of the study, the findings were in agreement with other existing knowledge in previous studies (Greene and Meskell, 2017; Tuğral, Virén and Bakar, 2017; Dai *et al.*, 2019; Mercier *et al.*, 2019) in various countries, where poor QoL and pain in patients with CO was reported.

In a sample of patients living in Turkey with unilateral lower limb lymphoedema, Tugral et al. reported an improvement in QoL after a 4 week of complex decongestive physiotherapy (CDP) (pre-post treatment: 5.2 ±2.1 to 7.1 ±2.2, p=0.003) (Tuğral, Virén and Bakar, 2017). These are in line with our findings indicating that treatment can improve patient's life to better physical, psychological, and social QoL. In Ireland, a sample of 90 patients with CLLO reported to have a poor QoL in each of four domains of LYMQOL tool and in the overall QoL measured score (5.7 compare to 5.4 in our study pre to intervention) (Greene and Meskell, 2017). A recent international, multicentre, prospective study by Mercier et al. in six countries with a total of 1094 patients reported that the impact of chronic oedema was high in all LYMQOL domains (i.e. poor) and was more in case of lower limb oedema than upper one (Mercier *et al.*, 2019). However, compare this to our results, our findings showed poorer scores in the symptoms domain (2.35 in our study compared to 2.13), function domain (2.65 in our study compared to 2.21) and overall VAS (5.4 in our study compared to 6.3) which could be linked to the fact that combination of impairments (MS and CLLO) with low physical activities may have a contribution

with our outcomes. Supporting this assumption, interesting results was reported in Dai et al. study on a Japanese sample (Dai *et al.*, 2019). A generic QoL score (LYMQOL VAS) of 5 was reported in those who were inpatient and 8 in outpatient which indicate that less physical activities may have a strong impact on patient's QoL. This suggests that patients with chronic oedema and low physical activities are more likely to have poor QoL than those with more activities in their daily life.

Regarding the pain, our finding indicates that CLLO can have a significant physical consequence which can complicate and challenge the performance of patient's daily activities. The change in pain, muscle strength and symptom severity (EDSS) can be associated with changes in QoL. These associations may indicate that PRE is a treatment that contributes to reductions in pain and MS symptom severity which transforms into improvements of QoL, however a future study is needed to test this theory.

6.9 Phase two strengths and limitations

This is the first known study of intervention of CLLO on pwMS which is a strength in that it adds to our understanding about this population and can be the bedrock and template for future research. Added to this, the study was not selective in terms of disease type where the majority of MS studies are limited to relapsing-remitting MS type and it was carried out in two hospitals. However, several factors may limit the interpretation of this phase results and the understanding of the PRE effects on CLLO in pwMS. Firstly, the small sample size which may compromise generalizability of the findings. Secondly, the evaluator and participants were not blind to the study protocol which may have contributed to the high reliability rating. However, it is unlikely that the evaluator

can remember each specific number of the tape measurements, since around 20 measures were taken for each participant during pre and post assessments. Thirdly, limb volume measurement was limited to only one measure (tape measure), which may not present the other changes that may influence the limb volume reading such as muscle mass and fat tissue. The final limitation of this phase was the lack of control group of those with MS but no oedema or a control doing no intervention.

A future randomized control trial with a larger sample size and with different outcome measures is required to support these effects further. In addition, using the data from this study would help future study to determine the sample size.

6.10 Conclusion

Progressive resistance exercise (PRE) for 12-week has no significant difference in the leg volume, however, change was seen in segmental volume (adjacent to the proximal than distal part of the leg) which may indicate change in CLLO. The intervention has a significant impact on participants'' overall QoL and pain. In addition, significant improvement was found in the EDSS and muscle strength for both side dorsi-flexion and right plantar flexion. These findings suggested that PRE may be a potential treatment for CLLO in pwMS and further studies are required to determine the limitations.

Exploring issues specifically for this population through a qualitative study to facilitate the development in the clinical practice and to evaluate our practice from various perspectives is needed and this is the aim of the next chapter.

CHAPTER 7: CHRONIC LOWER LIMB OEDEMA IN PEOPLE WITH MULTIPLE SCLEROSIS: A QUALITATIVE STUDY OF PATIENTS AND HEALTH CARE PROVIDERS' EXPERIENCES OF PROGRESSIVE RESISTANCE EXERCISE

4.5 Introduction

Emotional well-being including psychological and social changes experienced by CLLO patients following treatment is a crucial concern and can have an impact on quality of life (QoL) (Morgan, Franks and Moffatt, 2005). To develop an in-depth understanding of an intervention it is important to engage with different factors such as the views of patients and health care providers. We need to understand the whole picture in order to change or improve practice. As reported in the previous chapter, participants reported improved QoL following progressive resistance exercise. However, gaining an understanding of the perspectives of patients can improve the robustness of the research and inform recommendations for the implementation of interventions in future studies. Qualitative approaches aim to provide powerful subjective data, deeper understanding and sufficient access to perceptions of participants in order to deliver individualized and needs led care (De Valois, Asprey and Young, 2016). This chapter presents the last phase (qualitative) of the study, in which participants who undertook PRE were interviewed individually to explore their experiences of the intervention. Physiotherapists specializing in lymphoedema management in both hospitals were also interviewed in order to provide a deeper understanding and common language of their knowledge and beliefs about their current practice. The objectives of phase three were to:

1) Identify and explore factors that contribute to successful or unsuccessful use of PRE from the perspectives of participants.
2) Explore the knowledge and understanding developed by physiotherapists of CLLO in pwMS and of current lymphoedema practice in terms of exercise therapy.

7.2 Ethical Approval and Consideration

As highlighted in chapter 2 (sub-heading 2.5), this phase of the study was developed (together with phase one and two) after the initial protocol was approved by the Research Ethics Committee (REC) in King Khaled University Hospital (KKUH) (Reference Number: E-17-2733), and King Faisal Specialist Hospital and Research Centre (KFSH&RC) (Reference Number: ORA/0247/39).

Participants who expressed an interest in taking part were invited to participate in the interview study (phase three). However, participation in this (and the previous) phase was entirely voluntary and the CF emphasised that participants who indicated they wished to be involved in phase three should not feel obligated to take part in the interview and could withdraw at any time without giving a reason. Participants were assured that their withdrawal would not affect the quality or quantity of their future medical care.

All interviews were transcribed verbatim and anonymised using the same identification code that was used in phase two. Each digital audio recording was password-protected after copying the audio record electronically and was saved under the same file code (highlighted in sub-heading 2.6 Data Protection, chapter 2).

7.3 Methods

This study utilised qualitative methods to gain an in-depth understanding of the intervention from perceptions of the participants treated for CLLO. The qualitative study also aimed to explore the views of physiotherapists, especially their awareness of CLLO and their current practice regimes in terms of therapeutic exercise. Individual, face-to-face, semi-structured interviews were

chosen to generate live discussion and uncover subjective views of each participant. Unlike focus groups and paired interviews, individual interviews allow for an undiluted focus on the individual interviewee (Ritchie and Lewis, 2003).

7.3.1 Sample

I) Patient participants

Participants who completed the intervention (phase two) were eligible to participate in phase three and take part in the individual interviews. Out of 14 participants, ten responded that they wished to participate in an individual interview. The remaining four participants who decided not to participate in the qualitative study did not provide a specific reason for declining.

II) Therapy participants

All therapists who had experience in the management of lymphoedema were invited to participate in phase three of this study. Therapists were asked to read and sign the consent form including information about the study. Participation in the study (phase three) was voluntary. All physiotherapists with lymphoedema experience based in KKUH (n=3) and KFSU&RC (n=3) who met the inclusion criteria agreed to be interviewed.

7.3.2 Individual Interview

Qualitative researchers have to make a choice individual interviews and focus groups. The choice of method depends on three key factors: type of data required, the subject area and the nature of the study group (Ritchie and Lewis, 2003). Researchers can explore personal history or experience more effectively by focusing on the individual through in-depth interviews. Moreover, interviews can provide an opportunity to understand and investigate a person's

perspective by uncovering important underlying issues and are often described as a “form of conversation” (Burgess, 1982). Guest et al. (2017) found in their randomized study comparison of focus groups and individual interviews that the latter was more effective at generating a broad range of items (Guest *et al.*, 2017).

Other qualitative methods such as focus groups offer less opportunity for generating a detailed account of the studied phenomenon by a lower average speaking time per participant. Although focus groups are less expensive and allow for faster data collection, individual views and behaviour can be influenced by the responses of others and by group dynamics (Liamputtong, 2011). Moreover, reserved participants are less likely to share their views in front of other people especially when a group includes participants who are vocal or confident. The voices of participants with ‘diffident’ personality traits may be lost in focus groups.

Individual interviews are the most suitable research method when researching very complex or sensitive experiences. Intangible and more abstract topics are well-matched to focus groups, where discussion between participants can tackle the subject (Liamputtong, 2011). Group discussions can be used at initial stages of research to raise issues that need to be explored and taken forward through in-depth interviews (Ritchie and Lewis, 2003). In-depth interviews represent a more complete picture of the studied phenomenon and distinguish personal opinions about unfamiliar or new topics such as treatment. Given the limited evidence on the effects of PRE on pwMS who have CLLO, in-depth interviews can therefore provide the valuable information required to understand the individual views and experience of the intervention. Opinions,

views, and experiences related to the intervention in a relaxed familiar atmosphere can allow for collection of data that strengthens the PhD study by informing understanding of the use of the intervention from a wider perspective. The method chosen for the interview was a semi-structured interview method which is often used to guide the interview rather than an unstructured method (Given, 2008). Moreover, the responses to each question is not in a fixed range like the structured method (Blaxter, Hughes and Tight, 2010). Semi-structured interview might help also when interviewing individuals with problems in memory or concentration who may have tendencies to deviate from the topic (Given, 2008). At the same time, it does not frame their answers and limit responses such as in methods that use close questions.

7.3.3 Data collection

Two versions of semi-structured individual interview with a topic guide informed by both the review of the literature as well as the other components of the study were developed. Because not all questions were related to both groups of participants, each group had a set of questions related to the interview objectives. Interviews were recorded using the “voice memo” app on the interviewer’s mobile phone. The researcher was responsible for the collection, transcription, and analysis of the interviews. Before the start of the interviews, participants were assured that confidentiality and anonymity would be maintained at all times, and it was explained that the interview would be recorded. Participants were encouraged to take their time to answer the questions and to use their own words. When a participant was unable to understand the question, the questions was re-worded and re-phrased using simple language.

On completion of the interview, the researcher transcribed each interview immediately verbatim. Data quality checks were undertaken to assure the accuracy of the transcription by listening to the recordings whilst reading the transcripts. Electronic data that included study database for phase three was held securely by password protected encryption and access was restricted by user identifiers and passwords.

I) Individual interviews with CLLO participants

The CLLO participants' interview question guide (Table 7.1) was designed based on findings emerging from the literature review (De Valois, Asprey and Young, 2016). The introductory question was asked to evaluate the awareness and understanding of the participants regarding their problem and the intervention. Transition questions were related to participants' feelings when they were diagnosed with CLLO. Key questions were related to the objective of this phase, where participants' opinions and perceptions about the intervention were collected. Finally, ending questions were related to their opinions about future research.

The structured interviews lasted from 20 to 25 minutes and were held in the same intervention room (outpatient clinic room) at the rehabilitation department in both hospitals. Interviews were carried out in session number 23 of study week 12. Participants were reminded about the interview prior to the session commencing and advised to allow for extra time for the visit. Session 23 was chosen because the post-intervention measurements took place in the last session (session number 24). It was not possible to extend the duration of the last session to accommodate an interview because of concerns about tiredness

and the availability of participants. Due to these constraints, interviews were scheduled to occur in the penultimate session before discharge.

Table 7. 1: Interview questions

Introductory	What was the research that you participated in?
Transition	Did you know or hear about the terms chronic oedema or lymphoedema before? How did you feel about having CLLO? And did you notice the oedema in your lower limb?
Key	Before participation, how can you describe your general health? After participation, how can you describe your general health? What is your opinion about the intervention in terms of frequency, intensity and number of sessions? What were the most difficult tasks encountered during your participation? What are the most important aspects you liked in the intervention?
Ending	What do you think if the intervention was more than 12 weeks? Would you recommend this intervention to patients with similar problems? Why or why not?

All interviews were all conducted in Arabic. To assure the accuracy of transcription and eliminate translation-related problem, three elements were considered: back translation, consultation and collaboration with other people during the translation process (Birbili, 2000). The original Arabic transcription was translated into English by one person and then back translated to Arabic by a different person. The researcher did the original Arabic transcription and then translated it to English and an independent transcriber (who spoke with the same Arabic dialect as the participants) translated the English version back to Arabic. The English version was approved when both Arabic versions were matching.

II) Individual interviews with physiotherapists

The interview questions were designed to meet the objectives. The questions were categorized into questions related to knowledge and others related to their current practice. The first version of the interview guide was piloted with three physiotherapists from other hospitals and based on the interviewee feedback one additional question was added. The question was related to therapist understanding about 1-RM definition which is related to exercise progression. The therapist interviews were held between May and June 2018. Individual interviews were held in a meeting room in the rehabilitation department in each hospital. The meeting rooms were private and reserved in advance to avoid interruptions during the interview. Coffee and water were available in order to help create a comfortable and relaxed atmosphere. The interviewer introduced herself initially, explained the purpose of the study and provided an opportunity to ask questions before the interview commenced. She also gave reassurance that attendance was voluntary and that participants were free to withdraw at any time without giving a reason. A set of pre-determined open questions was used to explore potential themes. The option was given for participants to be interviewed in English or Arabic, however, the therapists preferred to be interviewed in English language.

7.3.4 Data analysis

Qualitative data analysis is a continuous, iterative and reflexive process (De Valois, Asprey and Young, 2016) in which “researchers seek to learn about and interpret life experiences” (Sword, 1999, p.270). It requires a researcher’s skills and experience, a blend of inspiration and hard-working commitment (Ritchie and Lewis, 2003). One of the challenges of qualitative research is to ensure

that the analysis is transparent and systematic, and delivers the maximum insight into the meanings expressed by the participants (Creswell and Creswell, 2018).

There are many ways to interpret qualitative data. However, the aim is similar to all i.e. finding meaning within the data, making sense of the evidence and creating files of summarized data (Ritchie and Lewis, 2003). Making sense of data depends, in part, on the method used to organize and categorise data, but it relies mainly on the person's creativity of theoretical thinking and clarity (Greene, Caracelli and Graham, 1989). Many analysis processes are shaped and associated with specific research disciplines together with the philosophical underpinnings (Gale *et al.*, 2013). Regardless of the chosen analysis type, making sense of data is the core of the whole process.

Within a broad family of qualitative analysis methods, inductive reasoning and developing themes is a common characteristic. One of these approaches is the constant comparative method that adopts inductive data coding to produce categories of themes that may help to generate a social theory (Holloway, 2005). Unlike other approaches, data are reviewed across a matrix to facilitate constant systematic comparative style that can refine each theme by systematic comparison across cases is the feature of the framework analysis method (Gale *et al.*, 2013).

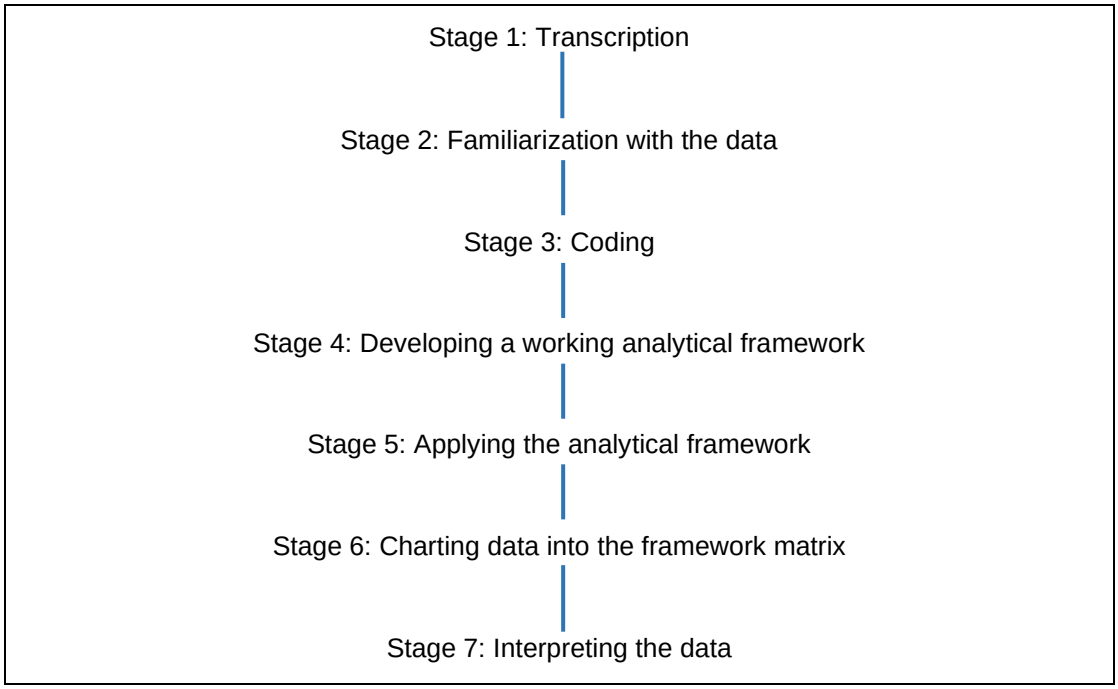
Framework Analysis is a data analysis method that is used to understand raw data in a matrix based analytic system. It was developed during the 1980s at the National Centre for Social Research and is becoming widely popular and used by qualitative researchers (Ritchie and Lewis, 2003). The method allows analysts to move between different levels of "analytical hierarchy" without

"losing sight of the raw data" (ibid, p.220). Every theme is displayed in its own matrix, where each raw sentence or data represents participant's responses, each column symbolizes a different subtopic (subtheme) and each cell summarises data. The matrix shows connections clearly between each individual's views and other aspects of their account (Gale *et al.*, 2013).

I) Framework data analysis procedure

Phase three data were analysed using the Framework Method (Figure 7.1) that is inspired by Ritchie and Lewis (2003). In the first stage, audio recordings were transcribed verbatim by the researcher and then listened to again whilst reading the transcripts in order to check their accuracy. Each transcript was printed and read multiple times until it was felt that the diversity of the data had been understood and a thorough familiarity was gained with the words and ideas. This level represents stage two (Ritchie and Lewis, 2003). Creswell and Plano Clark (2018) suggests that using software programme such as NVivo for coding process can improve the quality of the research, however, due to practical and time constraints of this thesis, the researcher adopted manual analysis instead of the electronic (Ritchie and Lewis, 2003).

Figure 7. 1: Procedure for framework analysis of interview data



While reading the interviews transcripts, the next stage (3) was to assign initial codes by underlining words and sentences that have the same meaning or kept reappearing using the left-hand margin of the paper to describe the content. It was extremely useful as well to note the idea and codes on Post-it Notes in order to arrange and identify similarity of ideas emerging during reading of the transcript. Coding is a vital stage in interpretation where data are arranged into small groups that represent possible categories (Creswell and Plano Clark, 2017). The coding process was first undertaken by the researcher herself and was reviewed later by a different researcher (a member of the supervisory team) to ensure that one particular perspective did not dominate. (Gale *et al.*, 2013). After completion of the coding process, the next stage (4) consisted of developing a working analytical framework. The researchers met to discuss the codes that were assigned to each transcript. Each code was discussed in terms of what it stated about:

- the participant's views and experiences
- how this might be useful in addressing the research aims and
- why these codes were considered important

In general, there was an agreement between the researchers about assignment of codes to the highlighted text. In the minority of instances where different codes were assigned, the differences related to terms used. In one instance, for example, the first researcher coded one piece of dialogue as "feeling the difference" whereas the other researcher thought that the term "motive" described the meaning more accurately. Despite differences in language, both researchers agreed that the participant was talking about elements that motivated her to complete the intervention. Re-visiting the transcripts together resulted in agreement that the code "motives" captured the idea and was applied. The coding index of themes was then entered into an Excel spreadsheet and colour coded which was then used to label data in the transcript in the next stage. After reading and refining the codes, a five-code index related to CLLO participants (Table 7.2) and a three-code index related to physiotherapy participants (Table 7.3) with supporting sub-themes were identified.

Table 7. 2: Stage 4 colour coded index and sub-themes of CLLO Participants

Coding index	Subthemes
1. Life history	1.1 Facing difficulties
	1.2 Limited activities before intervention
2. Motives	2.1 Feeling the difference (physical changes)
	2.2 Psychological changes
	2.3 Experienced new way of treatment
	2.4 Not less, not more
	2.5 Therapeutic relationship
3. Uncertainty	3.1 Lack of knowledge and awareness
	3.2 There is a sense of something
	3.3 Underestimated my power
4. Barriers	4.1 Too much
	4.2 Hard to manage
5. Lift up the voice	5.1 Could be little but it matters
	5.2 No more fears
	5.3 Open to changes

Table 7. 3: Stage 4 colored coded index and sub-themes of physiotherapists participants

Coding index	Subthemes
1. Career pathway	1.1 limited sources
2. Lymphoedema treatment	2.1 No adjustments
	2.2 Time-consuming
	2.3 Slim knowledge
3. Awareness on CLLO in pwMS	3.1 Underestimated other non-oncology patients

Following stage 4, the analytical framework (stage 5) was applied by labelling each transcript using highlighter pens with the same code colours in order to identify similarities between transcripts. Each word and sentence was attached to its related themes and sub-theme (Ritchie and Lewis, 2003). This stage was a labour-intensive and time-consuming exercise because each paragraph had to be read line by line and re-read to decide which label to apply.

After applying labels to the data, the next stage (6) required generating a matrix in which data were charted using Microsoft Excel. The matrix included references to quotations tagged with a page and line references (Table 7.4). Spreadsheets were used to generate the matrix and each one represented a category. In one spreadsheet, each participant occupied one row and each code occupied one column. The data from the transcripts were summarised and inserted into the corresponding cell in the matrix. The challenge in this stage was in the ability to provide a balance between summarizing the data and holding the same feeling and meaning of the original one (Gale *et al.*, 2013).

Table 7. 4: Example of an extraction from the "motives" matrix of CLLO participants

Motives	2.1	2.2
Source	**[Quot.#] feeling the difference (physical changes) (page & line#)**	**[Quot.#] psychological changes (page &line#)**
KK4	[1] I felt my legs started to be stronger (1, 21) [2] When I touch my muscle, I can feel it … it is bigger (1, 24) [3] also I started to feel more in that area (1, 24) [5] I felt the muscle power (2, 39)	[1] Actually I was enjoying attending the sessions (2, 36) [2] myself, I would like to continue and not stop (2, 46)
KK5	[1] After participating I start to be almost normal (3, 73) [2] Because before I knew that after 10 min, I will be tired and fatigue but now much much better (3, 75) [3] every session I can see the improvement (4, 86)	[1] I started to walk without any fear because I do not feel tired or fatigue like before (3, 73) [2] and I started to be passionate about walking (3, 74) [3] I wish if the session was longer (4, 87)
KK7	[1] Everything improve the muscle power and the balance (5, 113) [2] I feel the difference and I improved 80% (5, 125)	[1] I wish if the intervention is longer than this (5, 116)

Abbreviation: Quot.=quotations, KK4, KK5, KK7= participants' ID in the study.
Due to space constraints, this table depicts a sample of one thematic chart which included more columns. The first column in this table is allocated to the participant's ID and the next two columns each represent different sub-themes. Each row relates to one participant.

By reviewing the matrix and making connections between and within the data, final themes were generated, and this was the final stage (7) of the analysis. During the interpretation stage, it was very important to study the narratives of individual cases but also to go beyond this point to develop themes that offered possible justifications for what was happening within and between the data (Ritchie and Lewis, 2003). Going back and forth between the data and interrogating it in many ways helps to develop explanations but this was a time-

consuming yet vital stage of the study. However, one of the benefits of this exercise is that it allowed the analyst to become more familiar with the data which informed her ability and skills in understanding the qualitative data analysis. Three main themes in CLLO participants and two main themes in physiotherapists participants emerged with supporting sub-themes (Table 7.5).

Table 7. 5: Main themes and sub-themes in both CLLO and physiotherapists participants

Themes	Sub-themes
CLLO participants	
1. Life experience before having PRE intervention	1.1. Limited life activities 1.2. Uncertainty and recognition of the need to care
2. Participants' experiences after having PRE intervention	2.1 Reading my physical changes 2.2 Psychological changes associated with PRE intervention 2.3 Finding new and feasible treatment 2.4 Therapeutic relationship 2.5 Unhelpful aspects of the intervention
3. Little changes, but it matters	
Physiotherapists participants	
1. Awareness about CLLO in pwMS	1.1 Knowledge deficits
2. Current lymphoedema practice	2.1 Fear of crossing comfort zone

Abbreviation: PRE= progressive resistance exercise.

It was very important to choose the themes in a way that gave voice to participants' perceptions. Therefore, after considering the final themes, transcripts were re-read to ensure that the themes were an accurate representation of the data. Once confirmed that the data fulfilled the study

objectives, a review process was initiated aiming to enhance the trustworthiness of this phase. One of the supervisors acted as a second reviewer and revised the final themes and sub-themes.

7.3.5 Trustworthiness in phase three

Unlike quantitative research that is concerned with reliability and validity, the robustness of qualitative research is based on authenticity, credibility, transferability, dependability, and conformability to establish trustworthiness.

I) Authenticity

Taking into account that some participants' stories may be influenced by memory impairment, the researcher focussed on the originality of participants' experiences and stories, and acknowledged that participants' narratives represented the truth (Ritchie and Lewis, 2003). The researcher understands her position in reconstruction and presenting of stories and aimed to keep the details to present the stories as truthful accounts.

II) Credibility

As with reliability in quantitative research, Lincoln and Guba (1985) suggest that the term credibility is equally significant for qualitative research (Lincoln and Guba, 1985). Credibility is the agreement and harmony of the findings with reality. The concept is more related to the correctness and calling what is identified by the "right name" (Ritchie and Lewis, 2003). For example, are the finding appropriately identified, truthful and described in depth? The data was transcribed and analysed with the supervisor's guidance to ensure that the interpretations were not coming from one person only (Creswell and Creswell, 2018). The triangulation of the findings from the mixed method study helped to confirm and improve the clarity of the research.

III) Transferability

Rich detailed accounts were provided which may enable other researchers to transfer the findings to other settings. The data were organized meticulously including all the records of analysis and process. All transcripts, Microsoft Word and Excel documents were labelled, and all supervision sessions were documented and uploaded on the PGR record system.

IV) Dependability

Dependability is an important element in trustworthiness process because it makes the findings consistent and repeatable. The researcher must ensure that there are no gaps in data collection, analysis and findings which would allow other researchers to arrive at similar results and conclusions. However, since people's lives are always changing, differences in the findings could be found with the same study methods. In-depth explanations of the study design, data collection methods and organisation were provided earlier in this chapter.

V) Conformability

Each qualitative study is unique in itself, but researchers can take steps such as documenting the procedure for checking and re-checking data, revealing negative instances to ensure conformability (Ritchie and Lewis, 2003). The researcher documented methodological decision making and presented study strengths and limitations.

7.4 Results

The themes and sub-themes were derived by the Framework Analysis (Ritchie and Lewis, 2003). Two groups of participants, CLLO participants (n=10) and physiotherapist participants (n= 6), were interviewed individually to fulfil phase three objectives. All participants are referenced using an ID code to maintain

anonymity. The participants' verbatim extracts are presented and identified using the ID code number which initiated with either KK for King Khalid hospital participants or KF for King Faisal hospital and followed by a number for CLLO participants (example, KK4) and the initial of the first and surname name in the physiotherapists participants (KF, ND).

7.4.1 Participants' demographic characteristics

Both groups were demographically varied, (Table 7.6), the CLLO participants were aged 36 - 55 years and the physiotherapists participants were aged between 29 – 47. The majority of participants in both groups were females and all were of Saudi origin except for one Egyptian participant in the CLLO group. The course of MS seen amongst the CLLO cohort ranged from 9 to 20 years, 70% of them were having RRMS and their disability scored between 4 and 6.5 on the EDSS scale. As seen in Table 7.6, 50% of the CLLO participants and 67% of the physiotherapy participants reported being educated to a bachelor (undergraduate) degree. Only 40% of the CLLO participants were working and 40% were divorced or separated. The experience level of the physiotherapy group varied from one to 19 years.

Table 7. 6: Characteristics of participants

Characteristics	Number
CLLO participants (n= 10)	
Gender	Female: 8 Male: 2
Marital status	Married: 4 Divorced/separated: 4 Widowed: 0 Single: 2
Education	School: 1 Diploma: 4 Degree: 5 Master: 0 PhD: 0
Employment	Working: 4 Retired: 1 Housewife: 2 Unemployed: 3
MS type	RRMS: 7 PPMS: 1 SPMS: 2
EDSS	EDSS 4: 3 EDSS 6: 3 EDSS 5: 1 EDSS 6.5: 2 EDSS 5.5: 1
Physiotherapists participants (n= 6)	
Gender	Female: 5 Male: 1
Education	Diploma: 0 Bachelor degree: 4 Master: 2 PhD: 0
Certified and working in lymphoedema management	*KK, SK: 5 Y **KF, ND: 19 Y *KK, KR: 1 Y **KF, SH: 2 Y *KK, ZM: 11 Y **KF, FM: 9 Y

Abbreviation: MS= multiple sclerosis, EDSS= Expanded Disability Status Scale, RRMS= Relapsing Remitting multiple sclerosis, PPMS= Primary Progressive multiple sclerosis, SPMS= Secondary Progressive multiple sclerosis, Y= years. * King Khaled university hospital participants. ** King Faisal Specialist Hospital and Research Centre participants.

7.4.2 CLLO participant findings

The identified themes and sub-themes as highlighted in Table 7.5 result from participant descriptions of their experiences of the progressive resistance exercises (PRE) used to treat their CLLO. The first theme is life experience before receiving the PRE intervention which included limited life activities, and uncertainty and recognition of the need to care. The second theme is the participants' experiences following the PRE intervention, including reading physical changes, psychological changes associated with PRE, finding a new and feasible treatment, the therapeutic relationship, and unhelpful aspects of the intervention. The final theme is about small changes, although they matter.

I) Life experience before receiving the PRE intervention

Disability level varied between participants; however, similar physical issues and QoL were reported. Encountering daily difficulties as a person with MS that fluctuates from one day to the next limited every life. Moreover, the inexperience and lack of awareness of CLLO added to their pain and poor QoL without understanding the rationale behind this problem which caused further psychological issues. Some participants expressed uncertainty and confusion when they reported the changes in their lower limb and the need to care, which may suggest that there is a lack of knowledge about the impact of CLLO among health care providers.

a) Limited life activities

Trying to avoid normal daily activities such as walking, sit to stand and socializing because of MS symptoms led to a lock down of the person in his/her body and limiting life activities.

Participant KK5 said: "*My walks are limited and any journey with long distances I tried to avoid it.*"

While participant KK4 reported that: "*My general situation is deteriorating with the time because I do have PPMS. I am not using any medication to control it. In my daily life I'm facing a lot of difficulties the MS controlling my life.*"

For some, depending on others or assistive devices such as a walking frame or cane was psychologically frustrating.

Participant KK11 stated that: "*I had heaviness in my legs with difficult walking and imbalance and because of this I am always nervous …. I cannot do 3 to 4 steps without any help*."

Participant KK12 reported that: "I have to *lean or depend on anything like cane to do sit to stand*."

Some interviewees underestimated their ability and muscle power to do new activities.

Participant KK13 said that: "*I never imagine myself able or capable to carry weights.*"

While participant KK4 said that: "*I do have some weight at home belongs to my son when he practices but I never try it.*"

Participant KK5 reported that this was: "*first time …. I never did in my life weights lifting*."

The lack of knowledge was further apparent when participants recognized changes in their lower limb, but their experience was fraught with uncertainty.

b) Uncertainty and recognition of the need to care

All participants reported lack of knowledge and awareness of CLLO.

Participant KK4 stated that "*I heard about it first time from you …. It is a new information for me that people with MS could develop CLLO.*"

Participant KK5 reported that "*it was my first time …. although I am always updated in what is new in the MS field but never ever come across such a terms."*

Participant KK7 said that: "*My first time .... [patient laughed]… even I can't say lymphoedema*."

Participant KK8 was also in a line with the other and said that this was: "*first time to hear from you and I am very thankful for that*."

Uncertainty and confusion over CLLO were also noted. Some participants felt and had a sense that something is not normal, but they linked the feeling to MS.

Participant KK4 said that: "*I felt it was heavy, but I thought because of the MS.*"

Participant KK5 noticed that her feet: "*shifted from a normal form into spongy feeling .... I mean, I cannot complete any walk because of this problem*."

Participant KK10 stated that she felt "*nothing more than heaviness*."

Four participants noticed oedema in their lower limb and reported it to their health care practitioner (HCP), but they had been neglected.

Participant KK9 said that: "*I felt heavily and oedema in my legs …. actually my doctor did not …. he is always in hurry and he never spend time looking at me …. what mater for him is my MRI images and lab results*."

Participant KK11 stated that: *"…. I though it is nothing serious …. I noticed that and I talked to my doctor about it but he never told me that it could be chronic oedema and he did not even give me any medication for it …. the doctor was always rushing out my appointment."*

Participant KK12 reported that she: "*have it from very long time and I remember that my physiotherapist is the one who noticed that and referred me back to my doctor and he did refer me to the vascular clinics …. but I did not go. The appointment was very far, and I was fine at that time …. No one told me it is a serious condition."*

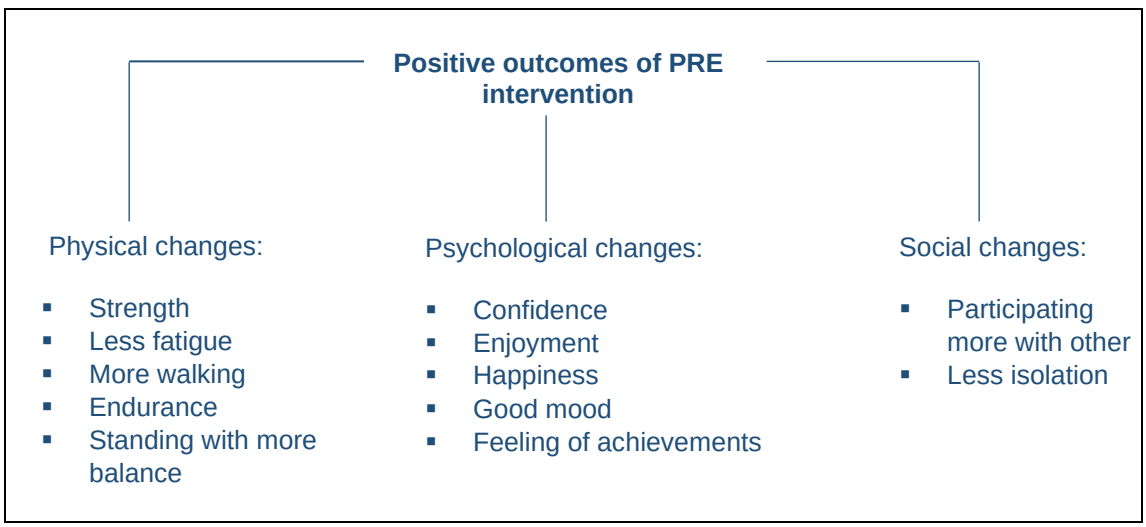
Participant KK13 reported that: "*my doctor did not do anything although I had mention it several times to him*."

Throughout the interviews, confusion and uncertainty were reported. Most participants stated that they did not feel they were given adequate medical attention. This lack of medical awareness among HCPs about CLLO in pwMS could create anxiety among the participants thinking that their MS symptoms are worsening or that the medication is not improving their condition.

II) Participants' experiences after having PRE intervention

For all participants, this was an unknown form of intervention and participants held initial doubts about their capability to perform the exercise. All participants reported that they felt the positive outcomes at the end of the intervention. Furthermore, they reported that the intervention was a positive experience which resulted in physical, psychological, and social changes, as summarised in figure 7.2, which contributed to a positive perception of the intervention.

Figure 7. 2: Participants' positive effects of progressive resistance exercise (PRE)



a) Reading my physical changes

Understanding the problem and the feeling of more control of their body raised the bar of the participants' expectations about their physical capability. The subjective and objective outcomes that the participants experienced throughout the intervention period were markers of success that measure the intervention. Changes in muscle strength, power and mass was expressed by most of the participants.

> Participant KK4 said that: "*I felt my legs started to be stronger …. When I touch my muscle I can feel it, it is bigger …. I felt the power in my muscle."*
>
> *Participant KK7 reported that: "Everything improve the muscle power and the balance.*"
>
> Similarly, participant KK8 said that: "*I felt my muscle become stronger." and participant KK10 reported that: "The general health improved, and I can feel my both legs is lighter now*."

Several participants talked about having their life back to normal and how their physical health would deteriorate if they did not participate in this programme.

> Participants KK5 stated that: "*After participating I start to be almost normal …. every session I can see the improvement …. every day is better than the one before*."
>
> Participant KK4 reported that: "*my situation now is deteriorating, not because of the intervention but because of the disease course itself. This physio sessions for 3 months, which I didn't have such this exercise before, if I did not do it my situation would be worse …. and this is my belief*."
>
> Participant KK12 said that: "*I'm good once I started with you*."

Common physical benefits of this intervention included the ability to walk a longer distance than they used to, sit to stand more easily and feeling more independent during their daily living.

> Participant KK4 said that: "*sit to stand position from my chair started to be easier.*"
>
> Participant KK5 shared her experience as "*before I knew that after 10 minute I will be tired and fatigue but now much much better."*
>
> Participant KK10 stated that she: "*can climb the stairs depending on my both legs rather than one …. I have noticed the benefits*."
>
> Participant KK11 reported that: "*I can do 3 to 4 steps without any help or support."*
>
> Participant KK12 said that: "*I improved a lot …. I started to do sitting and standing more easily than before without leaning or depending on anything like cane …. I'm good once I stared with you."*
>
> Participant KK13 mentioned that: "*I became more active and walk without help.*"
>
> Participant KF14 stated that: "*my ability to walk in terms of time improved, before I can do 10 min and now I can do more …. I liked the results*."

Interestingly, some participants noticed and felt the improvement and the reduction in their swelling.

> Participant KK9 replayed that she "*have been improved in terms of swelling*."
>
> Also participant KK10 reported that: "*The general health improved, and I can feel my both legs are lighter now …. I have noticed the benefits*"
>
> Participant KK11 said that: "*felt better and my leg heaviness became very very light …. swelling of my legs decreased and everyone notice that in both legs and feet …. I saw the changes*."

> Participant KK13 reported that: "*I became more active and walk without help, swelling decreased …. add to this I am more flexible and the tightness that I fell in my legs and knees decreased.*"

One participant (KK4) noticed sensory changes in her lower limb, she said that "*I started to feel more in that area.*" Other participant experienced changes in their balance which reflected positively on their gait.

> Participant KK7 said that: "*Everything improved, the muscle power and the balance.*"
>
> Participant KK11 reported that her: "*gait became easier and everyone around me noticed this.*"
>
> Participant KK13 said that: "*movement became faster and balance improved 80%.*"
>
> While participant KF14 notice "*little improvement in terms of balance*."

Some participants evaluated their physical improvement as percentages. Participant KK13 said that she improved between "*85% to 95%*" and participant KK7 felt "*80%*" improvement. No one spoke about physical discomfort or injury during the intervention period.

b) Psychological changes associated with PRE intervention

The psychological and emotional impact of progressive resistance exercise was described by several participants. Some of them described the psychological benefits as they felt *"psychological comfort*" (participant KK13), "*reaching an achievement*" (participant KF14) and "*enjoying attending the sessions*" (participant KK4).

An improvement in mood and happiness was highlighted as positive results by several participants.

> Participants KK12 said that: "*I'm good once I started with you*."

Participant KF14 reported that she: "*liked the results …. I felt I am reaching an achievement.*"

Participant KK4 expressed her experience by saying: "*myself, I would like to continue and not stop …. I was enjoying attending the sessions*."

Participants KK5 said that: "*every day is better than the one before*."

One participant (KK5) reported feeling of improved confidence and normality, and overcoming her fears: "*After participating I start to be almost normal …. I started to walk without any fear because I do not feel tired or fatigue like before …. I started to be passionate about walking.*"

Feeling the enjoyment from participating in the intervention was also reported. Participant KK4 said that "*I was enjoying attending the sessions*." Also, participant KK9 state that "*rather than sitting in the home with no movement I prefer to come and do this exercise*." Furthermore, the feeling of enjoyment, improved confidence and feeling of normality resulted in more social interaction for some participants. Participant KK5 valued the effects of the intervention on her social life as "*before any journey with long distance*" she "*tried to avoid it*" but after the intervention she "*started to be passionate about walking and I want to attend the *Eid[1] while I'm wearing my high heel.*"

For all participants, this was a new/unknown form of experience, and some of them felt initially uncertain about the effects of this intervention. Participant KK11 said that "*I was looking forward to see the results*", and participant KF14 reported that her "*situation was worse than now*" but after the intervention she "*did improve and liked the results*."

[1] Eid: is a Muslim festival and they celebrate it two times per year.

c) Finding a new and feasible treatment

Participants appreciated that the PRE was an intervention that was new to them. The PRE was seen as a "*convenient*" (participants KK4 KK5, KK8 and KK11), "easy" (participant KK10) and "very nice" (participant KK12) intervention. Several participants expressed their wish to continue after the intervention period ended and also wished that the sessions and timeline were longer.

> Participant KK4 said that: "*I think it is convenient, may be if it is less than that I may not notice any improvement.*"
>
> Participant KK7 stated that: "*I wish if the intervention is longer than this*."
>
> Participant KK5 also said that: "*I wish if the session is longer*."

Moreover, the intervention was seen as a possible form of exercise to learn and perform. Participant KK4 reported that "*carrying weights as an idea did not terrified me*" and participant KF14 said that "*I never imagine myself able or capable to caring weights …. I felt I am reaching an achievement*."

d) Therapeutic relationship

Narratives describe participants' frustrations with their doctor's unfamiliarity when they reported oedema in their legs as highlighted in the sub-theme 'uncertainty and recognition of the need to care'. Most participants reported difficulties in the communication and relationship with their doctors. Difficulties were associated with limited medical awareness and lack of knowledge about CLLO in pwMS. Moreover, the way healthcare messages were delivered to patients by medical doctors was perceived as harsh which was also reported as one of the reasons for poor communication.

> Participant KK12 reported that: "*I'm good once I started with you …. but the physiotherapist before, she told me that I will be on a wheelchair*

if I do not do the exercises … she hurt my feeling a lot …. that's why I hated to come to physio clinic again."

In contrast, good communication during the intervention with the researcher was one reason adherence to the intervention was maintained. The interviews show that beside the new device and the new method of treatment, the therapist-patient relationship was perceived as one of the biggest benefits of the intervention when the participants were asked about "what was the most you like about the intervention?".

Participant KK11 said that: "*I liked you … you have an amazing personality and I pray for you every time I went out of the session."*

Participant KK4 stated: "your personality."

Participant KK12 reported that: "*I'm good once I started with you …. To see you as the most thing I liked.*"

Participant KK13 said that: "*First, I liked you …. you are incredible …. second, the bicycle and weights lifting those moved my joints and muscle a lot and add flexibility and decreased the tightness that I fell in my legs and knees …. do you believe that the sound in my knees disappeared … the sound that I had before …. and I improved 95%*."

Participant KK14 said: "*You doctor, and I felt I am reaching an achievement and I did improve*."

e) Unhelpful aspects of the intervention

The interviews also show the disadvantages of taking part on the intervention when the participants were asked about "What were the most difficulties encountered during your participation?". One area of responses was related to time management specially for the employed participants or carer. One participant (KK11) said: "*nothing but the only difficulty I faced is to manage my time because my work as a teacher".* Another participant (kk9) reported that: "it

might be difficult …. every time *I need to arrange the time based on my husband's working hours …. You know he is the one who brings me to the session.*"

Transportation was also reported as an unhelpful aspect during the intervention.

Participant KK13 stated that: "*traveling to take this session*" was the only difficulty she faced. Also, participant KK12 reported the "t*ransportation*" and participant KK9 stated that "*the difficulty would be in my transportation specially for the one who is going to bring me here*."

All except two participants (KK10, KK14), expressed an interest in participating if the intervention continued for longer than 12 weeks. For those who commented they would not value taking part if the intervention was for longer than 12 weeks reported that "*It might be boring for me*" (participant KK14) or "*it will be a lot*" (participant KK10).

III) Little change but they matter

The positive outcomes were felt by participants, even if the changes were objectively minimal for them the results were satisfying.

> Participant KK11 reported that: "*we are as MS patients look for any changes in our situation even if it just 30% that for us is a record.*"
> Participant KK4 said that: "*even if I did not achieve 100% improvement, at least I can have 50% or 70% improvement and not reach to this oedema*."

The participants through this experience challenged their physical impairments such as lower limb weakness, lack of balance and fatigue, which reflected positively on their fear of trying a new path of treatment. Some participants stated that the satisfaction and improvement they felt would encourage them to

participate in such a programme even if the timeline was longer than 12 weeks. Some participants believed that a longer treatment duration would bring more positive outcomes.

> Participants KK5 said that: "*I will participate, and it will be better than 12 weeks and even the session time I would like to be longer than this ….. I wish if the session was longer.*"
> Participant KK11 stated that: "i*f there is a satisfaction results like now I would do it.*"
>
> Participant KK8 reported that he: "*will come even if it is more than 12 weeks*."
> Participant KK7 was in a line with the other and "*wish if the intervention is longer than this*."

The need for such a treatment was evident. They were passionate to carry out and share their experience with other pwMS.

> Participant KK11 stated that: "*actually I did recommend this treatment already to my MS friends because I saw the changes.*"
> Participant KK8 said that: "*I recommend this treatment for strengthening and feeling light.*"
> While participant KK5 felt that "*it is impossible that people with MS is not doing this treatment.*"

7.4.3 Physiotherapy participant findings

The identified themes and sub-themes highlighted in Table 7.5 result from participants' descriptions of their knowledge and understanding of CLLO in pwMS and the current lymphoedema practice in terms of exercise therapy. The first theme is awareness about CLLO in pwMS which includes knowledge deficits. The second theme is current lymphoedema practice, including the fear of crossing their comfort zone.

I) Awareness about CLLO in pwMS

All of the physiotherapists reported knowledge deficits about CLLO in pwMS. Even those with greater professional experience of lymphoedema management expressed uncertainty in understanding the development of CLLO in pwMS. The knowledge deficits reported seemed to relate to an insufficient theoretical foundation and practical knowledge before and after entering the specialty. Interestingly, all participants were trained by the same certified lymphoedema trainer who completed her training 20 years previously in oncology related lymphoedema and primary lymphoedema. She is the first Saudi Arabian physiotherapist to introduce lymphoedema management in physiotherapy practice. Her scope of practice is mainly with breast cancer-related lymphoedema.

a) Knowledge deficits

All participants articulated that they were unaware of the possibility of developing CLLO in pwMS as a result of immobility or lack of physical activities.

> Participant K.R-KF said: "*No, I never treated MS patient with CLLO*."
>
> Participant Z.M-KK with 11 years' experience in lymphoedema management said: "*no didn't treated MS …. actually, my first time to know they might develop CLLO.*"
>
> Participant N.D-KF stated that: "*for my whole career I didn't receive any referral for treating MS patient with lymphoedema …. mainly 95% of my patients are breast cancer patients.*"
>
> Participant S.K-KK said: "*no I never treat MS patient before*."
>
> Participant F.M-KF: "*for 9 years I didn't receive a referral for MS patient*."
>
> Participant S.H-KF: "*in our hospital, mainly we are treating breast cancer patients and I never have MS patient in my clinic*."

Some participants reported that the information and training provided in the certified lymphoedema therapist course related primarily to breast cancer patients and primary lymphoedema.

> Participant K.R-KF said: "*I was certified one year ago, and the training was in two parts, theoretical and practical and we learned how to treat breast cancer lymphoedema with compression therapy, MLD and CDT*."
>
> Participant S.H-KF: "*I attended an intensive course with (N.) and we did the exam to be certified …. The training we had about anatomy of lymphatic system and the course of lymphoedema and how we can treat the patients with MLD, compression and CDT*."

However, four participants reported that they developed their skills by attending workshops and courses in the USA, the UK and Germany.

> Participant Z.M-KK stated that she had her first training: "*In Riyadh with (N.) as she provided an intensive course about lymphoedema …. Can't remember exactly the content …. this was long time ago…. but it was about oncology …. mainly breast cancer and how we use the CDT, MLD and compression therapy …. I also attended courses in the USA* "
>
> Participant F.M-KF reported that: "*9 years ago …. When I joined the hospital, there was a need for a male therapist in lymphoedema clinics and I got my practice and certificate in the management of lymphedema patients … but also I was attending so many courses online or I travel to build up my skills …. I went to America and Germany to get courses in lymphoedema treatment …. mainly my training related primary lymphoedema and oncology patients."*
>
> Participant S.K-KK said: "*I had a course with (N.) and learned how to diagnose the lymphoedema, the anatomy of lymphatic system and the treatment program such as CDT, MLD and bandaging or compression*

…. But listen I also had a certificate from Germany and also I did my master in the UK and my dissertation was in lymphoedema field."

Participant N.D-KF said that: "*I earned my certificate from America 20 years ago and I became an official trainer in lymphoedema management …. I can't remember exactly but I came across all the area related to lymphoedema*."

Gaps in knowledge were further evident when participants expressed their views about current lymphoedema practice.

II) Current lymphoedema practice

All participants were certified before working with lymphoedema patients. Their knowledge was acquired from courses and workshops after their bachelor's degree. Two participants completed their education and earned their master's degree, one was in the field of breast cancer-related lymphoedema from the UK (participant S.K-KK) and the other participant was related to health care management in Bahrain (participant N.D-KF).

a) Fear of crossing comfort zone

The participants reported that they were treating their patients based on protocol that includes CDT, MLD, compression therapy and exercise. Answering the question to what kind of treatment options they are offering to their patients:

Participant K.R-KF said that: "*MLD, education, home exercise, skin care, compression therapy*."

Participant S.H-KF: "*MLD, education, home exercise, skin care, compression.*"

Participant F.M-KF: "*MLD, compression therapy, active ROM for some of the patients. Exercise only I give it for those who are physical not active.*"

Participant S.K-KK: "*MLD, compression therapy, treadmill, bicycle, home exercise and hydrotherapy for lower limb only. Always the compression therapy is my treatment. Not always I used exercise.*"

Participant Z.M-KK: "*It is depending on the patient's situation either I do CDT or MLD with compression therapy, exercise and education*."

Participant N.D-KF: "*MLD, education, home exercise, skin care, compression therapy.*"

Limitations in knowledge were not only in the participants' awareness about CLLO in pwMS, but also in their practice and thinking out of the box when they face an unfamiliar case.

Participant S.H-KF said that she faced "*only one*" patient that she could not use for her compression therapy as the "*Patients was referring to the clinic with unknown cause of abdominal swelling and pain after uterus cancer. I could not use the compression therapy for her abdomen because fluid was getting out when there is a compression and the fluid was under investigation*."

PI: *what did you use as alternatives?*

Participant S.H-KF: "*nothing, I referred her back to her doctor. I was afraid that if I will do something it might aggravate her situation*."

Participant F.M-KF stated that he could not use the compression therapy with patients that was having a "*cardiac problem or hypertension or allergic to garment such as sarcoma*" and when he asked about what alternatives did he use he said "*depend on the patients may be gentle exercise such as ROM exercise*."

Participant Z.M-KK reported that she faced "*some patients who does have wounds and only used bandages but no garments. Some patient also I cannot use garment with them because they feel uncomfortable and allergic to it."*

PI: *what did you use as alternatives?*

Participant Z.M-KK: "*depend on the patient age, and her welling to do the treatment …. MLD, exercises, education*."

In terms of exercise therapy, fear of crossing their comfort zone and doing what other therapists are doing was reported by some participants.

Participant S.H-KF said that: "*Some of my choice is based on evidence but for the other we do follow same program in the hospital*."

Participant F.M-KF stated that he only uses: "*active ROM and only TheraBand as resistance exercise **….** I don't use weight with my patients …. It might trigger their lymphoedema or could cause pain …. my knowledge is based on courses I attended*."

Participant Z.M-KK said: "*My advised in terms of exercise is just what the other do not based on evidence.*"

The resistance exercise given to patients was only limited to one type of exercise. TheraBand was the only resistance exercise noted which is available in different colours and each has a different intensity which does not need to be calculated.

Participant K.R-KF said: "*Only TheraBand*"

Participant S.H-KF reported that: "*we do follow same program for all our patients which included pumping exercise for hand, active ROM, active assistant with cane for those who has tightness, stretching and strengthening and I used antigravity exercise and isometric. No weight, only TheraBand*."

Participant F.M-KF stated: "*Only TheraBand as a resistance exercise*."

Participant Z.M-KK also said: "*I never used any exercise with weight …. only TheraBand …. I started with the yellow*."

Participant N.D-KF said: "*functional strengthening exercises with TheraBand.*"

One participant (S.K-KK) only reported her use of PRE: "*Just recently this year I used PRE for upper extremity, but with restrictions such as after one-*

month post-operative and this was after I did my master degree in this area …. before I did not use any PRE with my patients."

All participants expressed unfamiliarity with term 1-RM. Participant N.D-KF said that "*… because we do not use weights …. we don't have time to do exercise with patients and we give exercise only as home instruction and without weights.*"

7.5 Discussion

Phase three of this study aimed to identify and explore factors that contribute to successful or unsuccessful PRE from the perspectives of the participants, to explore the physiotherapist knowledge and understanding of CLLO in pwMS and the current lymphoedema practice in terms of exercise therapy.

7.5.1 Perspective of CLLO participants about PRE

The perceptions of ten CLLO participants with MS who participated in PRE for 12 weeks were positive overall with minor undesirable effects which are not related to exacerbation of signs and symptoms of the MS or chronic oedema. Transportation issues and time management required to attend sessions were two unhelpful aspects of the intervention. One way to overcome this is to use tele-rehabilitation which obviates the need to travel (Fjeldstad-Pardo, Thiessen and Pardo, 2018). It could save time and travel costs compared to out-patient rehabilitation (Khan *et al.*, 2015).

All participants showed an interest in participating when questioned about the acceptability of completing an intervention which continues beyond 12 weeks. However, two people reported that longer PRE might be boring or too much for them. Feelings of boredom can be experienced when exercise schedules are not varied (Dodd *et al.*, 2006). Therefore, it is important to introduce different

exercises from time to time to maintain the motivation. No participants reported deterioration in their MS condition, which is in line with other reported studies (as highlighted in Chapter 4), neither did they feel that their oedema increased which indicates the positive effects of the intervention.

Findings reported that there is uncertainty and lack of awareness about CLLO among pwMS which corresponds with Keeley *et al.* (2017). A self-reported survey of pwMS indicates that 38% of the CLLO cases were not recognized by the participants themselves (Keeley *et al.*, 2017). Williams et al. (2004) also undertook interviews with different types of lymphoedema patients and reported uncertainty of some participants who developed swelling, and associated anxiety and illness for many years before being diagnosed. The delay in providing diagnosis occurred due to health care providers' poor understanding and knowledge about lymphoedema and the many different presentations (Williams, Moffatt and Franks, 2004). These findings correspond with the findings of this PhD study, especially the dilemma and feelings of uncertainty and confusion that resulted in the development of anxiety among participants. The natural progression of the condition and the impact of delayed diagnosis and treatment has physical and psychological consequences that can influence participants' QoL. This suggests that different educational materials in written, digital or video format, need to be considered to increase awareness and facilitate early detection and diagnosis of CLLO. In addition, health care providers need to improve their knowledge of the different aetiologies of chronic oedema and lymphoedema and not limit scope of practice to oncology-related patients in order to better support and deliver early treatment to those in need.

The quantitative analysis in the previous chapter was not statically significant in terms of participants' lower limb volume reduction, however, the qualitative findings painted a different picture. Although not experienced by all, some participants reported that they felt the changes in their limb with expressions such as "*my both legs are lighter now*, (KK10)", "*my leg heaviness became very very light …. swelling of my legs decreased* (KK11)" and "*swelling decreased*, (KK13)" which indicate that there was a positive reaction to the intervention. The most likely reason for the disagreement between the findings is the increase in the muscle mass which could mask the reading of volume reduction. This assumption could be supported by most of the participants' responses as they detected an increase in muscle strength and some of noticed the increase in the mass as KK4 said "*I felt my legs started to be stronger …. when I touch my muscle I can feel it, it is bigger*". Moreover, comments from some participants about improvement in their balance, sit to stand, the ability to walk more steps and to walk safely without an aid indicate that there were improvements in muscle strength. These findings are consistent with findings from other studies (chapter 4), showing that the PRE for 12 weeks in pwMS is associated with improved physical outcomes which reflected positively on the participants' adherence. Dodd and colleagues (2006) undertook interviews with 9 pwMS at the end of 10-week of PRE and highlighted that many of the participants valued the physical and psychological improvements which were associated with better exercise adherence (Dodd *et al.*, 2006). This is matched with Clarke and Coote (2015) as participants raised the positive effects of the intervention on fatigue which is the key factor in programme completion (Clarke and Coote, 2015). Like those participants interviewed in both studies, these participants bring about

similar opinions suggesting that reaching participants' expectations is the motive to adhere to the treatment sessions and reaching the desired results.

Moreover, some participants suggest that people who have a good relationship with the therapist and see signs of progression might be more likely to complete the intervention. This assertion is confirmed by findings of Learmonth et al. (2013) whose participants appreciated the support of physiotherapists (Learmonth *et al.*, 2013). Similarly, Clarke and Coote (2015) suggested that verbal encouragement and delivering clear instructions to participants can have a major impact on patient's commitment to complete the treatment (Clarke and Coote, 2015). This suggests that the communication between therapists and patients including educational and verbal encouragement can be one of the factors that can optimise outcomes.

Although so many participants mentioned the value of reaching the researcher and the good relationship with her, however, the fact that the intervention and interviews has done by the same person must be taken into consideration. It can mean that the participants would be less able to present a less favourable impression of the intervention itself because of the positive effect of the relationship. However, to minimize the social desirability bias the aim of phase three was anonymous and the participants was told that their opinions have to be truthful (Jo, 2000).

Although the PRE is an intervention that aims to improve physical functioning, psychological benefits were also reported. The majority of the participants reported significant psychological benefits which mirrored the quantitative findings in phase two in terms of overall improvement in QoL. Words such as comfort, returning to normality and enjoyment were used by several participants

to describe their psychological benefits. This is confirmed by the findings of Dodd et al. (2006) and Learmonth et al. (2013) whose participants reported physiological and social benefits from participating in exercise programmes. Similarly, Clarke and Coote (2015) reported that participating in 12 weeks of exercise improves involvement in leisure hobbies such as gardening which can have secondary benefits for feelings of well-being. However, there is limited evidence in the literature about the psychological benefits of PRE from the perspective of people with CLLO. Further studies are needed to explore this area in greater depth.

Another factor that contributed to the participants' positive experience is the feeling of control and empowerment of their body (De Valois, Asprey and Young, 2016). People with MS experience different physical and psychological impairments during their life that leads them to be socially isolated (Aljumah *et al.*, 2013). The sense of improvement was the motive, as reported by some participants "even if the changes were little, it matters for pwMS". Such feelings as reported in De Valois et al. (2016) study enabled the participants to engage more in social activities such as family and friends' relationships.

Interestingly, none of the participants had prior experience of this type of exercise, therefore it was a novel experience for them. However, participants expectations about the intervention's outcomes were not taken into account, and it would be of interest if all the participants were asked about their expectations of PRE at the baseline and not only at the end of the intervention. This would bring additional information and could help clinicians to understand which aspect is driving the changes in the treatment outcomes. One participant at the beginning of the programme underestimated the physical improvement

that could be gained when she was chatting with the researcher as the participants experienced different MS rehabilitation programme and most of it were under her expectations.

Throughout the intervention programme, the perceived changes acted as the motive to complete the intervention. In addition, the interviews showed that there was an interest in continuing with PRE if it lasted for more than 12 week which reflect that the pwMS are open to changes toward the way of receiving therapy. These findings are consistent with findings of Dodd et al. (2006), 9 participants spoke about their desire to complete the 10-week PRE programme as they liked and believed in its beneficial effects. The results of our qualitative data suggest that PRE is a promising intervention that positively improve pwMS QoL through improving the physical and psychological functioning without provoking an MS attack. The feeling that some participants had regarding their oedema which contradicts our quantitative findings suggests that future research should additionally measure the changes of the water in the tissue and not the only the limb volume size.

7.5.2 Physiotherapist knowledge and understanding of CLLO in pwMS and the current lymphoedema practice

Gaps in knowledge about CLLO in pwMS were reported by all participants. The lack of knowledge among the first medical contacts in Schulze et al. (2018) study, leads to misdiagnosis and under-treatment which impacts on health care outcomes. In addition, it could lead to life threatening consequences for the patients such as cellulitis (Moffatt *et al.*, 2019a). All participants reported that they are mainly treating breast cancer and cancer related lymphoedema patients and their skills, knowledge, and training focus on this population. This

limited practice can translate into a poor detection of non-cancer related patients and delayed treatment, which was confirmed by the ignorance that the CLLO participants felt when they reported their swelling to their physician. This ignorance among health care practitioners (HCPs) could be a result of poor basic education in the university.

In the Kingdom of Saudi Arabia, the existing knowledge gap in lymphoedema practice can be attributed in part to the fact that the field of lymphology is not currently included in undergraduate physiotherapy curricula. The speciality is being developed through individual efforts and through postgraduate education. This finding is consistent with a recent study of worldwide assessment of health personnel dealing with lymphoedema in 208 countries. The study reported that there is insufficient training in this field for Asian, North American and European countries, and lymphology should to be taught in medical school pre-registration in order to bridge the gap in knowledge (Schulze *et al.*, 2018). Davies (2011) also identified that 42% of physiotherapists indicated that teaching simple lymphatic drainage is needed and only 13% of HCPs felt that their lymphoedema education needs were mostly met (Davies, 2011). Unfortunately, many counties are not aware of the importance of this speciality and have not clear national strategy to address this problem which left the field unquantified until now (Stout, Brantus and Moffatt, 2012). This suggests that basic global structure which includes a strong knowledge foundation from an undergraduate level that is evidence-based for chronic oedema and lymphoedema management is needed to promote optimal health outcome for this patient population.

The framed knowledge among the participants pose barriers to their practice. As a result, some participants experienced difficulties in making a decision when they face unfamiliar conditions. Similar to Schulze et al. (2018), the unbalanced education and training among physiotherapists who focused mainly on oncology patients have led to their limited clinical experiences. In addition, limited experiences can drive practitioners to be more inattentive which can lead to misdiagnosis and delayed treatment to those unfamiliar conditions and generate confusion and uncertainty among the patients. This suggests that being a lymphoedema specialist entails a life-long development of skills and refinement of clinical experiences that would stretch the practice to involve a wider spectrum of patients suffering from chronic oedema.

The findings also show that disparities between practice and research related to resistance exercises exist. Fear avoidance behaviours was observed in the interviews, as participants avoided using weights with their patients fearing that it might trigger the lymphoedema. Furthermore, some participants reported that their practice was not evidence-based and they were simply following the hospital protocol. This finding is consistent with Thomas (2018) study, suggesting as a first contact line with patients, HCPs need to provide evidence-based information and tailor the treatment to individual patients' needs. Like other studies, the findings reinforce the need for further education among HCPs and encourage the use of evidence-base practice (Williams, Moffatt and Franks, 2004; Davies, 2011; Stout, Brantus and Moffatt, 2012; Thomas., 2018). Future studies with a larger sample size are needed to ascertain what physiotherapists are currently practicing and advising patients.

7.6 Phase three strengths and limitations

This phase has a number of strengths. It explored for the first time the unique experiences and perceptions of pwMS who suffer from CLLO toward the PRE treatment. The physiotherapists' knowledge of CLLO in pwMS and the current practice in terms of treating chronic oedema were also explored. Furthermore, it addresses the overall effects of the treatment rather than focusing on specific physiological symptoms such as reduction in oedema. Another strength of this phase is the inclusion of unrecognized, undertreated, and under-researched group of people who requires more attention to improve their QoL.

The small sample size in this phase may limit the range of experiences and cannot be generalized to another group. However, it is important to acknowledge that this is a first study that tackled this area and future research with a larger sample size is needed to add to the findings. Further limitation is the lack of data about CLLO participants' concerns about prevention of symptoms deterioration and safety were not expressed in the interviews.

Since the researcher was the one who implemented the intervention and also conducted the interviews, it could be difficult for the CLLO participants to be honest about their opinions. Nevertheless, the continuity might have contributed positively by enabled them to feel relaxed and comfortable about sharing their experiences with the same researcher. There is a risk that the physiotherapists' identifty could be revealed inadvertently, since only 6 were interviewed and these are based in 2 organisations.

7.7 Conclusions

The qualitative data showed that the PRE was experienced to be a feasible and meaningful therapy. The physical and psychological changes that the

participants felt suggest that a PRE program may be a feasible fitness option for people with MS to encourage them to be more physically and psychologically stimulated and reduce the risk of developing CLLO. Participants valued the untraditional way of treatment that facilitated a transformation from disempowerment to feeling in control of their body. This finding highlights the need for qualitative analysis which captures positive effects of PRE that could not be measured by standard quantitative outcomes.

The lack of awareness among health care providers about CLLO in pwMS suggests that this specific gap in knowledge needs to be recognized in order to provide a meaningful treatment plan. Additionally, exploring the current lymphoedema practice in Saudi Arabia may suggest further insight into how to add strengths to our practice to involve more chronic conditions such as non-oncology related lymphoedema. The amount of qualitative data that were generated and the themes that were created warrant further research. In addition, the need to develop educational and information resources for public is recommended to improve the treatment and support pwMS with CLLO.

CHAPTER 8: OVERALL DISCUSSION AND CONCLUSIONS

8.1 Introduction

This mixed methods study was conducted at two centres in Riyadh city, in the Kingdom of Saudi Arabia. This innovative study introduced an intervention for a patient population with two distinct conditions (namely chronic lower leg oedema [CLLO] and multiple sclerosis [MS]) with a wide range of symptoms and different levels of impairments that creates difficulties when trying to tailor safe and convenient interventions.

This PhD study consisted of three distinct phases. Phase one determined the prevalence of (CLLO) in pwMS who reside in the Kingdom of Saudi Arabia and attend the King Khaled University Hospital (KKUH) or King Faisal Specialist Hospital and Research Centre (KFSH&RC). Moreover, this phase determined the main characteristics of those at high risk of developing CLLO and compared the findings with existing evidence. Phase two assessed the effectiveness of Progressive Resistance Exercise (PRE) in the management of CLLO and the impact of CLLO on quality of life (QoL) and pain. Phase three explored participants' experiences and opinions of PRE, and explored physiotherapists' understanding and knowledge of CLLO in pwMS (including current lymphoedema management options). Findings gained from this mixed method study provide a greater 1) exploration of the effects of PRE in treating CLLO in pwMS and 2) understanding of current health care practices.

In phase one, results demonstrated that CLLO is a common problem in pwMS which is under-recognised and under-treated. Similar to Solaro et al. (2006), Arpaia et al. (2010) and Keeley et al. (2017), the findings show that those who are less physically active, of higher age and BMI are more likely to develop

CLLO. However, the prevalence in this study was lower (21%) than that reported previously.

The results of phase two show that there is no significant difference in leg volume from baseline following the intervention, however, the intervention had a significant impact on QoL and pain. Although the findings indicated no reduction in leg volume overall, there was a reduction in the volume of leg segments adjacent to the proximal rather than distal part of the leg. Muscle strength and EDSS improved significantly. This suggests that PRE is a promising therapy that contributes to improving patient QoL, although further research is needed to confirm these results.

Phase three findings corroborate the findings of phase two in terms of physical and psychological changes that the CLLO participants experienced which resulted in an improved QoL. The data show that health care practitioners (HCPs) have a limited knowledge and awareness of CLLO in pwMS and their practice is focused primarily on oncology related patients. The CLLO participants expressed confusion and uncertainty about CLLO and reported that the condition is not recognised by their doctors. The most common motives to complete the intervention were good therapist-patient communication, new methods of treatment and visible signs of improvement.

Within this chapter, the aim of the study and the objectives are revisited to synthesize and discuss findings of this thesis. The main aim of this study was to gain an improved understanding of the prevalence and impact on CLLO in pwMS, and the contribution of progressive resistance exercise on its remediation. The following study objectives shape the structure of this discussion.

1) Measure the prevalence of CLLO in pwMS who are resident in the Kingdom of Saudi Arabia and attendees one of the two hospitals.
2) Determine the main characteristics of those at high risk of developing CLLO.
3) Assess the effectiveness of PRE in the management of CLLO in pwMS who are residents in the Kingdom of Saudi Arabia.
4) Determine the impact of CLLO on pain and Quality of Life (QoL).
5) Identify and explore the factors that contribute to successful or unsuccessful completion of PRE from the perspectives of the participants.
6) Explore the physiotherapists' knowledge and understanding of CLLO in pwMS and the current lymphoedema practice in terms of exercise therapy.

The chapter will also discuss the overall strengths and limitations, implications of the study, recommendations, and overall conclusions.

8.1.1 Measure the prevalence of CLLO in pwMS who are resident in the Kingdom of Saudi Arabia and attendees one of the two hospitals.

The purpose of phase one was to assess the frequency of CLLO in pwMS that has not been studied previously in the Kingdom of Saudi Arabia. The data demonstrated that CLLO is a common problem amongst pwMS. Eight percent of people screened with MS were found to have unrecognized CLLO. This resonates with studies conducted elsewhere (Solaro *et al.*, 2006; Arpaia *et al.*, 2010; Keeley *et al.*, 2017) in England and Italy. However, the study shows a lower prevalence rate compared to published international studies e.g. a prevalence of 45% in MS centre of the university of Genoa and the regional

centre of Italian Multiple Sclerosis Society of Italy (Solaro *et al.*, 2006), 85% in one neurological rehabilitation centre in Southern Italy, and 62% in one hospital in the South of England. This variation between our results and the other studies can be related to the sample characteristics. Participants involved in Solaro et al. (2006), Arpaia et al. (2010) and Keeley et al. (2017) studies were reported to present with more advanced MS symptoms than those screened in this study. The mean EDSS score was 2.4 (±2.0) in 92% of screened pwMS and none of them showed signs of CLLO whereas the mean EDSS scores in other studies were 5.227 (±2.11) in Solaro et al. (2006), >6 in Arpaia et al. (2010) and between 3 and 6 in Keeley et al. (2017). This indicates that patients who present with lower levels of disability and are more physically active are at low risk of developing CLLO.

Although CLLO is a common condition in pwMS, the problem is undiagnosed and under-recognised among HCPs which could have an impact on patient QoL and lead to life-threating consequences such as cellulitis (Moffatt *et al.*, 2019a). Delayed diagnosis leads to delayed treatment which makes the management of the CLLO condition a challenge. The findings of this study demonstrate that the majority of participants did not recognize that they have lower limb oedema which corresponds with a study conducted by Keeley et al. (2017). Lack of knowledge among pwMS about the possibility of developing CLLO and among HCPs in recognizing the condition was confirmed in phase three findings (qualitative phase) which highlights the need to increase awareness and education about this problem. To date, the focus of previous studies has been to estimate the prevalence of CLLO in specific groups of the population, hence, it is important to examine prevalence among a more heterogeneous population.

The scope of this study covers two hospitals in one region; however, the research provides important data that provide a bedrock foundation for future studies in the region.

8.1.2 Determine the main characteristics of those at high risk of developing CLLO.

Although the prevalence of CLLO in pwMS in the Kingdom of Saudi Arabia was lower compared to other studies, the characteristics of those at high risk of developing CLLO were comparable with previous research. Phase one showed that CLLO in pwMS is associated with advanced age, higher obesity and disability levels which corresponds with Solaro et al. (2006), Arpaia et al. (2010) and Keeley et al. (2017) studies. The findings show that pwMS who are of an older age (45 years, SD ±7.6) have 1.093 times higher odds of developing CLLO than those of a younger age. Moreover, patients with a higher BMI (28.8kg/ m^2, SD ±13) and higher level of disability (EDSS 5.4, SD ±1) have 1.047 and 2.735 time higher odds respectively of developing CLLO. However, a statistically significant relationship was not found between CLLO and disease duration (p= 0.140) or between CLLO and stage of MS (p= 0.061 for SPMS and p= 0.909 for PPMS). This is in contrast to Solaro et al. (2006) study who reported that disease duration of 20.5 (±11.3) years and secondary progressive MS (more than 50%) were associated with the development of CLLO.

CLLO in pwMS represents an additional burden to individual lives that further affects patient mobility and reduces their physical activities which culminate in a poor QoL and social isolation. Findings from phase one contribute to the understanding of CLLO prevalence in pwMS and identify the main characteristics of those at high risk of developing CLLO. This knowledge has

the potential to improve health care practices in the Kingdom of Saudi Arabia. Adding a few simple questions such as if the patient has noticed any swelling in lower limb and since when, to a neurological screening test can detect CLLO at an early stage.

CLLO is under-diagnosed, under-researched and under-treated within the MS population at the moment, CLLO treatment options offered in the Kingdom of Saudi Arabia are designed for the treatment of cancer-related CLLO which are not necessarily suitable for non-cancer related CLLO. There is a need to enhance the position of lymphology as a specialty and expand healthcare practitioners' understanding of CLLO which would lead to the development of innovative treatment options for specific CLLO patient groups. To improve the health care practices for this group of people (pwMS who developed CLLO) it is important to understand and acknowledge the causes of CLLO. Therefore, to treat CLLO or to improve CLLO, for the first time this study adopted an intervention that is not based on compression therapy or MLD technique. The phase two intervention was a progressive resistance exercise (PRE) which considered the individuality of each participant and tailored the progressive resistance exercise to each patient.

8.1.3 Assess the effectiveness of Progressive Resistance Exercise (PRE) in the management of CLLO in pwMS who are resident in the Kingdom of Saudi Arabia

The purposes of phase two were to demonstrate the effectiveness of progressive resistance exercise in the management of chronic lower limb oedema in people with multiple sclerosis and to determine the impact of CLLO on pain and quality of life. Circumference-based measurements were used to

estimate limb volume changes from mathematical formula. Compared to pre-intervention, the results show no significant reductions in overall circumference measurements and no significant reductions in the volume after 12 weeks of PRE. However, individual segment volumes responded differently to the intervention. Volume reduction increased in the proximal part of the leg compared to the distal, some areas were stable and other areas increased (more around the bulk of the calf muscle). These findings correspond to some extent with the findings of phase three in which some participants (4 out of 10) reported that they felt changes in their legs. Feelings such as “lightness in the limb” and “swelling reduction” were expressed by some participants which indicate that the intervention may have triggered a positive physiological reaction.

The most likely reason for the difference in findings is the increase in the muscle mass which could mask any volume reduction due to a reduction in oedema in some areas especially in the middle of the leg where our results found the most significant increase. This assumption could be supported by results from phase three since most of the participants reported an increase in muscle strength and some noticed an increase in the mass of the calf. These findings resonated with findings from studies conducted by Dalgas et al. (2010), Dodd et al. (2011) and Medina-Perez et al. (2014) who reported an increase in muscle mass, strength, power, and volume after a PRE programme. It is therefore possible that volume reduction could not be detected because circumference measurements can only reflect superficial changes, but the water content of tissues need to be measured by other measurement tools or devices. Supporting this, phase two also found that muscle strength improved following completion of the

intervention in both plantar-flexion and dorsi-flexion movements which is consistent with an increase in the muscle mass.

Although the reduction in volume was found in areas where tendons of the muscles are located (proximal and distal end of the leg), the reduction was not uniformly distributed. More reduction was notable in the proximal rather than in the distal part of the leg. This finding is consistent with Iker et al. (2019) and Mayrovitz et al. (2007) studies where lower limb lymphoedema was found to be more likely located in the distal part of the participants' extremities. On one hand, the effects of gravity could play a role in accumulating fluid especially because the participants in our study were in a sitting position where gravity is not eliminated and these factors could explain why less volume reduction was noticed in the distal portion. On the other hand, the mechanism of PRE with calf muscle and venous hemodynamic around this area could explain this finding (Keilani *et al.*, 2016). PRE in this study mainly targeted the leg muscle and not the foot muscles to support lymphatic flow in the leg through calf muscle pumping mechanism. Because the foot muscles did not bear weight during the intervention, the veins were not compressed and the venous foot pump mechanism may not have been fully activated which could explain less volume reduction around the distal part (Corley *et al.*, 2010).

As highlighted in chapter 6, conducting this study within the pwMS population with CLLO was challenging since the outcomes of the intervention could affect both the disability due to MS and the chronic oedema. Although there was no statistically significant reduction in leg volume, the improvement in muscle weakness due to MS had improved. The striking issue is the improvement in the pwMS EDSS without a real attempt of this study to benefit participants

functionally. However, the sense of physical changes in terms of oedema that the participants described in phase three cannot be neglected. Previous studies on cancer-related lower limb lymphoedema that aimed to assess the effects of PRE on developing or aggravating lymphoedema reported that the resistance exercise neither contributed to the development of lymphoedema in those at high risk of developing the condition nor worsened lymphoedema in those who already presented with the condition (Mayrovitz *et al.*, 2007; Katz *et al.*, 2010). This could improve our understanding of the result i.e., the increase in volume could be related to the hypertrophied muscle (muscle mass) and not the fluid. Further, unmeasured variables such as water content in tissues may account for the difference and future studies should consider these variables.

8.1.4 determine the impact of CLLO on pain and Quality of Life (QoL)

Although the circumference and volume reduction were not statistically significant in this study, findings show a positive impact on QoL and pain. Undoubtedly, the contribution of MS to a person's QoL in this study should not be neglected. The improvement in muscle strength and EDSS score indicates that the MS might have an impact on pain and QoL, however, measuring QoL in pwMS was not the focus of this study.

Given that participants in this study have combined impairments (MS and CLLO), this would lead to the possibility that the combination of both conditions will negatively impact their QoL. The findings from phase two were corroborated by the findings in phase three. There was evidence that participants experience a low QoL and pain which affect their activity of daily living which is in agreement with other existing knowledge published in previous studies (Greene and Meskell, 2017; Tuğral, Virén and Bakar, 2017; Dai *et al.*, 2019; Mercier *et*

al., 2019) in various countries. Some participants in phase three reported that they were actively trying to avoid certain daily activities such as walking, sitting to standing and socializing before they started the intervention to avoid the deterioration in MS symptoms which limited their life activities. In addition, participants stated that they were depending on others or assistance tools such as a walker or a cane to manage their activities of daily living which was psychologically frustrating. Before the intervention, comparing the LYMQOL scores with other studies (Mercier et al., 2019 and Dai et al., 2019), our findings showed worse QoL scores in symptoms domain, function domain and overall VAS. This may support the suggestion that CLLO in pwMS can have significant physical consequences which can complicate and challenge the performance of patient's daily activities.

A combined analysis of both the quantitative and qualitative data post-intervention showed that participants improved their physical, psychological, and social well-being. All participants showed changes in their pain score, muscle strength and symptom severity (EDSS) which reflected positively on their QoL. These findings may indicate that PRE is a treatment that reduces pain and MS symptom severity which then subsequently improves QoL, however, future research is needed to test this theory.

8.1.5 Identify and explore the factors that contribute to successful or unsuccessful of PRE from the perspectives of the participants

Phase three of this study aimed to identify and explore factors that contribute to successful or unsuccessful PRE from the perspectives of the participants. The perceptions of ten CLLO participants with MS were positive overall, a few participants reported minor undesirable aspects of the intervention. As

highlighted in chapter 7, the unhelpful aspects concerned transport and time issues related to session attendance. These aspects however did not affect adherence to the intervention. Phase two showed that 97% of participants completed the median number of sessions i.e., 23.21/24 sessions. This finding corresponds with previous research that reported 92%, 99%, 99% and 95% respectively (Dodd *et al.*, 2006; Dalgas *et al.*, 2009, 2010; Medina-Perez *et al.*, 2014).

Participants' high commitment to the completion of the intervention could be linked to many factors. Findings in phase three demonstrated that 1) the positive therapeutic relationship between the participants and the researcher, and 2) participants' sense of physical and psychological improvements were the drivers for the participants to continue with the intervention. In addition, 3) achieving patient's expectations can also contribute to the adherence to treatment sessions and obtaining the desired results. Evidence in the literature is consistent with these findings which suggest that HCPs should consider these key factors during clinical practice to achieve better patients' outcomes.

As part of their studies Dodd and colleagues (2006), and Clarke and Coote (2015) undertook interviews with pwMS at the end of PRE. Both studies report that the intervention had a positive impact on participants' physical and psychological well-being which contributed to the programme completion. Learmonth et al. (2013) study concluded that patients who have a good relationship with their therapist and see signs of progression may be more likely to complete the intervention. Moreover, verbal encouragement and delivery of clear instructions to participants can have a major impact on patient's commitment to completion of the treatment plan as highlighted by Clarke and

Coote (2015). In order to optimise patient's outcomes and enable changes in clinical practice, a balanced communication that includes educational and verbal encouragement, recognition of individual needs and expectations, and involvement of patients in tracking their changes must be taken into account when providing treatment.

Another factor that contributed to participants' positive experience is the feeling of control and empowerment of their body (De Valois, Asprey and Young, 2016). People with MS experience different physical and psychological impairments during their life that leads to social isolation (Aljumah *et al.*, 2013). The sense of improvement was the motive, as reported by some participants "even if the changes were little, it matters for pwMS". Such feelings as reported in De Valois et al. (2016) study enabled the participants to engage more in social activities such as fostering relationships with family and friends.

Interestingly, all participants except two showed interest in participating in an intervention that would continue beyond 12 weeks. Those two participants who were not interested reported that longer PRE might be boring or too much for them which resonated with findings from Dodd et al. (2006) study. Feelings of boredom can be experienced when exercise schedules are not varied (Dodd *et al.*, 2006). It is therefore important to propose different exercises from time to time to maintain patients' interest and motivation. The high adherence levels and determination to complete the intervention in this study may be explained by the progressive nature of the exercises that progressed in load, sets and repetitions.

Participants in phase three reported that there is uncertainty and lack of awareness about CLLO which corresponds with Keeley *et al.* (2017). Phase two

results indicate that 81% of participants with CLLO did not recognize the swelling which is almost double the results in Keeley et al. (2017) self-reported pwMS study where 38% of participants were not aware of their swelling. The participants' lack of awareness is linked to the poor understanding and knowledge about chronic oedema in pwMS among HCPs as indicated in the qualitative phase, which is in line with Williams et al. (2004). Lack of awareness of CLLO can result in delayed diagnosis, progression of chronic oedema and the development of anxiety (William, Moffatt and Franks, 2004). The natural progression of CLLO and the impact of delayed diagnosis and treatment has physical and psychological consequences that can influence participants' QoL. As highlighted before, some participants reported poor QoL, anxiety and psychological frustration which led to life adjustments to cope with the pain and impairments. This suggests that health care providers need to improve their knowledge of the different aetiologies of chronic oedema and lymphoedema and to not limit the scope of practice to oncology-related patients in order to better support and deliver early treatment to those in need. In addition, different educational materials are needed to increase the awareness of CLLO among pwMS. These recommendations can save patients from the development of feelings of confusion, uncertainty, and anxiety due to the CLLO changes.

The quantitative analysis in the previous chapter did not show statically significant findings in terms of participants' lower limb volume reduction, however, the qualitative findings showed a different picture. Although not experienced by all, some participants reported that they felt changes in their limb. Phrases such as "both legs are lighter now", "leg heaviness became very very light" and "swelling decreased" were reported. Importantly, none of the ten

participants articulated that they felt an increase in their oedema which corresponds with Mayrovitz et al. (2007) and Katz et al. (2010) research. Although bulkiness around calf muscle was reported by a few participants, the increase was linked it to the improvement in their muscle strength. Comments from some participants about improvement in their balance, the ability to sit to stand, and their ability to walk more steps and to walk safely without an aid indicate that there were improvements in muscle strength. These findings correspond with the quantitative findings in phase two that reports improvement in muscle strength and EDSS after the completion of the intervention. Furthermore, the data identified that no participants reported deterioration in their MS condition, which is consistent with other studies (Dalgas et al., 2009; Dalgas et al., 2010; Medina-Perez et al., 2014; Kjolhede et al., 2014) that described the PRE as a safe and tolerable treatment for pwMS patients.

Even though the PRE aimed to improve physical functioning, psychological benefits were also reported. The majority of participants reported significant psychological benefits and described these benefits in words such as ‘comfort’, ‘returning to normality’ and ‘enjoyment’. These findings correspond with the findings of Dodd et al. (2006), Learmonth et al. (2013) and Clarke and Coote (2015) whose participants reported not only physiological but also secondary psychological and social benefits from participating in exercise programmes. Currently, there is a limited evidence in the literature about the psychological benefits of PRE from the perspective of people with CLLO. Further studies are needed to explore this area in greater depth.

None of the participants had a prior experience of this type of exercise, therefore it was a novel experience for them. Participants’ expectations about the

outcomes of the intervention were not taken into account, however, it would be of interest if all the participants were asked about their expectations of PRE in the beginning and not only at the end of the intervention. This would provide additional insights and could help clinicians to understand which aspects are driving the changes in the treatment outcomes.

Throughout the intervention programme, the perceived changes acted as the driver to complete the intervention. In addition, the interviews showed that there was an interest in continuing with PRE if it lasted for more than 12 weeks. This finding shows that pwMS patients are open to changes in the way how their treatment is delivered. Results from the qualitative study suggest that PRE is a promising intervention that positively improve pwMS' QoL through improving the physical and psychological functioning without provoking an MS attack. The feeling that some participants expressed regarding their oedema contradicts our quantitative findings. Future research should additionally measure changes in the tissue water content and not the only changes in the limb volume.

8.1.6 Explore the physiotherapists knowledge and understanding of CLLO in pwMS and the current lymphoedema practice in terms of exercise therapy.

When the diagnosis and treatment were delayed, CLLO participants reported feeling of confusion and uncertainty. Findings in Phase Three showed that there were gaps in knowledge about CLLO in pwMS among all physiotherapists which resulted in physiological and psychological consequences that negatively impacted patients' QoL. These findings resonate with Schulze et al. (2018) findings who found that the lack of knowledge among the first medical contacts led to misdiagnosis and under-treatment which impacted on patient's health

care outcomes. A recent study (Moffatt *et al.*, 2019a) described the costs of delayed diagnosis and complications such as irreversible tissue changes or chronic wounds for CO patients.

All participants reported that they are mainly treating breast cancer and cancer related lymphoedema patients and their skills, knowledge, and training focus on this patient population. The limited focus of clinicians' practice can translate into a poor detection of non-cancer related CO and delayed treatment, which was confirmed by CLLO participants who felt their clinicians had a poor understanding of CO when they reported their swelling to them. This inexperience among health care practitioners (HCPs) could be a result of poor basic education in the university as highlighted previously. The existing knowledge limitations in lymphoedema practice can be attributed in part to the fact that the field of lymphology is not currently included in undergraduate physiotherapy curricula in the Kingdom of Saudi Arabia (KSA). The speciality is being developed through individual efforts and through postgraduate education. Current gaps in the educational system in the KSA are in line with other countries such as in Oceania, North America and Africa as indicated by Schulze et al. (2018) and Scotland in Davies (2011), who both found that undergraduate healthcare students received insufficient training in this field of lymphology. Unfortunately, many counties are not aware of the importance of this speciality and do not have a clear plan to address this pedagogical problem which left the field of lymphology unquantified until now (Stout, Brantus and Moffatt, 2012). Regardless of the potential reasons of knowledge limitations among HCPs, further education is needed to address the issue and promote optimal health outcomes for this patient population.

Furthermore, the limited knowledge among the participants poses barriers to the development of their practice. Unbalanced education and training among physiotherapists led to the restriction of their clinical experiences. The data show that some participants experienced difficulties in making decisions when they face unfamiliar conditions. This may generate confusion, distrust and uncertainty among patients and their HCPs. Being a lymphoedema specialist entails a life-long development of skills and refinement of clinical experiences that would expand their practice to involve a wider spectrum of patients suffering from chronic oedema.

This phase showed contrasting findings relating to the perception of resistance exercise and their practice by physiotherapists. In the qualitative interviews, physiotherapists did not state they avoid resistance exercises with their patients. However, when later asked about prescribing weights exercise to their patients, physiotherapists reported feelings of fear about whether weights exercise could trigger their patients' lymphoedema. Their fear of triggering lymphoedema led to the avoidance of using weight exercises. Even though there is a plethora of reliable evidence advocating the positive effects of resistance exercise on lymphoedema, disparities between practice and research related to resistance exercises exist which resonates with Thomas (2018) study. Moreover, some participants reported that their practice was not evidence-based, and they were simply following the hospital protocol which is consistent with Thomas (2018) findings that suggest that HCPs need to provide evidence-based and patient-centred care to meet individual patients' needs. Like other studies, Phase three findings reinforce the need for further education among HCPs and encourage the use of evidence-base practice (Williams,

Moffatt and Franks, 2004; Davies, 2011; Stout, Brantus and Moffatt, 2012; Thomas, 2018). Future studies need to ascertain what physiotherapists are currently practicing and advise patients and carers.

8.2 Overall Strengths and Limitations

Despite the challenges of this study, the study provides a template for future research and could be used as a guide to start a discussion about early diagnosis and treatment for CLLO in pwMS. One of the strengths of this study is the chosen mixed-methods study design. Gathering data through quantitative and qualitative methods enabled triangulation and developed our understanding of the studied phenomena.

Each phase of the study however had its limitations. In phase one, the prevalence study was conducted in two hospitals in one city. The findings from the prevalence study are specific to the geographical location and type of setting (hospital) and thus cannot be applied to the population of the Kingdom of Saudi Arabia (KSA). Conducting national prevalence studies is resource-expensive and time-consuming and would require a large research team. A population prevalence study was not the focus of this research. However, the fact that there is no national study of CLLO in pwMS in the KSA confirms the need for further prevalence studies that would map the issue and propose steps forward to the development of best clinical practice.

The sample sizes of the quantitative and qualitative studies in this PhD study were small, therefore, the findings should be interpreted with caution and cannot be generalized to other groups. Additionally, the researcher was the one who delivered and analysed both the quantitative and qualitative studies which means that the participants might be reluctant to present a less favourable

impression of the intervention during the interview. The researcher was unable to include neuro-immunology doctors to explore their knowledge of CLLO in pwMS. Due to time restrictions, the views and knowledge base of neuro-immunology doctors could not be presented in this study. Therefore, future studies need to consider involving their knowledge and awareness about CLLO in pwMS.

The researcher also acknowledges that it would have been of interest to have carried out interviews with the CLLO participants at the beginning of the intervention and compare any changes in opinions and expectations with the views expressed at the end of the intervention. Although 4 participants out of 10 did not participate in individual interviews that did not reduce the credibility of the qualitative study because saturation of the themes was reached. To strengthen future studies it may be pertinent to include a control group, involve a multi-disciplinary lymphoedema team e.g. nurses, doctors and social workers, and utilise additional limb volume measurements that can detect changes in the water content in the studied limbs.

8.3 Implications for Clinical Practice and Research

The results of this study have important implications for future research, education, and clinical practice for health care professionals. This section delivers the implications of phase one, two and three for better clinical practice and research.

8.3.1 Future research directions

This study is the first evidence of the effects of resistance exercise on CLLO in pwMS. Findings from this study suggest that more research is needed in pwMS

with CLLO. Suggestions on topics of future research include but are not limited to:

- Increase the number of chronic oedema and lymphoedema prevalence studies in the Kingdom of Saudi Arabia in order to improve our health care services and access hard-to-reach patients that require special and urgent care.
- More randomized controlled trials comparing different PRE parameters such as dose, frequency, intensity, and timing and determine which parameter has a positive impact on CLLO.
- The collection of longitudinal data in CLLO populations with MS to establish the need for long-term care.
- Use of more specific outcome measures that can detect the reduction in CLLO especially the water content of tissue.
- Future studies may assess when the responses to PRE emerge during the progression programme.
- Focus on interventional studies that involve pwMS patients with early stages of the disease who are able to participate in high level exercises.
- Further research examining whether there are methods to prevent the development of CLLO and early detection of risk factors that may lead to the development of CLLO.
- Further qualitative research exploring patients' and carers' perspectives that consider social and QoL domains.
- Finally, future research in CLLO in pwMS should focus on improving the methodological aspects such as large sample sizes and long-term follow-up.

8.3.2 Implications for practitioners

Chronic lower limb oedema (CLLO) in pwMS is a complex and challenging condition. Evidenced-based knowledge and awareness among HCPs needs to be increased and developed to enable people with different types of chronic oedema and lymphoedema to be treated and face less uncertainty and confusion. In addition, the definition of chronic oedema needs to be specified and adopted in the KSA and take into account non-oncology related lymphoedema. Further education for HCPs is needed as the sample of the physiotherapists in this study showed knowledge deficits and practice governed by fear of triggering oedema rather than delivery of evidence-based practice. HCPs should understand that the practice must not be based on “one size fits all” and treatment should be tailored to individual needs. In addition, they need to enhance their skills to screen those with early symptoms of chronic oedema in order to provide early treatment.

This study adds to previous evidence which suggested that pwMS with a low physical activity level, long disease duration and an EDSS score above 3 are at high risk of developing CLLO. Therefore, professionals must consider regular monitoring and conducting a full assessment with early detection and intervention. Early detection with early intervention e.g., PRE is likely to reduce the risk of worsening CLLO, however, longer and larger study is required to confirm this finding. The measures must not only limit the volume of swelling but should also be extended to address psychological and social well-being. Moreover, patient involvement has to be considered as well to enable both professionals and patients to reach optimal and feasible treatment outcomes.

This study identified the need for ongoing information and support for pwMS and carers. All health care professionals must educate their patients about early signs and symptoms of CLLO and how to access specialised lymphoedema services.

8.3.3 Implications for education

Bridging the gap between education and practice is important, so that HCPs are ready to treat their patients with confidence using evidence-based practice. In the KSA undergraduate healthcare courses should be assessed and gaps in CO education should be addressed to provide students with the necessary knowledge and skills.

In terms of patient education, different forms of educational materials must be provided such as video films and webinars to deliver information in an attractive and easy-to-understand way. Sharing patients' experiences through written publications or face-to-face encounters such as webinars or conferences can strength the educational tool.

8.4 Overall Conclusion

In this thesis, the systematic review summarised the prevalence of CLLO in pwMS demonstrating that CLLO is a common, unrecognized, and under-treated problem which requires more attention from the health care system. Our analysis shows that the frequency of CLLO in the Kingdom of Saudi Arabia is lower than in other countries, however, early detection and treatment of CLLO can prevent patients from developing secondary conditions such as acute infection and permanent damage. Progressive resistance exercise (PRE) in the systematic review study was found to be safe, tolerable, and effective for the development of muscle strength in pwMS.

Although the results from the quantitative study show that PRE had no effect on the overall CLLO in pwMS, patient QoL and pain improved significantly after the intervention. The qualitative data showed important improvements in patients' physical and psychological well-being; however, this finding was not confirmed by statistical analysis. Meaning that a larger quantitative future study is needed to confirm the finding of the qualitative data. The lack of awareness among health care providers about CLLO in pwMS suggests that this specific gap in knowledge needs to be recognized in order to provide a meaningful treatment plan.

This study used a single measurement method to capture changes in limb volume, however, given the small sample size this study was unlikely to detect subtle changes in CLLO in pwMS. Further research is needed with larger samples and more sensitive measurements that can detect the water content in tissue beside muscle mass. This mixed methods approach offers a powerful tool and useful framework that contributed to the illumination of clinical practice and improvement of policy.

8.5 Recommendations for Changing Practice

All MS patients who are undergoing medical follow-up in MS clinics should receive information about CLLO, especially if the person is at a risk of developing the condition. CLLO is a progressive condition, however, it can be maintained and controlled when diagnosed and treated in a timely manner. Routine neurological visits should include simple screening questions to detect and diagnose chronic oedema at an early stage to avoid potential complications. Findings from phase three reported that participants (physiotherapists) possess a limited knowledge of CO and its consequences.

Providing information verbally alone is not sufficient because some pwMS may have difficulties with memory, it is therefore important to provide information about CLLO in alternative formats (such as written text, audio or video files). Leaflets should be available in many locations not only inside the clinic but also in the waiting area. The language used must be simple delivering clear messages. The leaflet may include a patient story and should also promote the benefits of exercise and good nutrition. The information materials must be reviewed from time to time and updated if based on evidence-based practice.

Currently, the evidence and knowledge of the beneficial effects of exercise in pwMS with CLLO is insufficient. Added to this, timing of when starting the exercise is also slipped and less attention is given to this aspect. Therefore, interprofessional working is required between doctors and physiotherapists to serve each individual based on their needs. MS patients must understand the rationale behind the timing and the type of exercise.

This study has identified the scarcity of knowledge about CLLO in pwMS among physiotherapists. HCPs should be able to access different national and international educational resources such as accredited educational courses, conferences, and workshops to develop their skills and improve their knowledge. Furthermore, educational systems for undergraduate and postgraduate students should be re-assessed and improved to reduce gaps in the curriculum.

To initiate improvement in knowledge, I would recommend launching an awareness campaign for HCPs in hospitals in different KSA regions to reach front line practitioners. Moreover, the campaign should also be communicated via social media to reach more healthcare professional and patient groups.

8.6 Dissemination of the Study Findings

Phase two findings of this study were presented at the Skin Integrity International Summer School at the University of Nottingham in September 2017, at the University of Tokyo, Japan in August 2018, and at Nottingham Trent University in September 2019. In 2019, the findings were also presented at the 7th International Conference & Exhibition on Physiotherapy & Physical Rehabilitation in Italy in March, and the 9th International Lymphoedema Framework (ILF) conference in the USA in June.

In January 2020, the researcher was invited to become the lymphoedema research chair in the King Saud University to support and oversee research that can contribute to the improvement of current lymphoedema practice and education. However, because of the COVID-19 pandemic the research work was postponed to October 2020. Once the thesis is complete, the study results will be prepared for submission to International Scientific Indexing (ISI) journals.

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Appendices

Table of Appendices

Appendix 1: Ethical approval from King Khalid university hospital (KKUH)

King Saud University (034)
P.O. Box 7805 Riyadh 1172
Tel.: +966 11 4670011
Fax: +966 11 4671992
http://medicalcity.ksu.edu.sa

جامعة الملك سعود (٠٣٤)
ص.ب ٧٨٠٥ الرياض ١١٤٧٢
هاتف: ٤٦٧٠٠١١ ١١ ٩٦٦+
فاكس: ٤٦٧١٩٩٢ ١١ ٩٦٦+

جامعة الملك سعود
King Saud University

المدينة الطبية الجامعية

13.12.2017 (25.03.1439)
Ref. No. 17/0984/IRB

To: **Ms. Asma Abdullatif Alderaa**
Lecturer
King Saud University College of Applied Medical Sciences
Department of Rehabilitation
Email: aalderaa@ksu.edu.sa, Deraa4_pt@yahoo.com
Principal Investigator

Cc: Mrs. Hind Alenazy – Halenazy@ksu.edu.sa
Mr. Nawaf Alzain – nalzain@ksu.edu.sa
Co-Investigators

Subject: **Approval of Research Project No. E-17-2733**
Study Title: "Chronic Lower Limb Oedema in a Population of Saudi Arabian Residents with Multiple Sclerosis: An Evaluation of Progressive Resistance Exercise"
Type of Review: Full-Board
Date of Approval: 07 December 2017
Date of Expiry: 13 December 2018

Dear Ms. Asma Abdullatif Alderaa,

I am pleased to inform you that your submitted proposal with the above-mentioned title was **approved** following a full-board review at the IRB Meeting 03 (Academic Year 1438-1439) held on 07 December 2017 (19 Rabi-I 1439). You are now granted permission to conduct this study as approved by the IRB.

Please be informed that in conducting this study, you as the principal investigator, are required to abide by the rules and regulations of the Government of Saudi Arabia, the KSUMC IRB policies and procedures and the ICH-GCP Guidelines. This approval shall remain valid until the expiry date noted above assuming timely and acceptable responses from the IRB's periodic requests for surveillance and monitoring information, with the following terms and conditions:

1. **Modifications to Research/ Amendments to the approved project:** any modifications to the research (including changes to the informed consent document(s) must receive IRB approval prior to implementation of the changes. Substantial variations may require new submission.
2. **Annual Reports:** continued approval of this project is dependent on the submission of annual reports. If you wish to have your protocol approved for continuation, please submit a completed request for reapproval of an approved protocol form (KSU-IRB 017E) at least 30 days before the expiry date. Failure to receive approval for continuation before the expiration date will result in automatic suspension of the approval of this protocol on the expiration date. Information collected

الرقم
التاريخ
المرفقات

Kingdom of Saudi Arabia
King Saud University (034)
P.O. Box 7805 Riyadh 1172
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http://medicalcity.ksu.edu.sa

المملكة العربية السعودية
جامعة الملك سعود (٣٤)
ص.ب ٧٨٠٥ الرياض ١١٤٧٢
هاتف: ٠١١ ٤٦٧٠٠١١ +٩٦٦
فاكس: ٠١١ ٤٦٧١٩٩٢ +٩٦٦

جامعة الملك سعود
King Saud University

المدينة الطبية الجامعية

following suspension is unapproved research and can never be reported or published as research data.

3. All unforeseen events that might affect continued ethical acceptability of the project should be reported to the IRB as soon as possible.
4. Any serious unexpected adverse events should be reported within 48 hours (2 days).
5. Personal identifying data should only be collected when necessary for research.
6. Secondary disclosure of personal identifiable data is not allowed.
7. **Monitoring:** projects may be subject to an audit or any other form of monitoring by the IRB at any time.
8. **Retention and storage of data:** the PI is responsible for the storage and retention of original data pertaining to the project for a minimum period of five (5) years. Data should be stored securely so that a few authorized users are permitted access to the database.
9. **Future correspondence:** please quote the project number and project title above in any further correspondence.

The IRB is registered with the Office for Human Research Protection (OHRP) with OHRP Institution Registration No.: IORG0006829, OHRP IRB Registration No.: IRB00008189 and IRB KACST Registration No.: HA-01-R-002. It is authorized to conduct the ethical review of clinical studies and operates in accordance with ICH-GCP Guidelines and all applicable national/local and institutional regulations and guidelines which govern Good Clinical Practices.

We wish you success in your research and request you to keep the IRB informed about the progress of the study on a regular basis by submitting a *Study Progress Report* every 6 months and a *Final Report* when the study has been completed.

Thank you!

Sincerely yours,

Dr. Ayman Al-Eyadhy
Chairman of IRB
Health Sciences Colleges Research on Human Subjects
King Saud University College of Medicine
P. O. B ox 7805 Riyadh 11472 K.S.A.
Email: aleyadhy@ksu.edu.sa

/rubie

Appendix 2: Ethical approval from King Faisal specialist hospital & research centre (KFSH & RC)

مستشفى الملك فيصل التخصصي ومركز الأبحاث
King Faisal Specialist Hospital & Research Centre
Gen. Org. مؤسسة عامة

Office of Research Affairs
☎24528 🖷 27894 ✉MBC 03

INTERNAL MEMORANDUM

TO: May Minkabou
Clinical Research Physical Therapist
Physical Therapy Department

DATE: 25 Jumada AlThani 1439
13 March 2018

FROM: Hassan Al Eid, MD
Deputy Chairman, Clinical Research Committee
Office of Research Affairs

REF: ORA/0257/39

SUBJECT: Project # 2181 021
A Pilot Evaluation of Progressive Resistance Exercise in the Management of Chronic Lower Limb Oedema in A Population of Saudi Arabian Residents with Multiple Sclerosis

Further to our memo (Ref: ORA/0247/39 dated 07 March 2018), your email (received by the Office of Research Affair (ORA) on 08 March 2018) as reply to the Clinical Research Committee (CRC) concern was reviewed by the Committee on 12 March 2018.

It is my pleasure to inform you that the Committee has accepted the reply as submitted and recommended the proposal for approval.

I would like to take this opportunity to congratulate you on behalf the CRC; I wish you the best in your research endeavors.

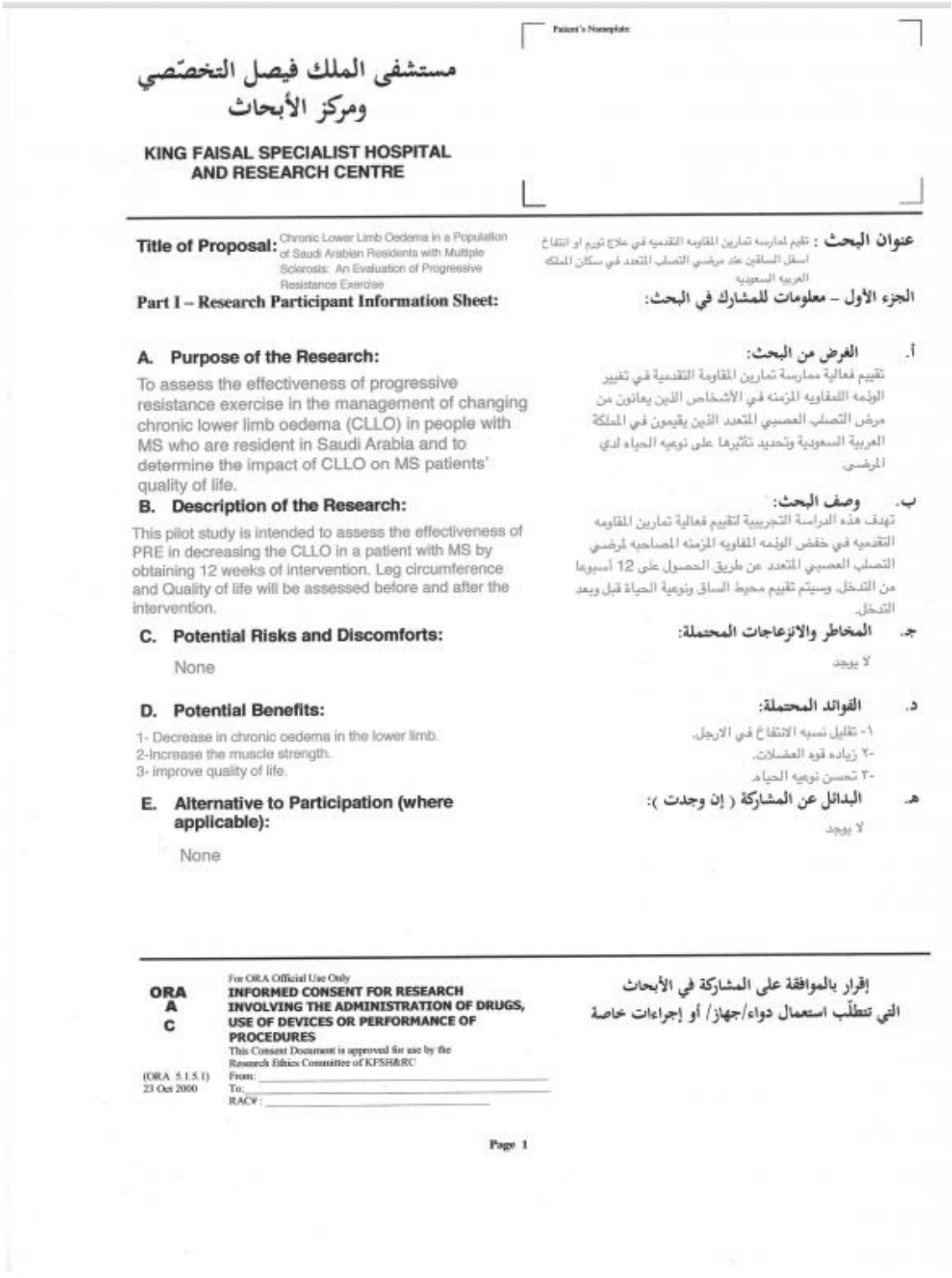
ORA Note: The Proposal not yet accepted by REC.

cc: [redacted]
RAC File

ORA
A
C

E-mail: [redacted]

Appendix 3: Patient information sheet (PIS) and Consent form (CF) for King Faisal specialist hospital & research centre (KFSH&RC) participants



Patient's Nameplate

مستشفى الملك فيصل التخصّصي
ومركز الأبحاث

KING FAISAL SPECIALIST HOSPITAL
AND RESEARCH CENTRE

Title of Proposal: Chronic Lower Limb Oedema in a Population of Saudi Arabian Residents with Multiple Sclerosis: An Evaluation of Progressive Resistance Exercise

عنوان البحث : تقيم لممارسه تمارين المقاومه التقدميه في علاج تورم او انتفاخ اسفل الساقين عند مرضى التصلب المتعدد في سكان المملكه العربيه السعوديه

Part I – Research Participant Information Sheet:

الجزء الأول – معلومات للمشارك في البحث:

A. Purpose of the Research:

To assess the effectiveness of progressive resistance exercise in the management of changing chronic lower limb oedema (CLLO) in people with MS who are resident in Saudi Arabia and to determine the impact of CLLO on MS patients' quality of life.

أ. الغرض من البحث:

تقييم فعالية ممارسة تمارين المقاومة التقدمية في تغيير الوذمه اللمفاويه المزمنه في الأشخاص الذين يعانون من مرض التصلب العصبي المتعدد الذين يقيمون في المملكة العربية السعودية وتحديد تأثيرها على نوعيه الحياه لدي المرضى.

B. Description of the Research:

This pilot study is intended to assess the effectiveness of PRE in decreasing the CLLO in a patient with MS by obtaining 12 weeks of intervention. Leg circumference and Quality of life will be assessed before and after the intervention.

ب. وصف البحث:

تهدف هذه الدراسة التجريبية لتقييم فعالية تمارين المقاومه التقدميه في خفض الوذمه المفاويه المزمنه المصاحبه لمرضي التصلب العصبي المتعدد عن طريق الحصول على 12 أسبوعا من التدخل. وسيتم تقييم محيط الساق ونوعية الحياة قبل وبعد التدخل.

C. Potential Risks and Discomforts:

None

ج. المخاطر والانزعاجات المحتملة:

لا يوجد

D. Potential Benefits:

1- Decrease in chronic oedema in the lower limb.
2-Increase the muscle strength.
3- improve quality of life.

د. الفوائد المحتملة:

١- تقليل نسبه الانتفاخ في الارجل.
٢- زياده قوه العضلات.
٣- تحسن نوعيه الحياه.

E. Alternative to Participation (where applicable):

None

هـ. البدائل عن المشاركة (إن وجدت):

لا يوجد

ORA
A
C

(ORA 5.1.5.1)
23 Oct 2000

For ORA Official Use Only
INFORMED CONSENT FOR RESEARCH INVOLVING THE ADMINISTRATION OF DRUGS, USE OF DEVICES OR PERFORMANCE OF PROCEDURES
This Consent Document is approved for use by the Research Ethics Committee of KFSH&RC
From: _____
To: _____
RAC# : _____

إقرار بالموافقة على المشاركة في الأبحاث
التي تتطلّب استعمال دواء/جهاز/ أو إجراءات خاصة

Page 1

Patient's Nameplate

مستشفى الملك فيصل التخصّصي
ومركز الأبحاث

KING FAISAL SPECIALIST HOSPITAL
AND RESEARCH CENTRE

F. Cost/s Reimbursements:

None

G. Termination of Participation (where applicable):

The participant can withdraw from the study at any time and this will not affect his right to treatment in the hospital.

H. Compensation / Treatment:

In the event of injury resulting from participation in the research study, KFSH&RC will make available to you, including admission, if required, its hospital facilities and professional attention. Financial compensation from KFSH&RC is not available.

I. Voluntary Participation:

Participation in this study is voluntary. You will suffer no penalty nor loss of any benefits to which you are otherwise entitled should you decide not to participate. Withdrawal from this research study will not affect your ability to receive alternative methods of medical care available at KFSH&RC.

Significant new findings developed during the course of the research study which might be reasonably expected to affect your willingness to continue to participate in the research study will be provided to you.

J. Confidentiality:

و. التكاليف / التعويضات المالية:

لا يوجد اي تكاليف او تعويضات

ز. إنهاء المشاركة (إذا أمكن):

بإمكان المشارك إنهاء المشاركه في اوقت و لن يؤثر ذلك على العنايه الطبيه التي يحصل عليها من المستشفى

ح. التعويضات / العلاج:

في حالة حدوث أي ضرر لا قدر الله من جراء مشاركتك بهذه الدراسة سيتكفل مستشفي الملك فيصل التخصصي ومركز الأبحاث بتقديم العناية الطبية اللازمة أو التنويم في المستشفي إذا لزم الأمر ولكنه لا يلتزم بمنح أي تعويضات مالية.

ط. المشاركة التطوعية:

المشاركة في هذه الدراسة طوعيه وإذا قررت عدم المشاركة فانك لن تتعرض لأي مضايقات أو لفقدان حقك للمشروع في المعالجة ، كما أن قرارك بالانسحاب من الدراسة لن يؤثر علي تلقيك لخدمة علاجية بديلة متوفرة في مستشفي الملك فيصل التخصصي ومركز الأبحاث()

سيتم إبلاغك بأي نتائج جديدة هامة تظهر خلال تطوّرات البحث مما قد يؤثر بطريقة معقولة على رغبتك في الاستمرار بالمشاركة في هذه الدراسة()

ي. السرية:

إقرار بالموافقة على المشاركة في الأبحاث
التي تتطلّب استعمال دواء/جهاز/ أو إجراءات خاصة

ORA A C

(ORA 5.1.5.1)
23 Oct 2000

For ORA Official Use Only
INFORMED CONSENT FOR RESEARCH INVOLVING THE ADMINISTRATION OF DRUGS, USE OF DEVICES OR PERFORMANCE OF PROCEDURES
This Consent Document is approved for use by the Research Ethics Committee of KFSH&RC
From: _____
To: _____
RAC# : _____

Patient's Nameplate

مستشفى الملك فيصل التخصّصي
ومركز الأبحاث

KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE

Your identity and medical record, as a participant in this research study, will remain confidential with respect to any publications of the results of this study. Furthermore, your medical record may be reviewed by the Research Advisory Council or the agency sponsoring this research in accordance with applicable laws and regulations.

كمشارك في هذه الدراسة ستكون هويتك ومحتويات ملفك الطبّي سرية في جميع المنشورات المتعلقة بنتائج الدراسة، ويمكن الاطلاع عليه من قبل المجلس الاستشاري للأبحاث أو الجهة الداعمة للدراسة في حدود النظم والقوانين المطبقة بهذا الخصوص0

K. Contact Person(s):

You may call the Section of Assurance & Compliance, Office of Research Affairs at 24724 or _____ pager # _____ for general questions concerning research at KFSH&RC or research subjects' rights. For any specific questions with regard to this study, or in the event of a research-related injury, please contact Dr. Asma Alderaa telephone # 0504261504 Ext. _____, Pager # _____.

A signed copy of the consent form will be given to you.

ك. الأشخاص الذين يمكن الاتصال بهم:

في حالة وجود أي استفسار عليك الاتصال على قسم رقابة وجودة البحوث في مكتب شئون الأبحاث على هاتف رقم 24724 أو _____ أو على جهاز النداء رقم _____ لتوجيه أي أسئلة عامة تتصل بالبحوث بمستشفى الملك فيصل التخصّصي أو تتعلّق بحقوق المشارك. وفي حالة وجود أسئلة محدّدة تتعلّق بهذا البحث أو في حالة حدوث أي إصابات تتصل بالدراسة، نرجو الاتصال على الدكتور أسماء الدرع على هاتف رقم ٠٥٠٤٢٦١٥٠٤ تحويلة رقم _____ أو جهاز نداء رقم _____.

سيتم تزويدك بنسخة موقعة من هذا الإقرار0

PART II - Authorization for Administration of certain drugs, use of devices or performance of certain procedures to:

الجزء الثاني: تفويض باستعمال علاج أو جهاز أو إجراء طبي:

Patient Name: _____

اسم المريض: _____

MRN #: _____

رقم الملف الطبي : _____

إقرار بالموافقة على المشاركة في الأبحاث التي تتطلّب استعمال دواء/جهاز/ أو إجراءات خاصة

ORA A C

(ORA 5.1.3.1) 23 Oct 2000

For ORA Official Use Only
INFORMED CONSENT FOR RESEARCH INVOLVING THE ADMINISTRATION OF DRUGS, USE OF DEVICES OR PERFORMANCE OF PROCEDURES
This Consent Document is approved for use by the Research Ethics Committee of KFSH&RC
From: _____
To: _____
RAC# : _____

Patient's Name/date:

مستشفى الملك فيصل التخصّصي
ومركز الأبحاث

KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE

1.a I authorize Dr. Asma Alderaa and his/her associates at KFSH&RC to administer the following drugs, use the following devices or perform the following procedures during my treatment (or the treatment of the person named above for whom I am responsible):

Ankle dorsiflexion and plantar flexion progressive resistance exercise will be obtained twice a week for 12 week. during this time, every 2 weeks the external weight will be used as a progression in the intervention.

1-أ بهذا أفوض الدكتور: أسماء الدرع أو أحد المشاركين معه في مستشفى الملك فيصل التخصصي ومركز الأبحاث باستعمال الدواء أو الجهاز أو الإجراء الطبي التالي – خلال معالجتي الطبية (أو معالجة الشخص المذكور أعلاه والذي أنا ولي أمره):

سيتم تطبيق تمارين المقاومه التقدميه لفصل الكاحل في كلتا القدمين مرتين اسبوعيا لمدة ١٢ اسبوع باستخدام اوزان مدرويه و مختلفه كل اسبوعين

1.b I also agree that the following body fluids and tissues may be sampled for research analyses and related purposes (include volume and frequency of each):

This point is not required to do

1-ب كما أوافق على أخذ عينات من سوائل أو أنسجة الجسم وذلك لأغراض تحليله متعلّقة بالبحث (أذكر الكمية وعدد المرات لكل نوع):

هذا البند غير مطلوب

2. I understand that the above-mentioned drugs, devices or procedures are being studied to determine the extent to which they may be of value in treating my illness or condition (or the illness or condition of such patient named above, as the case may be).

2. أفهم بأن الدواء ، أو الجهاز ، أو الإجراء المذكور أعلاه سيتم دراسته لمعرفة إلى أي حد قد يكون مفيداً لمعالجة مرضي أو الحالة التي أعاني منها (أو المرض والحالة التي يعاني منها المريض والذي أنا ولي أمره).

3. I acknowledge that I have read, or had explained to me in a language I understand, the attached Research Participant Information sheet and that Dr. Asma Alderaa has explained to me the nature and purposed of the drugs, devices or

3. أقر بأنني قد قرأت – أو قد شرحت لي بلغة أفهمها – جميع المعلومات المتعلّقة بالمشاركة بالبحث والمرفقة، وأن الدكتور/ أسماء الدرع قد أوضح لي ماهية وطبيعة الدواء أو الجهاز أو الإجراءات المذكورة في نموذج المعلومات للمشارك والغرض منها والفوائد المرجوة منها

إقرار بالموافقة على المشاركة في الأبحاث
التي تتطلّب استعمال دواء/جهاز/ أو إجراءات خاصة

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This Consent Document is approved for use by the Research Ethics Committee of KFSH&RC
From: _____
To: _____
RAC# : _____

(ORA 5.1.5.1)
23 Oct 2000

Page 4

Patient's Nameplate

مستشفى الملك فيصل التخصّصي
ومركز الأبحاث

KING FAISAL SPECIALIST HOSPITAL
AND RESEARCH CENTRE

procedures described in the Research Participant Information Sheet as well as any benefits reasonably to be expected, possible alternative methods of treatment, the attendant discomforts and risks reasonably to be expected and the possibility that complications from both known and unknown causes may arise as a result thereof. I have had the opportunity to ask any questions I had with respect to such drugs, devices or procedures and all questions I asked were answered to my satisfaction.

والطرق العلاجية البديلة لها والمخاطر والانزعاجات المتوقع حدوثها وكذلك احتمال حدوث مضاعفات لأسباب معروفة أو غير معروفة نتيجة لذلك.
كما أنه قد أتيحت لي الفرصة الكافية لعرض الأسئلة فيما يتعلّق باستخدام الدواء أو الجهاز أو الإجراء الطبي وتلقيت الإجابات الكافية عنها.

4. I understand that I am entitled for reimbursement for expenses incurred as a result of my participation in this study

4. من المفهوم لديّ بأنني استحق استرداد المصروفات التي نتجت عن مشاركتي في هذه الدراسة.

5. I voluntarily accept the risks associated with the use of the above-mentioned drugs, devices or the performance of the above-mentioned procedures with the knowledge and understanding that the extent to which they may be effective in my treatment (or the treatment of the patient named above, as the case may be) has not been established, that there may be side effects and complications from both known and unknown causes and that these drugs, devices, or procedures may not result in cure or improvement.

5. إنني وبمحض إرادتي أقبل المخاطر المتعلقة باستخدام الدواء أو الجهاز أو الإجراءات المذكورة في هذا الإقرار مع علمي وفهمي التام بأن مدى فائدتها في علاجي (أو للشخص الذي أتولى أمره) لم يتم إثباته بعد. وأن هناك مضاعفات وآثار جانبية متوقعة ولأسباب معروفة أو غير معروفة. وإن هذه الأدوية أو الأجهزة أو الإجراءات الخاصة قد لا تؤدّي إلى تحسّن حالتي أو الشفاء التام منها.

6. I understand that I am free to withdraw this consent and discontinue treatment with the above-mentioned drugs, devices or procedures at any time. The consequences and risks, if any, which might be involved in the event I later decide to discontinue such

6. وأفهم أن لي مطلق الحرية بسحب موافقتي وقطع المعالجة بهذا الدواء/الجهاز/أو الإجراء في أي وقت. وقد شرحت لي جميع العواقب والمخاطر المترتبة (إن وجدت) على انسحابي من الدراسة.

إقرار بالموافقة على المشاركة في الأبحاث
التي تتطلّب استعمال دواء/جهاز/ أو إجراءات خاصة

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To: _____
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Patient's Nameplate:

مستشفى الملك فيصل التخصّصي
ومركز الأبحاث

KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE

treatment have been explained to me. I understand that such withdrawal will not affect my ability to receive any medical care made necessary by the performance of such studies or to which I might be otherwise entitled.

كما أفهم بأن انسحابي من هذه الدراسة لن يؤثر على حقي في تلقّي العناية الطبية اللازمة (كنتيجة للمشاركة في هذه الدراسة). أو التي تمنح للمشاركين بالدراسة أو التي أستحقها في الأحوال العادية.

7. I confirm that I have read, or had read to me, the foregoing authorization and that all blanks or statements requiring completion were properly completed before I signed.

7. بهذا أؤكد بأنني قد قرأت (أو قرأ لي) هذا التفويض وأن جميع المعلومات اللازمة قد تمت تعبئتها بدقة قبل توقيعي عليه.

Patient/Surrogate: _____ _____
Signature Date

التوقيع: _____ التاريخ: _____

Print Name: _____
(If signed by Surrogate)

الاسم: _____

Relationship: _____

صلة القرابة: _____

8. I confirm that I have accurately translated and/or read the information to the subject or his/her surrogate.

8. أؤكد بأنني قد قرأت/ ترجمت جميع المعلومات المذكورة بدقة للمريض أو لولي أمره.

Witness: _____

Print Signature Name: _____

توقيع الشاهد: _____

الاسم _____

KFSH&RC ID #: _____

رقم البطاقة: _____

Date: _____

التاريخ : _____

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إقرار بالموافقة على المشاركة في الأبحاث
التي تتطلّب استعمال دواء/جهاز/ أو إجراءات خاصة

Patient's Nameplate:

مستشفى الملك فيصل التخصّصي
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9. I have fully explained to the above patient/ relative/ guardian the nature and purpose of the foregoing drugs, devices or procedures, possible alternative methods of treatment which might be advantageous, the benefits reasonably to be expected, the attendant discomforts and risks involved, the possibility that complications may arise as a result thereof and the consequences and risks, if any, which might be involved in the event the patient/ relative/ guardian hereafter decides to discontinue such treatment. It is my understanding that the above patient/ relative/ guardian understands the nature, purposes, benefits, and risks of participation in this research before signing of this informed consent. I have also offered to answer any questions the above patient/ relative/ guardian might have with respect to such drugs, devices or procedures and have fully and completely answered all such questions.

(Signature of Principal Investigator/ Delegate):

_____

Print Name: _____

Title: _____

Date: _____

9. أقر بأنني قد شرحت بصورة كاملة للمريض / أو قريبه (ولي أمره) طبيعة والغرض من هذا العلاج/ الجهاز / الإجراء، والطرق العلاجية البديلة والتي من المحتمل أن يكون لها الأفضلية والفوائد المحتملة والمخاطر والانزعاجات المتوقع حدوثها والتي قد يترتّب عليها حدوث مضاعفات.

كما أنني قد أوضحت النتائج أو المخاطر المختلفة في حالة قرار المريض (أو قريبه أو ولي أمره) قطع المعالجة بالدواء / الجهاز / الإجراء قد الدراسة.

من المفهوم لديّ بأن المريض المذكور أعلاه (أو قريبه أو ولي أمره) قد فهم طبيعة الدراسة والهدف منها والفوائد والمخاطر المترتبة على المشاركة فيها قبل توقيعه على الموافقة بالمشاركة.

وقد قمت بتوضيح استعدادي للإجابة على جميع أسئلة المريض/ قريبه/ ولي أمره بالإجابة على تلك المتعلقة بالدواء/ الجهاز/ الإجراء موضوع الدراسة وقمت فعلاً بالإجابة كاملةً على جميع الأسئلة بطريقة واضحة ومرضية.

توقيع الباحث الرئيسي: _____

الاسم: _____

الوظيفة: _____

التاريخ: _____

إقرار بالموافقة على المشاركة في الأبحاث
التي تتطلّب استعمال دواء/جهاز/ أو إجراءات خاصة

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To: _____
RAC# : _____

Appendix 4: Patient information sheet (PIS) and Consent form (CF) for King Khalid university hospital (KKUH) participants (Arabic and English copy)

King Saud University
Vice Rectorate for Graduate Studies & Scientific Research
Deanship of Scientific Research
Research Ethics Committee

جامعة الملك سعود
وكالة الجامعة للدراسات العليا والبحث العلمي
عمادة البحث العلمي
لجنة أخلاقيات البحوث

For REC use only:
Full Board [✓]
Expedited [ ]
Proposal No. E-17-2732

إقرار بالموافقة على المشاركة في التجارب السريرية
Form # KSU-REC 005-A
جامعة الملك سعود - الرياض- المملكة العربية السعودية

رقم الدراسه
اسم المشارك
رقم السجل الطبي
عنوان الدراسة : تقيم لممارسه تمارين المقاومه التقدميه في علاج تورم او انتفاخ اسفل الساقين عند مرضي التصلب المتعدد في سكان المملكه العربيه السعوديه
الباحث الرئيس : الاخصائيه / اسماء الدرع
العنوان : الرياض، المملكه العربيه السعوديه
رقم الهاتف : ٠٥٠٤٢٦١٥٠٤

سيشرح لك عضو من فريق البحث محتويات هذه الدراسة وتأثيرها عليك. و يصف هذا الإقرار إجراءات الدراسة ، والمخاطر والفوائد من المشاركة ، وكيفية الحفاظ على سرية المعلومات. الرجاء اخذ الوقت الكافي في طرح الأسئلة لكي تتخذ قرارك ما إذا كنت ستشارك أم لا. وهذه الموافقة تسمى الموافقة المستنيرة. إذا قررت المشاركة في هذه الدراسة ، سيطلب منك التوقيع على هذا الإقرار وستعطي نسخة لسجلاتك. وطوال هذا الإقرار اللفظ "أنت" سوف يشير إليك أو إلى طفلك ، حسب الاقتضاء.

لماذا تجري هذه الدراسة؟
أظهر بحث حديث وجود عدد قليل من الدراسات التي تهدف إلى تقييم انتشار تورم او انتفاخ اسفل الساقين المزمن مع مرضى التصلب العصبي المتعدد. ومع ذلك، لم يتم أي تدخل لعلاج هؤلاء المرضي. وبالنظر إلى الأدلة المحدودة في هذا المجال، فإن هذه الدراسة التجريبيه تقييم (للمرة الأولى) فعالية ممارسة تمارين المقاومه باستعمال الاوزان مع مرضى التصلب العصبي المتعدد المصابين بتورم اسفل الساقين المزمن وسوف تكون الأولى في المملكة العربية السعودية.

كم عدد المشاركين في هذه الدراسة ؟
١٢ مشارك في الدراسه ككل.

ما هو المتوقع مني خلال هذه الدراسه (ما هي مسؤولياتي)؟

نتوقع منك حضور جميع جلساتك دون انقطاع إلا إذا كنت ترغب في إيقاف مشاركتك.

ما هي مدة مشاركتي في هذه الدراسة؟

١٢ سبوعا و خلال الأسبوع الواحد سوف يتم حضورك للعلاج مرتين فقط.

كيف تتم عمليه العلاج؟

في الزياره الاولى لقسم العلاج الطبيعي سوف تقوم الاخصائيه أسماء الدرع بتحديد القدره القصوي للعضله لرفع ثقل و بعد تحديد هذه القدره سوف يتم احتساب من خلال عمليه حسابيه ٤٠٪ من هذه القدره و هي التي سوف تعتبر نقطه البدايه للمريض و عليه يتم زياده هذه النسبه كل فتره الي ان تصل الي نسبه ٧٠٪ .

مثال : اذا استطاع المريض حمل ثقل قدره ٥كيلو جرام لمره واحده من دون تعب، فهذا يعتبر "القدره القصوي للعضله" لحمل الاثقال. من بعدها نحسب نسبه ٤٠٪ من هذا الثقل وهي تقريبا ٢ كيلو جرام و نعتبرها نقطه البدايه للمريض و منها يستمر بحمل الاثقال الي

ان يصل الي حمل ٧٠٪ من الخمسه كيلو جرام من دون تعب و لعده مرات متتاليه.

**كل مريض تختلف قدراته عن الاخر في حمل الاثقال، وهذا المثال ما هو الا مثال تقريبي لفكره التمارين.

ما هي البدائل في حال عدم رغبتي بالمشاركه في هذه الدراسه؟

في حال عدم الرغبه بالمشاركه في هذه الدراسه التجريبيه فان الدكتور المختص في عياده الاعصاب سوف يوجه لعلاجك علي حسب الحاله الى القسم المختص.

هل أستطيع إنهاء مشاركتي في هذه الدراسة ؟

نعم. يمكنك أن تقرر التوقف في أي وقت. فقط اخبر الاخصائيه أسماء الدرع إذا قررت التوقف. لتوضح لك كيفية إنهاء مشاركتك بأمان. لا أحد سيحملك علي تغيير رأيك.

هل هناك مخاطر متوقعة إذا أنهيت مشاركتي في هذه الدراسة ؟

لا يوجد أي مخاطر اذا انهيت المشاركه.

ما هي المخاطر أو الآثار الجانبية التي يمكن حدوثها من جراء مشاركتي في هذه الدراسة ؟

لا يمكن أن تحدث أي اضرر أو آثار جانبية من هذه الدراسة بإذن الله. الشيء الوحيد الذي يمكن أن تشعر به في بداية العلاج التجريبي هو ألم عضلي بسبب التكيف العضلي مع ممارسة الرياضة.

هل هناك فوائد من مشاركتي في هذه الدراسة ؟

مشاركتك في هذه الدراسة قد لا تؤدي إلي تحسن حالتك ، ولكن يأمل الاخصائي من ان يكون التدخل اكثر فاعليه من العلاج المعتاد ولا يوجد دليل على ذلك حتى الآن.

ماذا يحدث لو أنني تعرضت للإصابة بسبب مشاركتي في هذه الدراسة ؟

من المهم أن تبلغ الاخصائيه إذا كنت تظن انك قد تعرضت للإصابة بسبب مشاركتك في هذه الدراسة. يمكنك أن تبلغه شخصيا أو الاتصال به على٠٥٠٤٢٦١٥٠٤ . و في حال تعرضك للإصابة سيكون العلاج متاحا. ستقدم لك جامعة الملك سعود تكاليف العلاج، ويتوقف ذلك على عدد من العوامل. عادة لا تقدم جامعة الملك سعود أي شكل آخر من أشكال التعويض عن الضرر. وللحصول على مزيد من المعلومات عن هذا الموضوع، يمكنك الاتصال بمكتب جامعة الملك سعود (**KSU-REC**) على الرقم 011/4691530 أو011/4691531. أو 011/4694532

وما هي تكاليف المشاركة في الدراسة ؟
لن تتحمل تكاليف أي من أنشطة الدراسة.

هل سأتقاضى اجر نظير المشاركة في هذه الدراسة ؟
لن يكون هناك اجر مقابل المشاركه انما هو عمل تطوعي.

هل سيتم الحفاظ علي سرية المعلومات الطبية الخاصة بي ؟
سنبذل قصارى جهدنا للتأكد من أن المعلومات الشخصية في سجلك الطبي تحظى بالسرية. ومع ذلك ، لا يمكننا أن نضمن الخصوصية التامة. قد يفصح عن معلوماتك الشخصية إذا اقتضى الأمر ذلك بموجب القانون. لن يتم الإفصاح عن اسمك أو معلوماتك الشخصية إذا تم نشر أو عرض نتائج هذه الدراسة.

ما هي حقوقي إذا وافقت على المشاركة في هذه الدراسة ؟

قرار المشاركة في هذه الدراسة من اختيارك. لك حرية اختيار المشاركة في هذه الدراسة أو لا .كما يمكنك إنهاء المشاركة في أي وقت. مهما كان قرارك ، لن يكون هناك أي عقوبة و لن تفقد أي من الفوائد العادية الخاصة بك. ترك الدراسة لن يؤثر على الرعاية الطبية المقدمة لك من جامعة الملك سعود. الاخصائيه اسماء الدرع قد تستخدم المعلومات التي تم جمعها قبل أن تترك لدراسة.

ونحن سوف نبلغك بكل المعلومات والمستجدات أو التغييرات في الدراسة التي يمكن أن تؤثر على صحتك أو على استعدادك لمواصلة الدراسة .

وفي حالة الإصابة الناتجة عن هذه الدراسة ،بتوقيع هذا الإقرار, لن تفقد أيا من الحقوق القانونية في طلب التعويض.

بمن يمكنني الاتصال إذا كانت لدي أي أسئلة أو مشاكل؟

قبل أن توافق على المشاركة هذه الدراسة ،ستتحدث إلى احد أعضاء فريق الدراسة المؤهلين ليخبرك عن هذه الدراسة . يمكنك أن تطرح الأسئلة حول أي جانب من جوانب البحث. إذا كان لديك المزيد من الأسئلة عن الدراسة ،يمكنك السؤال في أي وقت. يمكنك الاتصال مع الباحث الرئيس على الرقم ٠٥٠٤٢٦١٥٠٤.

إقرار بالموافقة
المشارك:
لقد تم شرح البحث والإجراءات لي. وسمح لي بأن اسأل أي سؤال لدي في هذا الوقت. ويمكنني أن اسأل أي أسئلة إضافية في وقت لاحق. ويمكنني إنهاء المشاركة في الدراسة في أي وقت دون ان يؤثر ذلك على الرعاية الصحية المقدمة لي.

سأحصل على نسخة موقعة من هذا الإقرار بالموافقة.

إنا اقر بالموافقة على المشاركة في هذه الدراسة. موافقتي طوعية, ولست بحاجة إلى التوقيع على هذا الإقرار إذا كنت لا أريد المشاركة في هذه الدراسة البحثية.

أوافق على أن الباحثين في هذه الدراسة والمتعاونين معهم سوف يستخدمون العينات الخاصة بي في هذه الدراسة ودراسات أخرى إذا لزم الأمر

توقيع المشارك:

التاريخ

الوقت ص ☐ م ☐

الشخص الحاصل على الموافقة:
لقد شرحت طبيعة الدراسة والغرض منها وما تنطوي عليه من مخاطر. وقد أجبت وسأجيب على الأسئلة على أفضل قدر من استطاعتي. سأعطي نسخة موقعة من الإقرار بالموافقة إلى المشارك المذكور أعلاه.

توقيع الشخص الحاصل على الموافقة

التاريخ

الوقت ص ☐ م ☐

الباحث الرئيس : أسماء الدرع

توقيع الباحث الرئيسي

الوقت ص ☐ م ☐

[قف! لا تستخدم خطوط التوقيع التالية إلا إذا طلبت موافقة طرف ثالث]

و / أو :

الممثل المخول قانونا
التاريخ
الشخص الحاصل على الموافقة
التاريخ
أو
الشخص المعني بالدراسة غير قادر على الموافقة بنفسه لأنه / إنها قاصر. من خلال التوقيع أدناه، أنت تعطي إذنك لطفلك بان يضمن في هذه الدراسة

الأبوين أو الوصي قانونا----------

التاريخ: / /

لمزيد من المعلومات، يرجى زيارة موقع لجنة أخلاقيات البحوث في جامعة الملك سعود(http://dsrs.ksu.edu.sa/ar/comm_Policies)

King Saud University
Vice Rectorate for Graduate Studies & Scientific Research
Deanship of Scientific Research
Research Ethics Committee

جامعة الملك سعود
وكالة الجامعة للدارسات العليا والبحث العلمي
عمادة البحث العلمي
لجنة أخلاقيات البحوث

For REC use only:
Full Board [✓]
Expedited [ ]
Proposal No. E-17-2733

INFORMED CONSENT FOR A CLINICAL TRIAL
Form # KSU-REC 005-E
King Saud University, Riyadh, Kingdom of Saudi Arabia

Protocol Number:

Name of Subject:

Medical Record Number:

Study Title:	Chronic Lower Limb Oedema in a Population of Saudi Arabian Residents with Multiple Sclerosis: An Evaluation of Progressive Resistance Exercise
Principal Investigator:	Asma Alderaa
Address:	Riyadh, Kingdome of Saudi Arabia
Telephone:	0504261504

A member of the research team will explain what is involved in this study and how it will affect you. This consent form describes the study procedures, the risks and benefits of participation, and how your confidentiality will be maintained. Please take your time to ask questions and feel comfortable making a decision whether to participate or not. This process is called informed consent. If you decide to participate in this study, you will be asked to sign this form and will be given a copy for your records. Throughout this consent form, "you" will refer to you or your child, as appropriate.

WHY IS THIS STUDY BEING DONE?
A recent search in the literature showed only few studies that aimed to assess the prevalence of Chronic Lower Limb Oedema with Multiple Sclerosis patients. However, no intervention was undertaken to treat Chronic Lower Limb Oedema with Multiple Sclerosis patients. In view of limited evidence in this area, this experimental study will assess (for the first time) the effectiveness of exercise intervention in Multiple Sclerosis patients with Chronic Lower Limb Oedema and will be the first one in Saudi Arabia.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?
16 participants in total.

STUDY LOCATION:
In Riyadh city.

WHAT IS EXPECTED OF ME DURING THE STUDY (What are my responsibilities)?

We are expected you to attend all your session without interruptions unless you would like to stop your

participation.

HOW LONG WILL I BE IN THE STUDY?

For 12 weeks and you will be attending 2 sessions per week.

WHAT IS THE PROCESDURE OF THIS INTEREVRNTION?

In your first session in the physiotherapy department the therapist Mrs Asma Alderaa will try to determine your muscle maximum ability to left a weight. After determining this weight, she will calculate 40% of this weight and from this she will consider this weight as your starting point.

For example: if the participant is able to left 5 kg one time with full range of motion this will be considered as "your muscle maximum ability to left a weight". From this, the therapist will calculate the 40% of this weight, which will be around 2kg and will consider it as your starting point. Then, gradually the therapist will increase the weight until you reach the 70% of your muscle maximum ability to left a weight.

**Each patient has different ability to left weights and the example above is just to clarify the idea to you.

WHAT IS THE ALTERVATIVE OPTION IF I DECIDED TO NOT PARTICIPATE IN THIS STUDY?

If you deicide to not participate in this study you doctor in neurology clinic will direct you to the proper clinic to receive other treatment.

CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop at any time. Tell the study therapist if you are thinking about stopping or you've decided to stop. He or she will tell you how to stop your participation safely. No one will try to get you to change your mind.

ARE THERE RISKS IF I STOP BEING IN THE STUDY?

No, there are no risks.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?

No harms or side effects could happen from this study. The only thing that you can feel at the beginning of the intervention is muscular pain due to muscular adaptation to the exercise.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Taking part in this study may or may not make your health better. While doctors hope the intervention will be more effective than the standard (usual) treatment, there is no proof of this yet.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell Mrs. Asma Alderaa if you feel that you have been injured because of taking part in this study. You can tell Mrs. Alderaa in person or call her at 0504261504. If you are injured as a result of being in this study, treatment will be available. The costs of the treatment may be covered by KSU, depending on a number of factors. KSU do not normally provide any other form of compensation for injury. For further information about this, you may call the office of King Saud University Institutional Review Board (KSU-REC) at **011/4691530 or 011/4691531 or 011/4691532**

WHAT ARE THE COSTS OF TAKING PART IN THE STUDY?

You will not be charged for any study activities.

WILL I BE PAID FOR MY TAKING PART IN THIS STUDY?

You will not be paid for taking part in this study.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

We will make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If this study is published, no personal info will be used.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from KSU. Mrs. Alderaa may use information that was collected prior to your leaving the study.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

We will tell you about any anticipated circumstances under which your participation may be terminated by the investigator without regard to your consent.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
Before you agree to be in this study, you will talk to a study team member qualified to tell you about this study. You can ask questions about any aspect of the research. If you have further questions about the study, you may ask them at any time. You may call **Mrs. Alderaa at 0504261504**.

CONSENT
Subject:

The research and procedures have been explained to me. I have been allowed to ask any questions I have at this time. I can ask any additional questions I may think of later. I may refuse to participate in the study, and I may quit being in the study at any time without any penalty and without affecting my health care.

I will receive a signed copy of this consent form.

I agree to participate in this study. My agreement is voluntary. I do not have to sign this form if I do not want to be part of this research study.

I consent that the investigators of this study and their collaborators will use my samples in this study and in other studies if required.

Subject Signature

Date
Time (AM ☐ PM ☐)

Person Obtaining Consent:
I have explained the nature and purpose of the study and the risks involved. I have answered and will answer questions to the best of my ability. I will give a signed copy of the consent form to the subject.

Signature of Person Obtaining Consent

Date
Time (AM ☐ PM ☐)

Principal Investigator: Mrs. Asma Alderaa

Signature of Principal Investigator
Time (AM ☐ PM ☐)

[STOP! Do not use the following signature lines unless third party consent is being requested and has been.]

AND/OR:

Legally Authorized Representative:----------
Date: --- / --- /------- (H); --- / --- /------- (G)
Person Obtaining Consent:----------
Date: --- / --- /------- (H); --- / --- /------- (G)
OR
The person being considered for this study is unable to consent for himself/herself because he/she is a minor. By signing below, you are giving your permission for your child to be included in this study.

Parent or Legal Guardian----------

Date: --- / --- /------- (H); --- / --- /------- (G)

Appendix 5: Characteristics of excluded studies in chapter 3

Author (year)	Reason for exclusion
Sarno et al. 2014	Not related, the topic or the aims of the studies did not fit the review inclusion criteria.
Amarenco et al. 2003	
Viswanathan et al. 2016	
Ninomiya et al. 2015	
Arpaia et al. 2011	
Akiyama et al. 2005	
Battafarano et al. 1995	
Yokota and Tanabe 1992	
Lassmann et al. 1976	
de Andrade Freitas Oliveira et al. 2013	
Llorenç et al. 2012	
Carrick et al. 2005	
Kisimbi et al. 2013	

Appendix 6: The Joanna Briggs Institute (JBI) prevalence critical appraisal tool.

	Author name (year)		
JBI prevalence critical appraisal tool question	**Solaro et al. (2006)**	**Arpaia et al. (2010)**	**Keeley et al. (2017)**
Q1: Was the sample representative of the target population?	N	N	N
Q2: Were study participants recruited appropriately?	Unclear	unclear	Y
Q3: Was the sample size adequate?	Y	Y	Y
Q4: Were the study subjects and the setting described in detail?	Y	N	Y
Q5: Was the data analysis conducted with sufficient coverage of the identified sample?	N	N	Y
Q6: Were objective, standardized criteria used for the measurement of the condition?	Y	Unclear	Y
Q7: Was the condition measured reliably?	Y	Unclear	Y
Q8: Was there appropriate statistical analysis?	Y	Y	Y
Q9: Are all important confounding factors/ subgroups/ differences identified and accounted for?	N	N	Y
Q10: Were subpopulations identified using objective criteria?	NA	N	NA
Overall appraisal	5/10 Included	2/10 Excluded	8/10 Included

Overall appraisal: Included or Excluded or Seek further info. **Answer:** Yes or No or Unclear or Not Applicable (NA).
NB: The green highlighted rows are the mandatory questions and the answer to those questions must be “yes” to include the study

Appendix 7: Characteristics of Excluded Studies in chapter 4

Author (year)	Reasons for Exclusion
Taylor et al. (2006)	Abstract only. Researcher was not able to get full text, not even from the library inter-loan system.
Plummer (2016)	
Hayes et al. (2011)	
De Souza et al. (2009)	
Aidar et al. (2017)	
Keller et al. (2016)	
Novotna et al. (2015)	Conference abstract.
Isner-Horobeti et al. (2014)	
Bernhardt et al. (2013)	
Jolk et al. (2013)	
Medina-Perez et al. (2012)	
Jolk et al. (2012)	
Bernhardt et al. (2012)	
Dodd et al. (2011)	
Bernhardt and Marziniak (2011)	
Aghaie et al. (2010)	
Dalgas et al. (2009)	
Kjolhede et al. (2013)	
Weikert et al. (2011)	Not related, the aims of the studies did not fit the review inclusion criteria.
Skjerbaek et al. (2013)	
White et al. (2004)	
Kjolhede et al. (2012)	
Wens et al. (2015)	
DeBolt et al. (2004)	
Hale (2004)	
Filipi et al. (2011)	
Summers (2000)	Dissertation

Appendix 8: Cochrane Collaboration's tool to assess the risk of bias in the included studies

1 Dalgas et al. (2009)

Methods	• Randomised, controlled trial conducted in Denmark. • Study period: 24 weeks (12 intervention + 12 follow-up) • Blinding of randomisation: no • Blinding of intervention: no • Complete follow-up: yes • Blinding of outcome measurement(s): yes
Participants	38 participants, RT: 19 & CG: 19, mean age: RT 49.1 y & CG 47.7 y, years after diagnosis: RT=8.1 & CG=6.6, EDSS: 3.0-5.5, mean in RT=3.9 & CG=3.7, MS type: only RR. Withdrawals: 7/38 (4RT & 3CG), final participant number was: RT=16 & CG=15. Reasons were worsened lower back pain and personal problems not related to the intervention. Adherence: 99%
Interventions	**RT:** 16 participants (F=10 & M=6) Warm-up on stationary bicycle for 5 minutes. Every session ended with a cool-down exercise. The intervention was performed with 2 sessions/week for 12 weeks. Weight machines were used for leg presses, knee extensions, hip flexions, hamstring curls and hip extensions. Between each set, a 2-3 minute recovery time was given. *During the follow-up time, the participants were advised to continue un-supervised training. The progression model was as follows:

Weeks	Sets	Repetition	RM
Week 1-2	3	10	15
Week 3-4	3	12	12
Week 5-6	4	12	12
Week 7-8	4	10	10
Week 9-10	4	8	8
Week 11-12	3	8	8

CG: 15 participants (F=10 & M=5)
Normal physical activity until week-12. During the follow-up period, the same progressive programme that was used with RT was given and measured in week-24.

Outcomes

Outcome measures were taken at baseline, week-12 and week-24. The week-24 measurement (de-training period) was taken to see if the dependent variables were maintained.

	Baseline		Week-12		Week-24	
	RT	**CG**	**RT**	**CG**	**RT**	**CG**
Knee flexor Maximum Voluntary Contraction (KF MVC)	174.8	168.6	194.8	171.6	190.8	190.1
Knee extensor Maximum Voluntary Contraction (KE MVC)	73.2	67.2	81.8	66.4	78.2	71.1
1 RM leg press	102.4	---	140.1	86.4	---	114.4
Functional Capacity Score (FS)	100	100	121.5	96.7	121	108.9
Chair Stand test (CST)	12.9	12.2	9.3	12.9	9.2	9.9
Stair-Climbing test (SCT)	12.5	14.7	10.8	16.1	10.8	14.9
10-minute walk test	7.7	7.3	6.6	7.9	6.7	7.6
6-minute walk test	440.9	437.8	495.4	436.2	494.6	455.9

Effects of PRE for 12 weeks:
The KE MVC and KF MVC were improved by 15.7% and 37.1%, respectively, in the RT group. In the CG, there were no changes. Also, the FS was improved in the RT by 21.5% vs 3.3% in the CG.

	Effects of 12-week follow-up period: Only the KE MVC and FS were maintained at the follow-up in the RT group. In the CG, the effects of PRE after the trial were similar to what the RT gained during the trial.
Notes	

Risk of bias		
Bias	**Reviewer's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information was provided other than "…randomly assigned)".
Allocation concealment (selection bias)	Unclear risk	No information was provided.
Blinding of participants and personnel (performance bias)	High risk	The participants and personnel were not blinded to the intervention.
Blinding of outcome assessment (detection bias)	Low risk	(… blinded pre-testing……) (post-testing and testing at follow-up were blinded)
Incomplete outcome data (attrition bias)	Low risk	Outcome data were reported for all randomised participants.
Selective reporting (reporting bias)	Low risk	Study protocol was available (NCT00381576).
Other bias	Low risk	Only RR was included.

2	Dalgas et al. (2010)

Methods	Randomised, controlled trial conducted in Denmark. Study period: 24 weeks (12 intervention + 12 follow-up) Blinding of randomisation: no Blinding of intervention: no Complete follow-up: yes Blinding of outcome measurement(s): yes
Participants	38 participants, RT: 19 & CG: 19, mean age: RT 49.1 y & CG 47.7 y, years after diagnosis: RT=8.1 & CG=6.6, EDSS: 3.0-5.5, mean in RT=3.9 & CG=3.7, MS type: only RR. Withdrawals: 7/38 (4RT & 3CG), final participant number was: RT=16 & CG=15. The reasons were: worsened lower back pain and personal problems not related to the intervention. Adherence: 99%
Interventions	**RT:** 16 participants (F=10 & M=6) Warm-up on stationary bicycle for 5 minutes. Every session ended with a cool-down exercise. The intervention was performed 2 sessions/week for 12 weeks. Weight machines were used for leg presses, knee extensions, hip flexions, hamstring curls and hip extensions. Between each set, a 2-3 minute recovery time was given. *During the follow-up time, the participant was advised to continue un-supervised training. The progression model was as follows:

Weeks	Sets	Repetition	RM
Week 1-2	3	10	15
Week 3-4	3	12	12
Week 5-6	4	12	12
Week 7-8	4	10	10
Week 9-10	4	8	8
Week 11-12	3	8	8

	CG: 15 participants (F=10 & M=5) Normal physical activity until week-12. During the follow-up period, the same progressive programme used with RT was given and measured in week-24.
Outcomes	Outcome measures were taken at baseline, week-12 and week-24. The week-24 measurement (de-training period) was taken to see if the dependent variables were maintained.
Notes	

	Baseline		**Week-12**		**Week-24**	
	RT	**CG**	**RT**	**CG**	**RT**	**CG**
Fatigue Severity Scale (FSS)	5.8	5.5	5.2	5.6	4.9	5.1
Multi-dimensional Fatigue Inventory (MFI-20)	12.9	11.6	12.1	13.7	12.7	11.8
Major Depression Inventory (MDI)	10.3	8.8	7.9	9.9	8.7	8.9
SF-36 for quality of life (physical component)	41.4	42.6	44.9	41.6	45.3	41.5
SF-36 for quality of life (mental component)	54.3	55	56.8	53.1	55.4	57.8

Effects of PRE for 12 weeks:
Fatigue, mood and QOL showed significant difference in RT than CG.

Effects of PRE at follow-up:
No deterioration was found in the RT group compared with the baseline scores. In the CG, improvements were recorded in fatigue and SF-36 for quality of life (mental component), however, the mood and SF-36 for quality of life (physical component) had no improvements.

Risk of bias		
Bias	**Reviewer's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear bias	No information was provided other than "…randomly assigned)".
Allocation concealment (selection bias)	Unclear bias	No information was provided.
Blinding of participants and personnel (performance bias)	High bias	The participants and personnel were not blinded to the intervention.
Blinding of outcome assessment (detection bias)	Low bias	(…blinded pre-testing……) (post-testing and testing at follow-up were blinded)
Incomplete outcome data (attrition bias)	Low bias	Outcome data were reported for all randomised participants.
Selective reporting (reporting bias)	Low bias	Study protocol was available (NCT00381576).
Other bias	Low bias	Only RR included.

3	Dodd et al. (2011)
Methods	Randomised, controlled trial conducted in Australia. Study period: 22 weeks (10 intervention + 12 follow-up) Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: yes Blinding of outcome measurement(s): no
Participants	52 F + 19 M = 76, RT: 39 & CG: 37, mean age: RT 47.7 y & CG 50.4 y, years after diagnosis: NA, Ambulation Index: between 2-4, MS type: only RR. Withdrawals: 5/76 (3 RT & 2 CG). Adherence: 92% (RT: 18.4/20 and CG: 6.2/10)
Interventions	**RT:** 36 participants. Warm-up and cool-down exercises were not reported in the study. The intervention was performed at 2 sessions/week for 10 weeks. Weight machines were used for leg presses, knee extensors, calf raises, leg curls and reverse leg presses. Between each set, a 2-minute recovery time was given. Each session lasted for 45 minutes. 2 sets and 10-12 repetitions of 10-12 RM. The weight was increased when 2 sets of 12 rep. could be completed. Between sessions, a 48-hour rest was given. *During the follow-up period, participants only had normal activity, with no PRE. **CG:** 35 participants. Normal physical activity and social program. The social program was given for 1 hour/week for 10 weeks. *During the follow-up period, the same program was followed.

Outcomes	Outcomes measures were taken at baseline, week-10 and week-22. The week-22 measurement (de-training period) was taken to see if there was any reduction in the dependent variables.

	Baseline		Week-10		Week-22	
	RT	**CG**	**RT**	**CG**	**RT**	**CG**
Primary outcome:						
2-minute walking test (2-MWT)	120.2	112.1	122..9	112.9	118.6	113.7
Secondary outcomes:						
Muscle strength	70.0	62.2	85.8	66.0	80.2	68.3
Muscle endurance	43.4	40.7	80.9	49.7	70.2	53.1
Muscle performance	30.8	27.4	37.3	28.5	35.8	32.1
Modified fatigue impact scale (MFIS)	41.9	40.0	31.7	37.0	39.0	36.2
Health related quality of life (WHOQoL-Bref)	3.8	3.9	4.2	4.0	3.7	4.0
Multiple sclerosis spasticity scale-88 (MSSS-88): stiffness	27.0	25.1	22.4	24.7	26.5	24.2
Multiple sclerosis spasticity scale-88 (MSSS-88): spasms	22.3	22.8	20.3	23.3	23.4	21.7

week-10:
Muscle performance: leg press strength in RT increased by 16.8% but did not exceed the 26% required for minimum important difference. However, the reverse leg press strength in RT increased by 29.8% which exceeded the 29% required for minimum important difference.
Fatigue and quality of life: total fatigue reduction in RT decreased by 5.9 units but did not exceed the 7.9 units required for minimum important difference. Similarly, in the QOL domain, the RT improved by 1.5 units, but this was less than the minimum important difference of 2.3 units.

	week-22: **Muscle performance:** after 22 weeks, there were no significant increases in muscle performance and endurance. However, the decline was not to the baseline measurement point. **Fatigue and quality of life:** the fatigue domains in RT did not decrease more than the week-10 point. After week-10, this gradually increased to the baseline level. In QOL, after week-22, the RT group returned to the baseline level again.
Notes	

Risk of bias		
Bias	**Reviewer's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence.
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque envelopes, containing the allocation written on a card inside.
Blinding of participants and personnel (performance bias)	High risk	Healthcare providers and participants were not blinded to the intervention.
Blinding of outcome assessment (detection bias)	High risk	Healthcare providers and participants were not blinded to the assessments.
Incomplete outcome data (attrition bias)	Low risk	Outcome data were provided for all randomised participants.
Selective reporting (reporting bias)	Low risk	Study protocol was available (ACTRN 12607000101482).
Other bias	Low risk	Only RR was included.

4	Kjolhede et al. (2015)

Methods	Two-centre, randomised, controlled trial conducted in Denmark. Study period: 48 weeks (24 intervention + 24 follow-up) Blinding of randomisation: no Blinding of intervention: no Complete follow-up: yes Blinding of outcome measurement(s): no
Participants	35 participants, RT: 18 & CG: 17, mean age: RT 43.2±8.1 y, median years after diagnosis: 5 (range between 0.5-28), median EDSS: 3 (range between 2-4), MS type: only RR. Withdrawals: 6/35 (1 RT & 5 CG), final participant number was 29 (RT=17 & CG=12). The reasons were: in RT: the drop-out was before the intervention began due to pain (x=1). In CG: time constraints (x=2), withdrawn at follow-up period due to time constraints and logistical difficulties (x=3). Adherence: 93±5%
Interventions	**RT:** 17/18 participants (one drop-out before the intervention period) Warm-up and cool-down exercises were not mentioned in the study. The intervention was performed at 2 sessions/week for 24 weeks with 48 hours separating the sessions. Weight machines were used for horizontal leg presses, hip flexions, prone hamstring curls, leg extensions, cable pull downs and cable triceps extensions. Between each set, a 2-3 minute recovery time was given. *During the follow-up time, the participants were allowed to continue community self-guided training. The progression model was as follows:

Weeks	Sets	Repetition	Intensity
Week 1-2	3	10	15 RM
Week 3-4	3	12	15 RM
Week 5-6	3	10	12RM
Week 7-8	4	10	10 RM
Week 9-10	4	8	8 RM
Week 11-12	4	6	6 RM
Week 13-14	3	10	12 RM
Week 15-16	4	10	10 RM

Week 17-18	4	10	10 RM
Week 19-20	4	8	8 RM
Week 21-22	4	6	6 RM
Week 23-24	5	6	6 RM

CG: 12/17 participants (two dropouts before the intervention period, 3 during the follow-up period). Normal physical activity until week-24. During the follow-up period, the same progressive programme was given.

Outcomes

Outcomes measures were taken at baseline, week-24 and week-48. The week-48 measurement (follow-up period) was taken to see if the dependent variables were maintained.

	Baseline		**Week-24**		**Week-48**	
	RT	**CG**	**RT**	**CG**	**RT**	**CG**
Time 25-ft Walk Test (T25FWT)	1.65	1.77	1.82	1.77	1.8	1.86
5-time Sit To Stand (5STS)	10.0	9.0	7.9	9.3	7.4	7.7
2-minute Walk Test (5MWT)	1.60	1.63	1.78	1.67	1.75	1.69
12-item MS Walking Scale (MSWS-12)	32.5	27.2	24.0	26.0	31.4	20.7
Ascending stairs climb test	11.0	12.6	9.6	13.1	9.9	12.0

Effects of PRE for 24 weeks:
All variables were improved during the intervention period in the RT group. In the CG, no changes were found in any of the variables.
Effects of PRE at follow-up:
After 48 weeks, the effects in the RT group were maintained, except for MSWS-12, which returned to baseline level.

Notes

Risk of bias

Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No words other than ("…subjects were randomised..")
Allocation concealment (selection bias)	Low risk	Allocation was concealed by sealed envelopes.
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel were not blinded to the intervention.
Blinding of outcome assessments (detection bias)	High risk	Participants and personnel were not blinded to the assessments.
Incomplete outcome data (attrition bias)	Low risk	All drop-out participants were included in the final analysis.
Selective reporting (reporting bias)	Low risk	Study protocol was available (NCT01518660).
Other bias	Low risk	Only RR was included.

5	Medina-Perez et al. (2014)

Methods	Multi-centre, randomised, controlled trial conducted in Spain. Study period: 24 weeks (12 intervention & 12 de-training) Blinding of randomisation: no Blinding of intervention: no Complete follow-up: yes Blinding of outcome measurement(s): no
Participants	23 F + 19 M = 42, RT: 30 & CG: 12, mean age 34.05 y, years after diagnosis in RT: 11.3±6.1 & in CG: 12.2±4.5, mean EDSS between 1-6 (RT: 4.5±2.1 & in CG:4.1±0.5), MS type: only RR. Withdrawals: no one. Adherence: all 42 participants completed the full intervention period with an average adherence of 22.9±1.5 out of 24 sessions.
Interventions	**RT:** 16 F + 14 M = 30 participants. Warm-up on stationary bicycle and 1 set of 5 repetitions with a light load. Every session ended with a cool-down exercise. The intervention was performed at 2 sessions/week for 12 weeks. Weight stack machines were used for knee extensors. Between each set, a 3-minute recovery time was given. Between sessions, a 48-hour rest was given. *During the follow-up period, any PRE or structured physical activity was avoided. The progression model was as follows:

Weeks	Set 1	Set 2	Set 3
Week 1-2	35% of MVIC, 10-12 rep.	50% of MVIC, 8-10 rep	35% of MVIC, 10-12 rep
Week 3-4	40% of MVIC, 10-12 rep.	55% of MVIC, 8-10 rep.	40% of MVIC, 10-12 rep.
Week 5-6	45% of MVIC, 10-12 rep.	60% of MVIC, 8-10 rep.	45% of MVIC, 10-12 rep.
Week 7-8	50% of MVIC, 10-12 rep.	65% of MVIC, 8-10 rep.	50% of MVIC, 10-12 rep.
Week 9-10	55% of MVIC, 10-12 rep.	70% of MVIC, 8-10 rep.	55% of MVIC, 10-12 rep.
Week 11-12	55% of MVIC, 10-12 rep.	70% of MVIC, 8-10 rep.	55% of MVIC, 10-12 rep.

	CG: 7 F + 5 M= 12 participants. Normal physical activity took place. *During the follow-up period, any structured physical activity was avoided.
Outcomes	Outcome measures were taken at baseline, week-12 and week-24. The week-24 measurement (de-training period) was taken to see if there was any reduction in the dependent variables. The dependent variables were:

	Baseline		**Week-12**		**Week-24**	
	RT	**CG**	**RT**	**CG**	**RT**	**CG**
Maximal Voluntary Isometric Contraction (MVIC)	754	615	811	606	755	604
Maximal torque:	300	238	323	235	300	234
Average muscle power	173	149	200	148	193	155
Muscle endurance	21	18	22	19	20	19

Notes

Risk of bias

Bias	**Reviewer's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information other than "randomly assigned".
Allocation concealment (selection bias)	Unclear risk	No information.
Blinding of participants and personnel (performance bias)	High risk	Blinding of intervention: no.

Blinding of outcome assessment (detection bias)	High risk	Blinding to assessment: no.
Incomplete outcome data (attrition bias)	Low risk	Outcomes were reported for all enrolled participants.
Selective reporting (reporting bias)	Unclear risk	The protocol was not available.
Other bias	High risk	One type of MS was included.

6	Medina-Perez et al. (2016)

Methods	Multi-centre, randomised, controlled trial conducted in Spain. Study period: 12 weeks of intervention Blinding of randomisation: no Blinding of intervention: no Blinding of outcome measurement(s): yes
Participants	77 participants were recruited, but after withdrawals, only 40 were included and analysed (RT: 20 & CG: 20), both genders: F = 20 & M = 20, mean age in RT = 45.6y & CG = 41.3 y, years after diagnosis in both groups 10.4 y, mean EDSS (RT: 3.9 & in CG: 4.2), MS type: only RR. Withdrawals: 37/77 participants. In RT: 18 participated in less than 75% of the sessions, 10 not assist to testing sessions and 2 dropped-out. In CG: 8 participated in structured physical activity and 11 not assist to testing sessions. Adherence: 95% = All 40 participants completed the full intervention period with an average adherence of 22.8 out of 24 sessions.
Interventions	**RT:** 10 F + 10 M = 20 participants. Warm-up on stationary bicycle. Every session end with a cool-down exercise. The intervention was performed at 2 sessions/week for 12 weeks. Weight stack machines were used for knee extensors. Between each set, a 3 minute recovery time was given. Between sessions, a 48-hour rest was given. The progression model was as follows:

Weeks	Set	Repetitions	MVIC
Week 1-2	3	10	40% of MVIC
Week 3-4	3	10	50% of MVIC
Week 5-6	4	6	50% of MVIC
Week 7-8	3	6	60% of MVIC
Week 9-10	4	4	60% of MVIC
Week 11-12	3	4	70% of MVIC

	CG: 10 F + 10 M = 20 participants. Normal physical activity took place.
Outcomes	Outcome measures were taken at baseline and at week-12. The dependent variables were:

	Baseline		Week-12	
	RT	**CG**	**RT**	**CG**
Maximal Voluntary Isometric Contraction (MVIC)	866.4	858.5	943.1	871
Maximal torque	360.2	353.8	392.9	358.3
Average peak power level of MVIC (40%)	266.2	278.5	317.5	269.1
Average peak power level of MVIC (50%)	288	291.9	324.8	279.8
Average peak power level of MVIC (60%)	276.3	287.5	321.8	278.9
Average peak power level of MVIC (70%)	237.1	267.8	274.3	240.2
Average peak power level of MVIC (80%)	211.5	223.8	242	189.2

All the variables were improved in the RT group, but no changes were found in the CG.

Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information was provided other than "(… participants were randomly assigned…)".
Allocation concealment (selection bias)	Unclear risk	No information was provided.
Blinding of participants and personnel (performance bias)	High risk	Each participant was informed about the study protocol before consenting to the intervention.
Blinding of outcome assessment (detection bias)	Low risk	The researcher who took the assessment was blind to the study outcomes.
Incomplete outcome data (attrition bias)	High risk	The drop-out participants were not included in the final analysis.
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available and it was difficult to know if there were deviations from the protocol.
Other bias	Low risk	Only RR was included.

7	Moradi et al. (2015)

Methods	Randomised, controlled trial conducted in MS Iranian society in Iran. Study period: 12 weeks Blinding of randomisation: could not determine Blinding of intervention: no Complete follow-up: no Blinding of outcome measurement(s): yes
Participants	20 males only, mean age 34.05 y, years after diagnosis in RT: 8.12±4.79 & in CG: 6.5±5.78, mean EDSS in both groups: 3, MS type: RT (5RR,3SP) CG (6RR, 4SP). Withdrawals: 2 in RT in the 1st week for personal reasons. Their matched controls were also excluded in the final evaluation. The other 8 RT participants completed the full intervention period with no MS related exacerbations reported.
Interventions	**RT:** Warm-up for 5-10 minutes on a stationary bicycle or treadmill, followed by stretching. Every session ended with a cool-down exercise for 5-10 minutes. The intervention duration was 30 minutes/session, for 3 sessions/week for 8 weeks. Conventional weight machines were used for seated rowing, chest presses, leg extensions & presses. Between sessions, a 24-hour rest was given. The progression model was as follows: **CG:** Normal physical activity took place.

Weeks	Sets	Repetition	1 RM
Week 1	1	6-10	50%
Week 2	1	10-15	60%
Week 3-4	1	10-15	70%
Week 5-8	1	10-15	80%

Outcomes	Outcome measures were taken at the baseline and at the end of the intervention (pre-intervention to post-intervention). • 10-metre time walk test: **RT:** decreased, **CG:** N/C • Three-minute step test: **RT:** increased, **CG:** decreased • Time up & go test: **RT:** decreased, **CG:** N/C • Flamingo stand test: **RT:** increased, **CG:** N/C • Seated rowing, chest presses, leg extensions & presses: **RT:** increased, **CG:** decreased • EDSS: **RT:** decreased, **CG:** increased
Notes	

Risk of bias

Bias	Reviewer's judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation according to random digits by a table of random numbers.
Allocation concealment (selection bias)	Unclear	Could not determine.
Blinding of participants and personnel (performance bias)	Unclear	Could not determine.
Blinding of outcome assessment (detection bias)	High risk	Blinding of outcome assessments: no.
Incomplete outcome data (attrition bias)	High risk	The withdrawal data were disclosed but were not included in the final analysis.
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available and it was difficult to know if there were deviations from the protocol.
Other bias	High risk	Only male participants were recruited and only mild to moderate MS was present.

Appendix 9: illustration of the average number of patients flow per week during screening phase (phase one)

Table 1: The number of clinics in each hospital and the average number of patients flow per week.

KKUH

	Number of clinics	Average of patients flow per week		
		Per clinic	Characteristic	In total
Multiple sclerosis clinics	2	7 in C1 15 in C2	C1= the majority were N C2= the majority were F/O	30
Neuro-rehabilitation clinics	6	1	All were F/O	6
Lymphoedema clinic	2	8	All were F/O	16
Medical day unite	This is an in-patient unite which included 62 patients until 31/Mar/2018			

KFSH&RC

	Number of clinics	Average of patients flow per week		
		Per clinic	Characteristic	In total
Multiple sclerosis clinics	3	8	On average 5 were N	32
Neuro-rehabilitation clinics	8	1	All were F/O	8
Lymphoedema clinic	4	4	The majority were F/O	16
Medical day unite	This is an in-patient unite which included 44 patients until 31/Mar/2018			

Abbreviations: KKUH= King Khaled University Hospital, KFSH&RC= King Faisal Specialist Hospital and Research Centre, C1=Clinic 1, C2=Clinic 2, N=New patient, F/O= Follow-up patient

Table 2: Researcher timetable during each week

Day	8-9	9-10	10-11	11-12	12-1	1-2	2-3	3-4
Sun	MDU				Lunch break	MDU		
Mon	MDU					MDU		
Tue	MDU					With Dr.Nora, KKUH (neurologist, MS clinic)		
Wed	With Dr.Mona, KFSH&RC (neurologist, MS clinic)					With Dr. Algawi, KFSH&RC (neurologist, MS clinic)		
Thu	With Dr.Mona, KFSH&RC (neurologist, MS clinic)					With Dr. Abdulgader, KKUH (neurologist, MS clinic)		

Abbreviations: KKUH= King Khaled University Hospital, KFSH&RC= King Faisal Specialist Hospital and Research Centre, MDU= Medical Day Unite

Appendix 10: Case report form (baseline template)

CASE REPORT FORM

Baseline Template

Chronic Lower Limb Oedema in a Population of Saudi Arabian Residents with Multiple Sclerosis: Evaluation of Progressive Resistance Exercise

Principal Investigator:

Name of Site:

Participant initials

Study code

CRF Instruction

General

- Complete the CRF using a pen and ensure that all entries are complete and legible.
- Avoid the use of abbreviations and acronyms.
- The CRF should be completed as soon as possible after the scheduled visit.
- Do not use participant identifiers anywhere on the CRF, such as name, hospital number etc., in order to maintain the confidentiality of the participant. Ensure that the header information (i.e. participant's initials and ID number) is completed consistently throughout the CRF.
- Each CRF page should be signed and dated by the person completing the form.
- The 'completed by' Name in the footer of each page must be legible and CRFs should only be completed by individuals delegated to complete CRFs on the Site Delegation log (and signed by the PI).
- Ensure that all fields are completed on each page:
  - If a test was Not Done record ND in the relevant box(es)
  - Where information is Not Known write NK in relevant box(es)
  - Where information is not applicable write NA in the relevant box(es)

Corrections to entries

- If an error is made, draw a single line through the item, then write the correct entry on an appropriate blank space near the original data point on the CRF and initial and date the change.
- Do NOT
  - Obscure the original entry by scribbling it out
  - Try to correct/ modify the original entry
  - Use correction fluid

Dates and Times

Complete all dates as day, month, year i.e. 13/05/2008. Partial dates should be recorded as NK/05/2008.

All times are to be recorded in 24 hours format without punctuation and always use 4-digits; i.e. 0200 or 2130. Midnight is recorded as 0000.

Storage

CRF documents should be stored in a locked, secure area when not in use where confidentiality can be maintained. Ensure that they are stored separately to any other documents that might reveal the identity of the participant.

Baseline (T0) template

Participant initials

Study code

Baseline (T0) CRF template

Date of Assessment: __ __ / __ __ / __ __ __ __
(DD / MM / YYYY)

Informed Consent	
Date that participant signed written consent form:	**__ __ / __ __ / __ __ __ __** (DD / MM / YYYY)
Name of person taking informed consent: _____	

Demographic Data	
Date of Birth:	__ __ / __ __ / __ __ __ __ (DD / MM / YYYY) estimated age: _____
Gender	○ Male ○ Female
Weight	_____ kg
Waist circumference (cm)	_____ cm

Past Medical History	
1. When did you diagnosed with MS?	_____ years ago
2. Have you experience any MS attack(s) in the last 6 months?	○ Yes when? _____ ○ No
3. When was your last MS attack?	_____
4. Do you have a history of any of the following:	Cardiac problem: ○ Yes when? _____ ○ No Renal problem: ○ Yes when? _____ ○ No Liver disease: ○ Yes when? _____ ○ No

Baseline (T0) template

Participant initials

Study code

5. Do you have any history of the following in the last 6 months:	Lower limb fracture ○ Yes when? _____ ○ No Ankle sprain: ○ Yes when? _____ ○ No Cancer: ○ Yes when? _____ ○ No If YES, are you under medication? _____

Range of motion (ROM)		
	R	**L**
Plantar flexion		
Dorsiflexion		

Muscle strength		
	R	**L**
Plantar flexion		
Dorsiflexion		

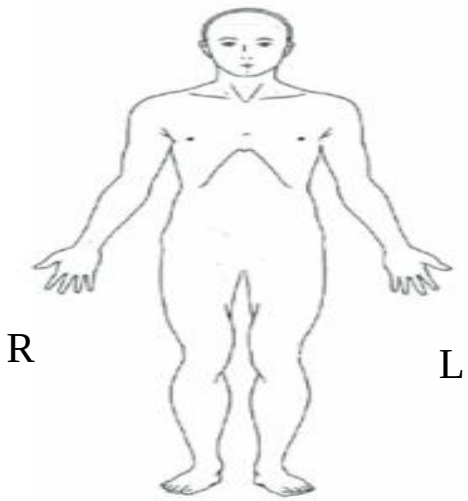
Skin condition				
Skin condition in both limb area is mainly:	**R**		**L**	
	+	**-**	**+**	**-**
Dryness				
Pigmentation				
Fragility				
Redness				
Warmth				
Cellulitis				
Fungal infection				
Scars, wounds and ulcers				
Stemmer sign				
Tissues in the affected area are mainly: soft / firm Sensory changes:				

Baseline (T0) template

Participant initials

Study code

Pitting oedema test (p=pitting, NP=none pitting)



Location	R	L
Toes		
Leg		
Thigh		

Lower Limbs circumference

Instruction on how to make the lower limb circumference: (Moffatt et al. 2006)

- Ask the patient to stand or sit with both feet firmly on the ground
- On the medial aspect of the leg* measure with a ruler and record the distance from the floor to 2cm above the middle of the medial malleolus†. Mark this point on the patient. This determines the starting point
- Mark the same point on the contralateral leg
- Seat patient on a chair with bottom as close to the edge as possible, or seat on a couch with the leg straight lie a ruler along the medial aspect of the leg and mark the limb at 4cm intervals from the starting point to 2cm below the popliteal fossa for swelling below the knee
- If swelling extends above the knee, ask the patient to stand or to lie on a couch.
- Continue the marks at 4cm intervals above the knee to 2cm below the gluteal Crease with the limb in a relaxed position, measure the circumference at each mark, placing the top edge of the tape measure just below the mark
- Note measurements above the knee in the correct section of the paper or electronic recording form
- Repeat the process on the other limb. Ensure there are the same number of measurements for both legs

Document the position the patient was in when measurements were taken

	Lower limb	
	R	L
Foot circumference (cm)		
Starting point (cm)		
Below knee (cm)		
Above knee (cm)		

Baseline (T0) template

Participant initials

Study code

Calculating one Repetition Maximum (1RM)							
In this part, the participant will select the starting weight	**Planter flexion**		**Dorsiflexion**		**Rest between attempts**	**Number of attempts**	**Note**
	R	**L**	**R**	**L**			
Final weight	Kg	kg	Kg	kg			Started weight:

Participant's PRE programme for 12 weeks										
	1-RM		**40% 1-RM**		**50% 1-RM**		**60% 1-RM**		**70% 1-RM**	
	R	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**
Planter flexion										
Dorsiflexion										

Week number	**Session number**	**% of 1RM**				**Repetitions**	**sets**	**Rest between sets**	**Note**
Week 1	Session 1	R	PF 40%= kg	L	PF 40%= kg	10	3	min	
			DF 40%= kg		DF 40%= kg				

Principal Investigator's Name:

Principal Investigator's Signature:

Appendix 11: **Case report form (follow-up template)**

CASE REPORT FORM

Follow-up template

Chronic Lower Limb Oedema in a Population of Saudi Arabian Residents with Multiple Sclerosis: Evaluation of Progressive Resistance Exercise

Principal Investigator:

Name of Site:

Participant initials

Study code

Follow-up template

Participant initials
Study code

Follow-up Template

Date	Week number	Session number	% of 1RM	Repetitions	sets	Rest between sets	Note	Signature
	Week 1	Session 2	40%= kg	10	3	min		
	Week 2	Session 3	40%= kg	10	3			
		Session 4	40%= kg	10	3			
	Week 3	Session 5	50%= kg	10	3			
		Session 6	50%= kg	10	3			
	Week 4	Session 7	50%= kg	10	3			
		Session 8	50%= kg	10	3			

Follow-up template

Participant initials
Study code

Date	Week number	Session number	% of 1RM	Repetitions	sets	Rest between sets	Note	Signature
	Week 5	Session 9	50%= kg	06	4			
		Session 10	50%= kg	06	4			
	Week 6	Session 11	50%= kg	06	4			
		Session 12	50%= kg	06	4			
	Week 7	Session 13	60%= kg	06	3			
		Session 14	60%= kg	06	3			
	Week 8	Session 15	60%= kg	06	3			
		Session 16	60%= kg	06	3			

Follow-up template

Participant initials
Study code

Date	Week number	Session number	% of 1RM	Repetitions	sets	Rest between sets	Note	Signature
	Week 9	Session 17	60%= kg	04	4			
		Session 18	60%= kg	04	4			
	Week 10	Session 19	60%= kg	04	4			
		Session 20	60%= kg	04	4			
	Week 11	Session 21	70%= kg	04	3			
		Session 22	70%= kg	04	3			
	Week 12	Session 23	70%= kg	04	3			

Appendix 12: **Case report form (discharge template)**

CASE REPORT FORM

Discharge Template

Chronic Lower Limb Oedema in a Population of Saudi Arabian Residents with Multiple Sclerosis: Evaluation of Progressive Resistance Exercise

Principal Investigator:

Name of Site:

Participant initials

Study code

Discharge (T1) Template

Participant initials

Study code

Discharge (T1) Template

Date of Discharge Assessment: __ __ / __ __ / __ __ __ __
(DD / MM / YYYY)

Week number	Session number	% of 1RM				Repetitions	sets	Rest between sets	Note
Week 1	Session 1	R	PF 40%= kg DF 40%= kg	L	PF 40%= kg DF 40%= kg	10	3	min	

Demographic Data	
Weight	_____ kg
Waist circumference (cm)	_____ cm

Range of motion (ROM)

	R	L
Planter flexion		
Dorsiflexion		

Muscle strength

	R	L
Planter flexion		
Dorsiflexion		

Skin condition

Skin condition in both limb area is mainly:	R		L	
	+	-	+	-
Dryness				
Pigmentation				
Fragility				
Redness				
Warmth				
Cellulitis				
Fungal infection				
Scares, wounds and ulcers				
Stemmer sign				

Tissues in the effected area are mainly: soft / firm

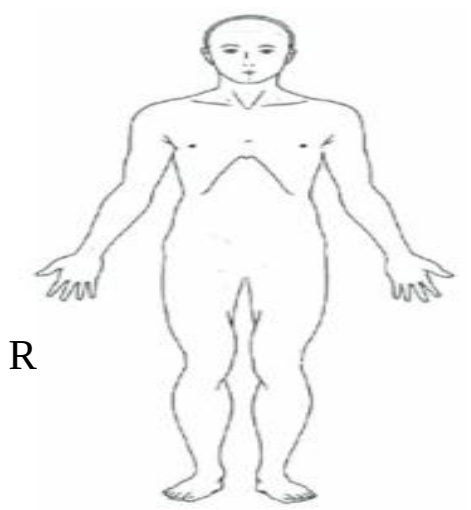
Sensory changes:

Discharge (T1) Template

Participant initials

Study code

Pitting oedema test (p=pitting, NP=none pitting)



Location	R	L
Toes		
Leg		
Thigh		

Lower Limbs circumference

Instruction on how to make the lower limb circumference: (Moffatt et al. 2006)

- Ask the patient to stand or sit with both feet firmly on the ground
- On the medial aspect of the leg* measure with a ruler and record the distance from the floor to 2cm above the middle of the medial malleolus†. Mark this point on the patient. This determines the starting point
- Mark the same point on the contralateral leg
- Seat patient on a chair with bottom as close to the edge as possible, or seat on a couch with the leg straight lie a ruler along the medial aspect of the leg and mark the limb at 4cm intervals from the starting point to 2cm below the popliteal fossa for swelling below the knee
- If swelling extends above the knee, ask the patient to stand or to lie on a couch.
- Continue the marks at 4cm intervals above the knee to 2cm below the gluteal Crease with the limb in a relaxed position, measure the circumference at each mark, placing the top edge of the tape measure just below the mark
- Note measurements above the knee in the correct section of the paper or electronic recording form
- Repeat the process on the other limb. Ensure there are the same number of measurements for both legs

Document the position the patient was in when measurements were taken

	Lower limb	
	R	L
Foot circumference (cm)		
Starting point (cm)		
Below knee (cm)		
Above knee (cm)		

Discharge (T1) Template

Participant initials

Study code

Study completion

Did participant complete the trial?	○ Yes ○ No, Please provide date of withdrawal and complete below: __ __ / __ __ / 2 0 __ __
Early Withdrawal: please provide the reason(s) of participant's early withdrawal:	
Principal Investigator's Name:	**Date of Signature:** __ __ / __ __ / 20 __ __
Principal Investigator's Signature:	
ONCE SIGNED, NO FURTHER CHANGES CAN BE MADE TO THIS CRF	

Appendix 13: Arabic version of short form of the McGill pain questionnaire (SF-MPQ)

الصيغة الموجزة مكجيل لاستبيان الآلم
رونالد ميلزاك

اسم المريض: _____ التاريخ: _____

	لا يوجد	خفيف	متوسط	مرتفع
الم نابض				
الم شديد				
الوخز				
حار				
التشنج				
القضم				
حرق شديد				
مؤلم				
ثقيل				
رقيق				
انشطار				
تعب. انهاك				
الغثيان				
الخوف				
الم قاس للغايه				

لا يوجد ألم |_____| أسوء ألم ممكن

مقدار الألم حاليا:

٠ لا يوجد ألم
١ خفيف
٢ مزعج
٣ مقلق
٤ مخيف
٥ موجع

Appendix 14: Arabic translation of quality of life measure for limb lymphoedema (LYMQOL) tool (lower limb part)

LYMQOL LEG

أداة نوعية الحياة لمرضى الوذمة اللمفية

صُمِّم هذا الاستبيان وتم التحقق من صحته للمرضى الذين يعانون من تورم او انتفاخ مزمن في إحدى الساقين أو كلتيهما لقياس نوعية الحياة.
يُرجى وضع علامة في المربع الذي يوفر أفضل وصف لما تشعر به بشأن كل سؤال من الأسئلة.

الاسم: ..... **رقم المستشفى:** .....

التاريخ: .....

(س١) ما مدى تأثير ساقك المتورمة على الأنشطة التالية؟
في حالة عدم انطباق أي عنصر على حالتك، يُرجى كتابة لا ينطبق في مربع (مربعات) الإجابة ذي الصلة.

	لا تؤثر على الإطلاق	قليلاً	إلى حد بعيد	كثيرًا
a) قدرتك على المشي				
b) قدرتك على الانحناء، على سبيل المثال. لربط أربطة الحذاء أو قص أظافر أصابع القدم				
c) قدرتك على الوقوف				
d) قدرتك على النهوض من وضع الجلوس على كرسي				
e) عملك				
f) قدرتك على أداء الواجبات المنزلية				

(س٢) هل يؤثر التورم في أنشطتك الترفيهية/حياتك الاجتماعية؟

يُرجى ضرب أمثلة على ذلك

.....

.....

(س٣) ما مدى حاجتك للاعتماد على أشخاص آخرين؟

	لا يحدث على الإطلاق	قليلاً	إلى حد بعيد	كثيرًا
(س٤) ما مدى شعورك بأن التورم يؤثر في مظهرك؟				
(س٥) ما مدى الصعوبة التي تواجهها للعثور على الملابس المناسبة؟				
(س٦) ما مدى الصعوبة التي تواجهها للعثور على الملابس التي تحب أن ترتديها؟				
(س٧) هل تجد صعوبة في العثور على الأحذية المناسبة؟				
(س٨) هل تجد صعوبة في العثور على الجوارب / الرداءات المحكمة / الجوارب النسائية المناسبة؟				
(س٩) هل يؤثر التورم في شعورك بنفسك؟				
(س١٠) هل يؤثر في علاقاتك مع الآخرين؟				
(س١١) هل تتسبب الوذمة اللمفية في شعورك بالألم؟				
(س١٢) هل تعاني من أي تنميل في ساقك (ساقيك) المتورمة؟				
(س١٣) هل تشعر بوخز "دبابيس وإبر" أو وخز في ساقك (ساقيك) المتورمة؟				
(س١٤) هل تشعر بضعف في ساقك (ساقيك) المتورمة؟				
(س١٥) هل تشعر بثقل في ساقك (ساقيك) المتورمة؟				

في الأسبوع الماضي....

	لا على الإطلاق	قليلاً	إلى حد بعيد	كثيرًا
(س١٦) هل واجهتك مشاكل في النوم؟				
(س١٧) هل واجهت صعوبة في التركيز على الأشياء، مثل القراءة؟				
(س١٨) هل شعرت بالتوتر؟				
(س١٩) هل شعرت بالقلق؟				
(س٢٠) هل شعرت بالتهيج؟				
(س٢١) هل شعرت بالاكتئاب؟				

(س٢٢) بوجه عام، كيف تقيم نوعية حياتك في الوقت الحاضر؟

يُرجى وضع علامة على درجتك على المقياس التالي:

٠	١	٢	٣	٤	٥	٦	٧	٨	٩	١٠
ضعيف										ممتاز

شكرًا لك لإكمال هذا النموذج.

إذا كانت لديك أي تعليقات أو استفسارات حول هذا الموضوع، فيُرجى مناقشتها مع .....

تم نسخ الأسئلة من 16 إلى 21 بإذن من EORTC.
تعد هذه الأسئلة جزءًا من استبيان QLQ-C30