Decongestive Progressive Resistance Exercise with Advanced Compression for Breast Cancer Related Lymphedema Management (DREAM): A Pilot Randomized Control Trial

by

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ABSTRACT

Introduction: More than one in five women who survive breast cancer will eventually develop lymphedema. Recent studies in breast cancer lymphedema management have demonstrated that resistance exercise can improve the survivors' quality of life without exacerbating their lymphedema. However, research has not yet considered other elements of the lymphedema management regimen that may promote arm volume reduction. Using both compression and the decongestive exercise sequence in a progressive resistance exercise program has the potential to improve not only the survivors' quality of life, but also their arm lymphedema volume.

Objectives: A randomized controlled pilot trial was conducted to investigate the feasibility and preliminary efficacy of combining exercise and compression to improve arm lymphedema volume, arm function, and quality of life.

Methods: Fifteen women with stable breast cancer related lymphedema were recruited through the Cross Cancer Institute and randomly assigned to one of the following three groups: (i) Standard care (n=6): home decongestive exercise regimen plus day time compression only, (ii) Decongestive Progressive Resistance Exercise (DPRE) plus use of a daytime compression sleeve during exercise (n=3), and (iii) DPRE plus use of an adjustable compression wrap garment during exercise (n=6).

Data analysis: Feasibility outcomes were analyzed descriptively. For the purpose of analyses for the pilot study, the two DPRE groups were combined into a single DPRE group (n=9). An Independent samples T-test was used to compare the outcomes of the two groups to inform point estimates and measures of variability for a future multi-center trial.

Results: Feasibility data demonstrated high study completion (93%), attendance (91%) and adherence to prescribed protocol of DPRE program (97%). A statistically significant between group difference was found in the mean change of excessive arm lymphedema volume (p=.027)

in favour of the DPRE group. Moreover, statistically significant between group improvements in favour of DPRE group were found for upper body strength (p=0.048), and vitality (p=0.007). **Conclusion:** This pilot study showed that a twice weekly supervised DPRE program is feasible in women with BCRL, with preliminary evidence of benefit for reducing lymphedema arm volume and fatigue, and improving muscular strength. Results will guide the design and development of a large scale RCT.

PREFACE

This thesis is an original work by Mona Moraybed Al Onazi. The research project, of which this thesis is a part, received research ethics approval from Health Research Ethics Board of Alberta: Cancer Committee, Project Name "Decongestive Progressive Resistance Exercise and Compression for Breast Cancer Related Lymphedema Management (DREAM): A Pilot Randomized Control Trial", No. HREBA.CC-16-1026, March 9, 2017.

DEDICATION

This thesis is dedicated...

*to my beloved mother, **Nourah**, the origin of my success who provided unflagging prayers and support, may God bless you.*

*to the soul of my father, **Moraybed**, who believed in me and encouraged me to reach for the stars, I love you and miss you so much.*

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DEFINITIONS AND ABBREVIATIONS

CANCER RELATED

- **Breast cancer:** is a cancerous (malignant) tumour that starts in the cells of the breast and can grow into and destroy nearby tissue. There are different types of breast cancer, depending on the tissue in the breast where the cancer starts; ductal carcinomas: are cancers that start in cells that line the ducts (the tubes that carry milk from the glands to the nipple), lobular carcinoma: start in the cells of the lobules (the groups of glands that make milk). Both ductal carcinoma and lobular carcinoma may be in situ (cancer is still where it started and has not grown into surrounding tissues), or invasive (they have grown into surrounding tissues). Other types of breast cancer are less common or rare such as inflammatory breast cancer and Paget's disease of the breast[1].

BREAST CANCER TREATMENT RELATED

- **Lumpectomy:** a surgical procedure that involves removing the cancer and some normal tissue around it; however the remaining breast tissue is preserved[1].
- **Modified Radical Mastectomy:** a surgical removal of the entire breast and is combined with an axillary node dissection[1].
- **Sentinel-lymph-node biopsy (SLNB):** A specialized procedure that involves the dissection of the first (sentinel) or first few lymph nodes that receive lymphatic fluid from the breast tumour[1].
- **Axillary lymph node dissection (ALND):** surgical procedure to remove some (traditional: levels I and II) or all (complete: levels I, II, and III) of the lymph nodes from the axilla (underarm) that may potentially contain cancer[1].
- **Metastatic breast cancer:** (also called advanced breast cancer or stage 4) The cancer has spread beyond the breast to other distant parts of the body. This usually includes the lungs, liver, bones or, less commonly, brain[1].
- **Radiotherapy or radiation therapy:** a local treatment that uses high-energy ionizing rays or particles to kill cancer cells, and stops them from growing and dividing. Radiotherapy may be used to reduce the size of the tumor in advanced stage disease[1].
- **Chemotherapy:** a systemic therapy that aims to target possible distant micrometastases (i.e. cancer cells that have moved to another area of the body). Treatment involves the use

of chemical agents to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing[1].

- **Deep vein thrombosis:** a serious condition that occurs when a blood clot (thrombus) forms in one or more of the deep veins in the body. Symptoms may include pain, swelling, redness, or warmth of the affected area[2].
- **Cellulitis:** a bacterial infection of the skin and subcutaneous tissue. It is a sudden, non-contagious infection of the skin, characterized by redness, swelling and heat, and may be accompanied by pain and tenderness[2].

LYMPHEDEMA RELATED

- **Lymphedema:** an accumulation of protein-rich fluid in the subcutaneous tissue of the affected body part as a result of decreased lymphatic transport capacity and/or increased lymphatic load after cancer treatment[3].
- **Breast Cancer Related Lymphedema (BCRL):** a chronic swelling that occurs in the arm, breast and chest wall on the side of the breast cancer as a result of breast cancer and/or breast cancer treatment[3].
- **The lymphedema absolute volume (LAV):** the total volume difference (millilitres) between the edematous arm the non-edematous arm[4].
- **The lymphedema relative volume (LRV):** is the percent difference in total limb volume between the edematous arm and the non-edematous arm[4].

STUDY DESIGN RELATED

- **Fast-track trial:** a study design where the control group receives the experimental intervention within study period. This type of design is used when participants may have a high preference for the experimental intervention.

INTERVENTION RELATED

- **Manual lymphatic drainage (MLD):** is a specialized manual massage technique follows a specific sequence that aims to redirect fluid from swollen areas to healthy lymphatic vessels[3].
- **Decongestive exercise:** an active, repetitive, non-resistive movements that follow a specific sequence of muscle contractions from proximal to distal in order to promote both venous and lymphatic return by stimulating lymphatic (or lymph) regions proximal to the edematous area first[3].

- **Decongestive Progressive Resistance Exercise (DPRE):** a method that incorporates progressive resistance exercise principles into the decongestive exercise regimen (sequence of muscle contractions from proximal to distal to promote both venous and lymphatic return).

CHAPTER 1: INTRODUCTION

Breast cancer is the most common cancer among women worldwide with 1.38 million women diagnosed every year[5]. In 2018, approximately 26,500 Canadian women will diagnosed with breast cancer and 87% will survive for at least five years[6]. Despite the advances in breast cancer detection and treatment which account for an increasing survivorship rate, many of these survivors still face health-related challenges that compromise their quality of life (QOL)[7-10]. Breast cancer-related lymphedema (BCRL) is one of the most distressing and debilitating side effects of breast cancer treatment feared by more than 50% of breast cancer survivors after breast cancer surgery[7]. BCRL is a swelling that occurs in the arm, breast and chest wall on the side of the breast cancer. Lymphedema is an accumulation of protein-rich fluids in the subcutaneous tissue of the affected body part as a result of decreased lymphatic transport capacity and/or increased lymphatic load after cancer treatment[3]. The reported incidence of lymphedema has varied among studies as a result of differences in lymphedema definitions and measurement methods, as well as length of follow-up. The incidence of BCRL increases with time, especially in the first two years post breast cancer diagnosis and surgery[9]. The recent estimated incidence, based on 30 prospective cohort studies[9], is 21%. Meaning that, on average, one in five women who are diagnosed with breast cancer will likely develop lymphedema.

1.1 BCRL and Quality of Life (QOL)

Lymphedema is a chronic and progressive condition that requires lifelong management[7-9]. Development of arm lymphedema results in disfigurement and physical disability as a result of increased size and weight of the affected limb[7-10]. Additionally, the condition can cause pain, impact shoulder range of motion and arm strength; and is often associated with recurrent limb infection[8]. Women with BCRL are twice as likely to develop

progressive upper-body functional limitations when compared to women with breast cancer without the condition[8, 10]. Living with lymphedema is also reported to be more stressful for women than living without a breast and can negatively impact body image[8]. Women report having lymphedema is a constant reminder of the disease, that a larger arm is difficult to hide, and wearing a compression garment on the arm can make them feel stigmatized[8, 11]. Moreover, a larger arm makes it hard for women to find proper clothing[8]. BCRL may limit the women's ability to take part in usual hobbies or work; and some women retire early due to inability to work[8]. As a result, developing BCRL may impact survivors financially[12, 13]. Overall, women with BCRL have been found to have poorer self-reported health and QOL compared with those without the condition[11, 14].

1.2 Etiology and Diagnosis

1.2.1 Causes and Risk Factors

BCRL remains a major problem facing survivors. Treatments for breast cancer, including surgery, lymph node dissection, radiotherapy, or chemotherapy, are the main risk factors for developing lymphedema[9, 15]. Strong evidence has shown that more extensive surgery and lymph node dissection, adjuvant radiotherapy, post-operative infection, and the presence of metastatic lymph nodes all increase the risk of lymphedema[9]. As an example, the rate is four times higher with axillary lymph node dissection (ALND) than with sentinel-lymph-node biopsy (SLNB)[9]. Other risk factors not directly related to the disease include being overweight or obese (BMI > 30 kg/m2), and leading a sedentary life style[9, 15].

1.2.2 Lymphedema Diagnosis

While early diagnosis and treatment of lymphedema is important for better outcomes[9], the current methods of clinical diagnosis by health care professionals rely mainly on observation and arm measurements. At present, a standardized definition of lymphedema is

lacking[11]. Conventionally, the most common documented criterion for clinical diagnosis of lymphedema has been a difference of two centimetres or more in arm girth (at any location), with the affected limb larger than the non-affected arm. Additionally, other methods used to quantify limb volume and serve as a diagnostic cut-point include a 200 ml limb volume increase or 10 percent limb volume increase[9, 16]. Paskett et al.[11] found that the 10% limb volume increase in the affected limb is more conservative than a 200 ml increase; and does not capture all of the lymphedema cases. While self-reported symptoms of pain, heaviness, and swelling are considered predictive of lymphedema[16]; patient reported incidence varies.

Once diagnosed, BCRL is further categorized by severity. This is determined using volume differences and evaluated as follows, if the excessive arm volume is >5 to <20%, it is categorized as mild; if the excessive arm volume is 20 to 40%, it is categorized as moderate; if the excessive arm volume is >40% increase, it is categorized as severe[17].

Numerous tools and instruments can be used to measure lymphedema. Measurement of circumference is one of the more common methods used in the clinical setting[11, 15, 16]. It is an inexpensive and reliable method if used by trained assessors[9]. Water displacement has long been considered the gold standard for lymphedema measurement, as it is a valid, reliable and the device is inexpensive to purchase[16]; however, issues related to infection control (cleaning of the tank between patients) and time required for testing (~30 minutes) make it impractical clinically[15]. Another method of quantifying lymphedema limb volume is through use of a perometer, an optoelectrical volumeter using infrared technology. The perometer has excellent validity and reliability, and is quick and easy to perform; however, the device is expensive to purchase[15, 16]. Bioimpedance spectroscopy is a tool to measure extracellular fluid and has been found to be sensitive to early changes in extracellular fluid[9, 11, 15]. Due to its potential to detect lymphedema in its earliest stages, bioimpedance spectroscopy is recommended as a measurement tool in the six-to-twelve month period after surgery when the risk of developing

lymphedema is high[9]. Using a combination of measurement methods including arm volume (i.e. perometry) and extracellular fluid (i.e. bioimpedance spectroscopy) is likely optimal for early detection.

1.3 BCRL Treatment

To date, there is no cure for lymphedema. Management of the condition focuses on limb swelling reduction or maintenance, and preventing lymphedema-related complications such as infection or cellulitis[11, 15]. Such management includes pharmacological therapy, surgical approaches, and conservative therapy[15]. At present, there is no evidence supporting the effectiveness of pharmacological treatments such as benzopyrones, flavonoids, diuretics, hyaluronidase, pantothenic acid, and selenium[15, 18]. Similarly, surgical approaches do not cure lymphedema[19]. The aims of surgery are to improve lymphatic flow using lymphovenous or lympholymphatic anastomoses; or to improve lymphedema symptoms by removing fibrotic tissue, subcutaneous adipose tissue and excess skin[15, 19]. Following surgery for lymphedema, use of a compression garment on the limb is required to maintain the results[19]. Thus, surgery does not remove the need for ongoing conservative management. Moreover, surgery can result in possible complications such as infection, recurrent swelling, and impaired wound healing[19]. As a result, surgery is generally only considered when the ratio of benefit outweighs the risk such as when conservative treatment fails to control the progression of lymphedema and/ or function of the limb is significantly compromised[15].

Conservative treatment, therefore, remains the mainstay of lymphedema management. Conservative treatment approaches aim to reduce the lymphedema limb volume and maintain the reduction over time. Complex decongestive therapy (CDT), known also as Complex decongestive physiotherapy (CDP) is the standard approach in lymphedema management[3]. It involves a two-phase treatment program. The first phase, or intensive phase, lasts for 2-4 weeks and includes skin care, manual lymphatic drainage (MLD), compression therapy using

multilayer bandaging, and decongestive (remedial) exercises[17]. The aim of this phase of treatment is to reduce the lymphedema volume. Immediately after phase 1, the second phase, or maintenance phase, is started, and aims to enhance or maintain the results achieved in the first phase. In the maintenance phase the survivor is fitted with a compression garment and is often instructed to continue the decongestive exercises, to perform self-MLD and/ or self-bandaging at night, and to follow guidelines for ongoing skin care[15, 17]. Adherence to the prescribed treatment regimen is essential for long-term control of lymphedema; and is used to prevent condition progression and complications[15].

1.3.1 Compression Therapy

Compression therapy is one of the main elements in lymphedema management and may be the sole therapy in Phase I[20]. Compression therapy is achieved using multi-layered short stretch compression bandaging or multilayer bandaging, velcro wrapping systems, and/or compression sleeves[22, 23]. Multilayer compression bandaging is used daily for a two-to-four week period to reduce and/or control the swelling and can be applied for use at night during the maintenance phase[24]. Compression bandaging uses low stretch tensor bandages that provide low pressure to the limb when resting (low resting pressure) and high pressure (high working pressure) when the muscles beneath the bandaging contract. The high working pressure helps to enhance the muscle pump effect on the deep lymphatic and venous systems, thus improving lymph flow[25]. The amount of resting and working pressure depends on the elasticity and compression level of the bandaging or garment[26].

Velcro wrap systems. One of the available options for applying compression to the arm is through use of a velcro wrap system. The system comes with adjustable straps that allow the woman with BCRL to adjust the compression. It is also known as an *adjustable compression wrap*. The wrapping system works on the principle, similar to short stretch compression bandaging, of applying low resting pressure and high working pressure[27]. These garments are

made of a soft, light fabric, and have short stretch straps with velcro that can be tightened to provide support and compression to the limb. The adjustability of the straps allows the woman to easily modify the degree of compression to the limb depending on the need[23, 27]. The garment is comfortable to wear, easy to apply, and not as bulky as compression bandaging. For these reasons, the garment can be used as an alternative to a compression sleeve during the day, or to replace night bandaging in the maintenance phase of treatment[27]. There are different types of adjustable wrap systems available on the market for women with BCRL; however, they are costly to purchase and the therapeutic benefit of their use during exercise is still unknown.

Compression sleeves. Following intensive lymphedema treatment (once the lymphedema volume has reduced and plateaued), the woman is fitted for a compression garment (sleeve). Compression sleeves prevent re-accumulation of the swelling in the arm and require daily use lifelong[17]. The compression garment is used each day during waking hours for a 10-12 hour period. There are several factors that are considered by a practitioner when prescribing compression garments such as severity of lymphedema, shape of the limb, and survivor's preferences in order to optimize adherence and effectiveness[22, 26].

The available compression sleeves are fabricated in one of two ways: circular knit (long stretch) or flat knit (short stretch)[22], and both are available as ready-to-wear or made-to-measure (custom-made) garments. The circular knit sleeves are made with light threads in a cylindrical pattern using continuous knitting, which results in a garment that is seamless and has a high level of elasticity[22]. Circular knit sleeves tend to be more comfortable and cosmetically elegant and are often preferred by survivors; however, due to the high elasticity, circular knit garments have high resting pressures (i.e. potential for tourniquet effect, thus not ideal for rest or sleep) and have low working pressures (i.e. not as effective to enhance muscle pump effect on the deep lymphatics)[26].

In contrast, flat knit compression garments have a low level of elasticity as they are fabricated with a higher number and heavier threads, giving a stiffer fabric finish[26]. The stiffness of the compression garment provides a higher working pressure[26], improves the muscle pump effect on the lymphatics, and consequently, helps with control of the swelling[26, 28]. Compression garments are prescribed with a specific compression level, which is generally between (~20-60 mmHg)[17]. There are three classes of compression that can be prescribed: class 1 (light compression), class 2 (medium compression), and class 3 (strong compression)[22]. With regular use the garment loses compression over time; thus, women with BCRL are advised to replace the garment every 4-6 months to maintain the required amount of compression on the limb[29].

Considering the survivor's level of activity is important when selecting the type and characteristics of the compression garment. There are numerous factors impacting the pressure amplitude under the compression garment when exercising. For instance, the exercise type and intensity; chosen muscle group and its efficiency; and compression material and level of pressure[30]. Hirai et al.[30] showed that using a stiffer or short stretch garment increases the amount of pressure under the garment during exercise, suggesting that short stretch garments may result in better muscle pump action when compared to circular-knit garments[30]. In theory, augmenting muscle pump activity may result in improved venous and lymphatic return, thus reducing lymphedema volume[30]. However, no study has been conducted to test whether the type of compression used during exercise influences arm lymphedema volume.

1.3.2 Exercises

Exercise is a key component of lymphedema management. Lymphedema-specific exercises known as the *decongestive or remedial exercise regimen,* comprise active, repetitive, non-resistive movements involving the trunk and limb[21]. The regimen includes diaphragmatic breathing and gentle movements that follow a specific sequence of muscle contractions from

proximal to distal[21]. The aim of the exercise sequence is to promote both venous and lymphatic return by first stimulating lymphatic (or lymph) regions proximal to the edematous area[3, 21]. Adherence to compression use and the decongestive exercise regimen during maintenance phase of conservative treatment is associated with better maintenance of limb volume reduction[3, 31].

To optimize health and wellbeing, women with BCRL are counseled to avoid sedentary behaviours and to engage in general physical activity. Recent evidence supports the safety of exercises such as aerobic and resistance exercise on BCRL and the efficacy of resistance exercise to improve lymphedema symptoms and reduce the frequency of relapses (i.e. flares) in lymphedema[32-34].To date, however, data is lacking on use, or nonuse, of compression during exercise, with studies either not reporting data related to compression use during exercise or making use of compression optional for participants[33, 34]. Thus, questions remain over whether women with BCRL need to wear, or would benefit from use of a compression garment during exercise.

1.4 Statement of the Problem

Current guidelines from the National Lymphedema Network (NLN) suggest beginning exercise with a resistance exercise program involving low resistance, a slow progression of intensity, and monitoring of the survivor's symptom response[21]. Clinicians, however, are often reluctant to prescribe progressive resistance exercise to women with BCRL due to the lack of a detailed protocol to guide the exercise prescription. Moreover, questions remain over the need for, and best type of, compression to use on the arm during exercise. To date, no studies have been performed combining all potential therapeutic targets to address lymphedema including: (1) progressive resistance exercise, (2) use of the decongestive exercise sequence and (3) wearing of compression on the limb during exercise.

In theory, having women with BCRL perform a progressive resistance exercise training program that follows the decongestive sequence, while wearing compression on the limb, has the potential to reduce lymphedema volume and symptoms, ultimately improving function and quality of life.

1.5 Clinical Research Questions

The objective of this randomized controlled pilot trial was to determine the feasibility and preliminary efficacy of combining compression with a specifically designed Decongestive Progressive Resistance Exercise (DPRE) program on arm lymphedema volume, symptoms, function and quality. If shown to be feasible, a future large-scale randomized trial will be conducted including the data from this pilot study.

1.6 Hypothesis

1.6.1 Hypotheses related to Feasibility

We hypothesized that combining DPRE program with or without advanced compression (AC) will be feasible in terms of survivor's:

1. ***Recruitment rate:*** (the percentage of participants who are eligible and consent to participated in the study).
2. ***Adherence rate:*** to exercise program (the percentage of sessions, sets, and repetitions completed by participants), and adherence to compression use during exercise and non-exercise day-time use (>80%).
3. ***Completion rate:*** (the percentage of participants who are completing study including the exercise intervention, and all follow-up assessments).

1.6.2 Hypotheses related to Study Outcomes

We hypothesized that:

1. Combining the DPRE program with or without AC will show promise in reducing arm lymphedema volume when compared to standard care;
2. Combining the DPRE program with or without AC will show promise in improving arm function, body image, and quality of life when compared to standard care;

CHAPTER 2: PAPER ONE

Title: A Combined Approach of Resistance Exercise with Compression for women with Lymphedema: Systematic Review and Meta-Analysis

Abstract

Purpose:

Lymphedema is the most common impairment presenting in approximately 21% of women with breast cancer, and is incurable, progressive, and chronic. To date, evidence supports a neutral effect of resistance exercise (RE) on arm lymphedema volume; however, little is known about the benefit of combining compression therapy with RE for breast cancer related lymphedema (BCRL).

Materials and Methods:

Searches were conducted including Medline, EMBASE, CINAHL, SportDiscus, and PEDRO for articles that evaluated the combination of compression therapy and RE as an intervention for BCRL. We included randomized control trials, controlled clinical trials, and single group studies that examined the effect of RE with compression on BCRL. We abstracted data on study design, sample size, intervention program type and duration, control group program, compression garment adherence, and key lymphedema outcomes.

Analysis:

The study results were combined, as appropriate, using a random effects models. When pooling was not possible, a qualitative analysis was conducted based on Putting Evidence into Practice.

Results:

Three hundred and fifty-two studies were found and nine met all inclusion criteria. Studies generally prescribed mild to moderate intensity RE in combination with use of a compression garment. Pooled data of three studies prescribing low intensity RE showed benefit in reducing lymphedema volume (Standardized mean difference: 0.618; p=0.01). Although the preliminary

findings suggest benefit from the combination of RE and compression, details were lacking on compression garment features and time worn.

Conclusions:

Findings suggest potential benefit from combined compression therapy and RE. Further high quality research is needed that includes reporting of data related to compression garment features and use during and following exercise sessions.

1.7 Introduction

Breast cancer is the most common cancer in women. In 2018, over 3.1 million women live with a history of breast cancer in the United States[35]. Advances in treatment and early detection have resulted in improved survival, with the number of survivors increasing yearly. This has brought attention to issues related to optimizing both quantity and quality of life (QOL). Many survivors face life-long issues due to the consequences of side effects of breast cancer treatment. Breast cancer-related lymphedema (BCRL) is one of the most common, and feared, effects of cancer treatment among survivors[9, 36]. It is an important cause of morbidity in an estimated 21% of women with breast cancer [9]. BCRL occurs as a result of damage to the lymphatic system after cancer or cancer treatment and it is characterized as a chronic progressive swelling of the affected arm, breast and trunk[36]. Lymphedema occurs as a result of the accumulation of protein-rich fluid in the interstitial spaces that is due to the obstruction or disruption of lymphatic system from surgery and/ or radiation therapy[9, 36]. Women with BCRL experience multiple physical and psychological impairments, such as pain, recurrent infections, and limitations in shoulder and arm mobility impacting ability to lift objects and perform tasks overhead.[36, 37]. Moreover, women may have difficulty finding clothing that can accommodate the swollen arm[36, 37]. Thus, women with BCRL may experience limitations in their ability to cook, clean, perform hobbies and sports, and work-related tasks. As a result, women with BCRL often report poorer QOL compared to survivors without the condition[8, 38, 39].

As lymphedema is a chronic progressive condition, survivors with BCRL must adhere to lifelong risk reduction practices and self-management guidelines. For decades, women with or at risk of BCRL were instructed to avoid any aggressive, repetitive or strenuous movements with their upper extremities[37, 40]. Over time, this advice was challenged, and several large-scale studies have supported the safety of resistance exercise (RE) and progressive resistance exercise (PRE), with no adverse effects found on lymphedema symptoms or the extent of the

swelling[41-50]. Moreover, the benefits of RE for QOL outcomes among breast cancer survivors have been established [45, 46, 50]. As a result, current recommendations advise women with BCRL to perform RE with supervision initially, and with gradual progression of exercise intensity over time[21].

At present, however, little is known about the use of compression garments during PRE, specifically detail is lacking related to garment features and adherence. During exercise, compression on the limb may potentially provide a counterforce against the muscle contraction, optimizing the muscle pump effect on the deep venous and lymphatic vessels, thus enhancing tissue fluid clearance and lymphatic return[51, 52]. However, the benefit or lack of benefit from use of compression during exercise may be influenced by factors such as the type of compression garment, elasticity of the garment material, and the level of compression in the garment[30]. Considering that compression therapy is one of the main strategies in lymphedema management, further investigation into the benefits of compression use during exercise is warranted. We performed a systematic review and meta-analysis to examine the evidence on the use of combined RE and compression therapy for BCRL.

1.8 Material and Methods

1.8.1 Research Question

What is the benefit of combined RE and compression therapy on breast cancer-related lymphedema? We used the PICO search method to organize the eligibility criteria for considering studies for this review.

1.8.2 Study selection

Two reviewers (MO, MM) screened the titles and abstracts and then the full text using the PICO search strategy. Studies were eligible if they met the following criteria:

P: women with a clinical diagnosis of breast cancer related lymphedema

I: intervention of any form of RE with compression use during exercise. Studies that used weight or strength training or gravity resistance exercise either as a supervised or home-based program were included. Studies were required to provide information on compression garment use, even if wearing the garment was optional during exercise program. If the use or non-use of a compression garment was not reported for participants in the exercise program, the study was excluded.

C: comparison with no exercise, no compression, an alternative intervention, or usual care. Studies with additional interventions were included if the effect of the combined compression and RE intervention effect could be isolated.

O: the study included the measurement of limb volume as an outcome. Secondary outcomes could include quality of life, ROM, muscle strength and lymphedema symptoms such as tension, heaviness, pain.

S: study designs included randomized control trials (RCT), and controlled clinical trials.

1.8.3 Search strategy

To identify all relevant trials, we conducted electronic database searches from the date of inception until April 2018 in the following databases: Medline, EMBASE, CINAHL, SportDiscus, and PEDRO. We used the following search terms: Breast cancer (Breast Neoplasm*, mastectomy, breast tumor, malignance, ductal, breast), lymphedema (lymphedema, lymphoedema, chronic swelling), Resistance Exercise (Resist* exercise* or weight training or resist* training or strength training or weightlifting or (lift* n4 weight*) or gravity resistive or isotonic or isometric), (Appendix A).

1.8.4 Data abstraction

We abstracted data on the study design, sample size, lymphedema status, intervention program including type and duration, control group intervention, compression garment adherence, limb volume change post treatment and outcome data relevant to function, and

quality of life.

1.8.5 Statistical analysis

After considering heterogeneity among the trials, we combined the study results, as appropriate, using random effects models. Trials were combined using Comprehensive Meta Analysis (Comprehensive Meta Analysis ™, Copyright © 1999 by Biostat®). Continuous data that were the product of a number of different scales or methods were summarized as the standardized mean difference (SMD). All similar studies were pooled and point estimates reported with their associated 95% confidence intervals (CI). Statistical heterogeneity was assessed using a chi-square test that considered a p-value of less than 0.10 to indicate significant heterogeneity. I-squared values were also used to quantify the proportion of the variability in study effect among the studies. Recommended cut-points for I-squared values of 25%, 50% and 75% were used to describe low, moderate and high heterogeneity, respectively[53].

1.8.6 Methodological quality assessment

The methodological quality of the included RCTs was appraised by two independent reviewers based on modified Jadad scale[54]: 1) sequence generation, 2) allocation concealment, 3) blinding of outcome assessors, 4) incomplete outcome data, 5) selective outcome reporting, 6) adherence to exercise program (> 80%), and 7) adherence to compression use (> 80%). We assessed the studies to determine whether they had low, unclear, or high risk of bias.

1.8.7 Synthesis of Findings

We used the research grading system from the Oncology Nursing Society (ONS) *Putting Evidence into Practice (PEP)* level of evidence guidelines in making recommendations for practice[55]. The weight-of-evidence categories were as follow: recommended for practice, likely to be effective, benefits balanced with harms, effectiveness not established, effectiveness unlikely, or not recommended for practice.

1.9 Results

A comprehensive literature search identified 352 studies as shown in Figure 1. An additional four studies were identified through grey literature and searching the studies' references for a total of 356 studies. After removing 172 duplicates, we screened the titles and abstracts of 184 studies for inclusion. We performed a full review of 23 manuscripts and a total of 9 studies including 354 participants[41, 42, 44-49,50], were deemed appropriate for inclusion in the review. Table 1 shows the characteristics of the 9 selected studies. The included articles involve seven randomized controlled trials examining exercise interventions[41, 44-,48,50], and two randomized cross-over trials examining the acute effect of exercise[42, 49].

1.9.1 Overview of Participants

Women had a mean age of 56.2 years, with a mean time since lymphedema of 45.7 months and a range of 4.8 to 93.6 months. One study[50] did not mention the timing relative to lymphedema diagnosis. No studies reported the lymphedema stage. Two studies[42, 49] examined the acute effect of RE on lymphedema volume with or without a compression sleeve use during exercise. The other seven studies prescribed an intervention program involving RE and compression[41, 44-48, 50].

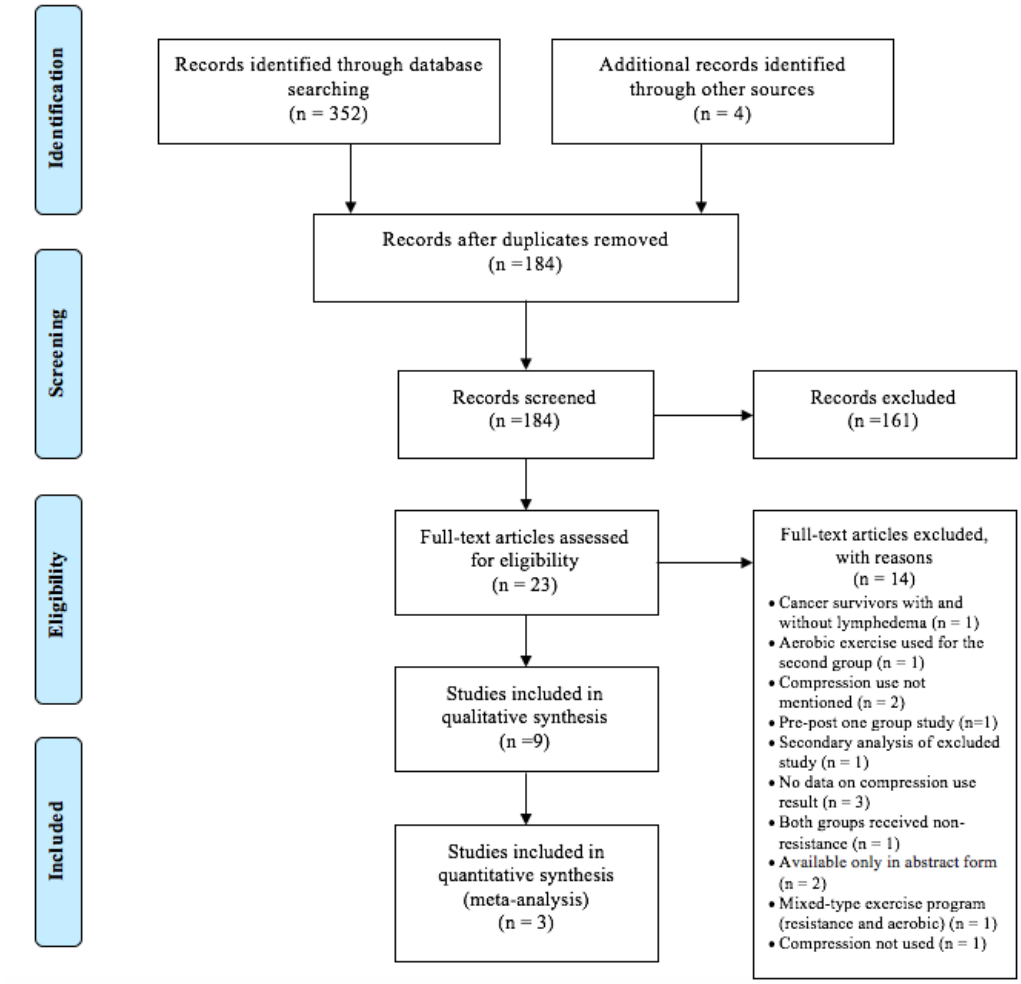

Figure 1: *Systematic review flow diagram*

1.9.2 Use and Characteristics of Compression Garments (*Table 2*)

Adherence to compression garment use during exercise

Using compression during RE was required[41, 44, 46-48, 50] or a component of the intervention[45] in the included studies. One study indicated that adherence was "high" without providing clear details about the adherence[44]. Jeff et al. (2013)[44] reported that 91.5% of the participants wore a compression garment "for the greater part of each day", however, it is not clear if that included wearing the garment during exercise. McClure et al. (2013)[45] reported monitoring adherence and covarying for use in the analysis. However, the authors did report the data on the actual adherence to wearing compression during exercise. Similarly, Schmitz

et al. (2009)[47] reported no significant difference between the exercise group and control group in their adherence to garment; however, no actual data was provided.

Adherence to compression garment use during the day

All the studies reported participants wearing a compression garment during the daytime; however, data was generally lacking on details of adherence in terms of days per week and hours per day worn. Reporting was generally vague with studies reporting that participants used garments "during exercise"[41, 46]; "daily and during exercise"[43, 47, 50]; 50% of the time [45], all times expect when they go to sleep[48] or for "the greater part of the day" [44].

Characteristics of compression garment

Only three of nine studies reported details on the compression garment characteristics, such as compression degree[48, 49] and compression sleeve type[44]. Additionally, two studies mentioned that the compression sleeve was 'new custom-fitted'[47],or 'well fitted' [50]. One of the acute exercise studies provided details about the compression sleeve used during exercise[49]; the other acute exercise study mentioned that five participants wore a "personally-fitted" compression sleeve and that other participants wore their own garments (details not provided)[42].

1.9.3 Overview Exercise Interventions (*Table 3*)

Studies of acute exercise intervention programs (single bout exercise)

Two studies with 53 participants measured the acute effect of low[49] and moderate[42] intensity RE on lymphedema with or without a compression sleeve. Johansson et al. (2005)[49] prescribed low-intensity RE session using dumbbells with and without compression; each session separated by one-day included five exercises that were performed 10 times for each arm, repeated for three sets with a two-minute rest in between each set. Singh et al. (2015)[42] prescribed a moderate-intensity RE program, with and without compression and a minimum of

six-day wash-out period. Each RE session included three sets of six exercises that were performed 10-12 times for each arm with a two-minute rest between each exercise and each set. The moderate intensity RE program was introduced over four familiarization sessions where the weight was progressed from low to moderate intensity[42].

Studies of short and long term intervention programs

Seven studies[41, 44-48, 50] with 301 participants involved short- and long-term RE programs. The duration of the intervention varied among the included studies with three studies of 8 weeks [41, 46, 50], one of 17 weeks[45] , two of 24 weeks[44, 48] , and one of 52 weeks duration[47]. Three studies provided supervised progressive RE program[41, 47, 50] using low intensity light weight upper body RE[41], and low to moderate intensity upper and lower body RE[47, 50]. A combined program of supervised RE intervention followed by a home program were prescribed in two studies[45, 46], including upper body concentric gravity-resistance exercise[45] or light weight upper body RE[46]. The other two studies prescribed a home program of gravity resistive isotonic arm exercises[44] or light resistance exercise (resistance type not specified)[48].

Frequency

Variability was also found across studies in the frequency of the exercise program. For the five studies prescribing mild intensity exercise programs, the frequency of exercise ranged from five days per week[46] to daily[41, 44, 45]. The three studies involving mild-to-moderate intensity progressive resistance exercise programs were carried out two to three times a week[47, 48, 50].

Equipment

Of seven intervention studies, three did not use any external weight in their RE program[44, 45, 48], one study reported using weight training [50], while two studies reported using dumbbells[41, 46]. The final study reported using a community fitness center for upper and lower

limb weight training exercise including machines for seated row, chest press, lateral or front raises, bicep curls, and triceps pushdowns, leg press, back extension, leg extension, and leg curl[47].

Adherence to exercise programs

Adherence to exercise programs was reported as attendance rates in three of seven intervention studies[44, 45, 47]. In general, attendance was higher in supervised exercise programs ranging from 96%[47]; however, attendance rates were found to drop overtime with longer duration studies[47] and reported to drop during the unsupervised component of a combined program[45]. One study prescribed a home program and reported an adherence rate of 84%[44].

1.9.4 Adverse Events

Of the two acute studies, one reported no adverse events[42], the other study reported no changes in the symptoms of heaviness or tightness[49]. Among intervention program studies, four studies reported no adverse events[44,45,46], or major adverse events[47], the other studies did not mention whether or not any adverse events occurred as a result of the exercise program[41,48,50].

1.9.5 Study Outcomes (*Table 4*)

Studies of acute intervention programs (single bout of exercise): effectiveness not established *(Table 5)*

Lymphedema status

Two studies examined the effect of a single bout of exercise and compression on lymphedema. Johansson et al. (2005)[49], in a cross-over trial showed a significant ($p>0.001$) temporary increase in arm volume after RE, using water displacement method, in both conditions: with and without compression. After 24 hours, no significant differences were found in arm lymphedema volume in either condition when compared to baseline, suggesting recovery over time, irrespective of wearing compression. In contrast, Singh et al. (2015)[42], in

a similar cross-over trial reported a significant immediate reduction of lymphedema when participants wore a compression garment during exercise and when measured by bioimpedance. However, no significant differences in measurement of circumference or bioimpedance score were found after 24 hours, irrespective of whether participants exercised with or without garment.

Lymphedema symptoms and RPE

There were no significant changes in the reported feeling of heaviness, tightness or pain measured by VAS after low[49] and moderate[42] intensity single bout exercise. The RPE scores were equivalent to low[49] or moderate[42] after each session whether participants were wearing the compression or not. However, Johansson et al. (2005)[49] found significant increase of the RPE in the group who did not wear the compression sleeve after second and third session ($p \leq 0.01$)

Studies of short and long term intervention programs:

Lymphedema outcome measure

Lymphedema outcome measurement methods varied among the included studies. Limb volume measurements using water displacement were used in two studies[47, 50], circumference measurements in five studies[41, 45, 46, 48, 50], Bioelectrical Impedance Analysis in one study[45], and perometry in one study[44]. Ultrasonography was used in a single study[41] to measure the thickness of the subcutaneous tissue and muscle. Lymphedema symptoms and self-reported severity of lymphedema were assessed in another study[47].

Lymphedema status

Mild intensity RE (no external weight): likely to be effective (Table 5)

There was insufficient information on the lymphedema outcomes data to pool all included studies. Three RE intervention studies[44, 45, 48], with 74 participants were included in

the quantitative synthesis as shown in Figure 2. Pooled analysis revealed a significant reduction (p=0.010) in lymphedema volume after the RE program with an effect size of 0.618, suggesting a potential moderate effect of RE on lymphedema volume.

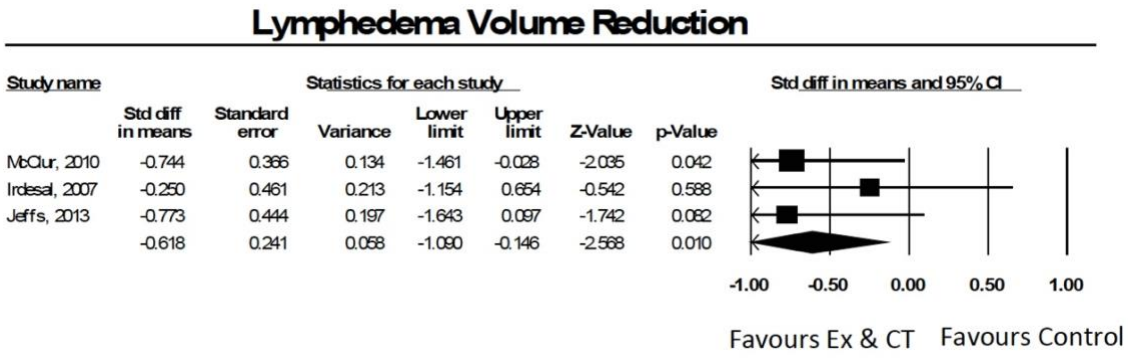

Figure 2: *Meta-analysis of resistance exercise program (no weight used) studies on lymphedema*

All three pooled studies prescribed a low-intensity RE either home-based[44, 48] or combined supervised and home-based[45] program. McClure et al. (2013)[45] reported significant improvement in lymphedema measurements (p = .049). However, when limb volume was calculated, findings were not statistically significant. Jeff et al. (2013) reported a significant within group reductions in arm volume (usual care group and exercise group), as measured by perometry, p=0.041, p=0.013, respectively; however, no significant between group differences were found. Irdesel et. al (2007)[48] compared exercise only with exercise and compression, and reported a significant *within group* improvement in distal measurements (based on measurement of circumference in the forearm) in the exercise and compression group, starting at week two (p = 0.032), and the improvement was seen at one-month (p=0.046), three-month (p=0.009) and six-month (p=0.008) follow-ups. Whereas the exercise only group showed improvement at proximal measurements (upper arm) in the first month (within group: p=0.043).

Mild to moderate intensity RE (using external weight): likely to be effective (Table 5)

Two studies[41, 46], out of five used external weight during RE, reported within group improvement in lymphedema volume measurements. These studies involved 95 participants and used low intensity RE. They reported within group improvement in proximal[41, 46] and in distal[41] lymphedema volume measurements using circumference measurements after eight weeks in RE group only. Bok et. al (2015)[41] found within group significant increase in the muscle thickness of proximal and distal arm with a reduction in the thickness of subcutaneous tissue in the RE group after the intervention program. Although, Schmitz et al. did not find any significant changes in lymphedema volume after a one-year RE program, they reported a lower incidence of lymphedema exacerbations and symptoms in favour of the RE group (between group difference: p= 0.03)[47].

Upper Limb Status and Function

Shoulder ROM was measured in three studies[44, 45, 48] using a goniometer. Muscle strength was measured in one study[47] using bench press and leg press. The results showed improvement in total active ROM[45] and upper limb muscle strength[47] and lower limb strength[47].

Quality of life

Four studies measured quality of life using the 36-Item Short Form Survey (SF-36)[45, 46, 50] and one using the lymphedema-specific 28-item LYMQOL questionnaire[44]. Two of the studies[45, 46] using the SF-36, found a significant improvement in specific domains of physical function, with general health found in one study at end of the program (8-week)[46], and vitality in another study at the 5-week point (end of supervised period of study) of a 17-week program[45].

1.9.6 Quality Assessment

Most of the included studies revealed unclear risk of selection bias, as the methods of sequence generation or allocation concealment method were often not described. Furthermore, blinding of the outcome assessment was either unclear or rated as high risk in the included studies. Out of the seven intervention RCTs, three reported adherence and only 2 (29%) met the standard for high adherence (> 80%) to exercise. Across all intervention studies, data was lacking on adherence to compression use specifically during exercise to allow for evaluation (Figure 3).

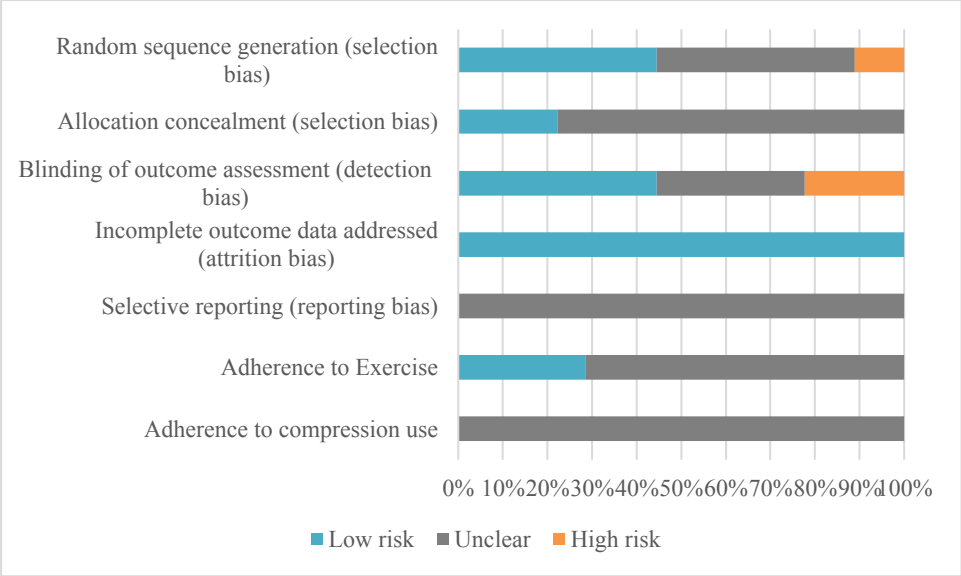

Figure 3: *Quality Assessment of Randomized Controlled Trials*

1.10 Discussion

Despite the fact that use of a compression garment is a key element in lymphedema management, there is still controversy about whether women should wear a garment when exercising. As a result, clinically, the decision to wear a compression garment or not during exercise is often left to the woman herself[42,49].

The available evidence from the two studies examining the acute effect (single sessions) of RE and compression showed that the RE does not exacerbate the lymphedema symptoms

such as pain, tightness, or heaviness regardless of garment use or non-use during exercise[42,49]. The studies also found that at the 24-hour follow-up, increases in arm volume were resolved whether a compression sleeve was worn or not during exercise. Yet, the immediate effect of RE and compression on arm volume differed across studies, with one study showing benefit and the other not. This may have resulted from the different lymphedema measurement methods, exercise protocols and exercise intensities (low versus moderate) among the two studies.

In intervention trials, use of a compression sleeve during low-intensity RE program (without using any form of external resistance weight) has been evaluated directly[48] or indirectly[44, 45]. Our pooled data from the three RCTs suggested potential benefits of RE in lymphedema management. (standardized mean difference: 0.618; p=0.01)[44, 45, 48]. These exercise programs are simple and can easily be prescribed to women with BCRL as a home program. However, more details are needed on compression garment characteristics, and adherence during and following exercise to provide better clarity on the relative benefit of compression during RE exercise.

At present, there is insufficient evidence on the effect of combined compression and RE (using weights) on arm lymphedema volume. The strongest evidence available by Schmitz et al. (2009)[47] did not show a statistically significant difference in lymphedema volume after 12-months of a low-to-moderate RE program, however, the authors reported benefit for lymphedema exacerbations and symptoms. The other studies failed to show significant between group differences in arm volume and/or subcutaneous fatty tissue[41, 46]. A pre-post single group study by Johansson et al. (2014)[43], showed a trend towards reduction of fat tissue in the upper arm (p=0.07) using MRI after 12-week of low to moderate weight lifting home program. They also reported a smaller increase in arm volume on the affected side compared with the healthy one, leading to a significant reduction of excessive lymphedema volume

(p=0.03) and percentage (p=0.005) post PRE[43]. These data suggest that using imaging methods such as MRI may help to better explain changes in arm volume and composition after RE program. Moreover, there is a lack of research examining moderate-to-high intensity RE.

The findings of this systematic review are not conclusive. Many of the included studies demonstrated a high risk of bias when considering adherence to both RE and compression therapy. In this review, we considered 80% or more as a high adherence to both exercise and compression. Studies generally did not report the adherence for the RE component or rates were not clear, and none of the studies reported details on adherence to compression during exercise. As there are currently differing opinions in regards to compression use or not during exercise, adequate reporting of adherence is needed to better understand the relative benefit, if any, from the addition of compression. Additionally, reporting the compression type and features needs to be considered in future trials. Jeff et al. (2013)[44] found a significant improvement in both groups at the mid-point of their intervention program (12-week) and the authors stated that this improvement in control group might be due to a large of proportion of the participants in this group who were wearing a flat-knit compression garment. A study by Hirai et al. (2001)[56] showed that the flat-knit garments are more beneficial in enhancing the muscle pumping during exercise. While the type of garment has not been formally tested in the research setting, clinically survivors with lymphedema report greater benefit from use of flat-knit compression garments for exercise and activity.

This review also revealed that adherence to an exercise program among participants was better with supervised programs compared with home programs. Moreover, declines in adherence were reported after the supervised period of two studies with supervised and self-directed components[45, 47]. Schmitz et. al, (2009) found that adherence was the highest during the supervised period (first 3 months) with a rate of 96%. They noted that adherence rates slowly declined in the self-directed period to 88%, 81%, and 75% in the second, third, and last

quarters of the year respectively. These findings suggest the need for using different strategies to increase the adherence to exercise program.

1.10.1 Clinical implications of the study

Using a combined therapy of a compression and RE for women with stable BCRL is likely to be effective and can help in reducing lymphedema limb volume and exacerbations symptoms. This combined approach may also help improve arm strength and quality of life.

1.10.2 Study Strength and limitations

To the best of our knowledge, this is the first review to examine the effect of combined therapeutic approach of RE and compression on BCRL. However, this review has several limitations, notably the poor methodological quality of most of the included trials with high risk of bias mainly in reporting details on exercise and compression therapy adherence. Additionally, due to limited number of eligible studies; and the use of different outcome measures and data reporting across these studies, we were not able to pool the data from all the studies.

This review reveals gaps in the evidence based intervention of BCRL. These gaps include (1) a lack of high quality research examining the effect of RE in conjunction with compression use on BCRL, (2) a need for standardization of outcome measurement methods to evaluate changes in lymphedema volume, and (3) better reporting of compression features and monitoring of adherence to compression both during and following exercise.

1.11 Conclusion

A combined treatment of low-to-moderate-intensity RE with compression use has the potential to reduce lymphedema limb volume. The findings of this review also support the finding of previous reviews on the potential benefits of RE program on survivors' QOL and lymphedema symptoms. However, there is a current gap in our understanding of the need for,

and best type of compression to use during exercise. Thus, future research on the effectiveness of RE with compression for women with breast cancer related lymphedema is warranted.

ACUTE EXERCISE STUDIES					
Author (year) & Study Design	**Participants, Mean Age (SD)**	**Exercise Intervention**	**Compression Features and Adherence**	**Control/ Comparison**	**Result**
Singh et al. (2015)[42] Multi-centre randomized cross-over trial	22 women with BCRL + **-Age:** 61.5 (9.2) **-Length of lymphedema:** 7.8 years (8.4) **-Lymphedema volume:** not reported	-One session of exercise with compression and one without compression separated by ≥ 6 day wash-out period. -Exercise: moderate intensity resistance exercise (3 sets of 10-12 repetitions, 2 min rest between exercises. -6 upper extremity exercises.	Five participants wore custom compression sleeve (23-32 mmHg). No details provided for other participants.	NA: Cross-over study	Statistically significant decrease in lymphedema arm volume following exercise when compression was worn (measure by BIS). P<.01 No statistically significant difference over the time (24-hour) between the two groups
Johansson et al. (2005)[49] Randomized cross-over trial	31 women with BCRL **-Age:** 55.3 ±7.3(40-68) **-Length of lymphedema (in months):** 66.7 ±51.7 **-Lymphedema volume (ml):** 396.7 ±163 **(%):**17.2±7	-One session of exercise with compression and one exercise session without compression: 3day wash-out period. Random assignment: to compression sleeve on either day 1 or day 4 of exercise training. Free weights/ dumbbells 5 exercises x10 rep. repeated in three sets with 2-minute rest in between.	-Standard type or custom-made compression sleeve of at least 23-32 mmHg. The sleeve was < 3 months old. Garment worn by participants: at least 2 weeks prior to study start: worn during the day and night or daytime only.	NA: Cross-over study	No significant differences in lymphedema arm volume with or without compression sleeve
SUPERVISED EXERCISE					
Author (year) & Study Design	**Participants, Mean Age (SD)**	**Exercise Intervention**	**Compression Features and Adherence**	**Control**	**Result**
Bok et al. (2016)[41] RCT	32 women with BCRL. RE group: 16 Non RE group: 16 **-Age:**	Progressive resistance exercise performed after standard conservative therapy **Mode:** series of exercises using	Participants wore a compression sleeve or applied multilayer bandage	Standard care: manual lymphatic drainage, non-	No significant difference in circumference between groups

	RE group: 45.4 (8.8) Non RE group: 53.3 (9.54) **-Length of lymphedema (in months)**: RE group: 17 (8.2) Non RE group: 18 (12.99) **-Lymphedema volume**: not reported	a 0.5 kg dumbbell. **Frequency:** 5 days, twice a day **Intensity:** the number of repetitions increased every week by adding five additional repetitions. **Duration:** 8 weeks 6 upper body exercises	during exercise. **Characteristic of garment and Adherence:** not mentioned	elastic bandage compression therapy, and skin care. **Time:** 1 hour a day **Frequency:** 5 days a week for two weeks.	No significant difference in the thickness of subcutaneous tissue of the affected limb between groups No significant difference in muscle thickness between groups
Schmitz et al. 2009[47] RCT	141 women with BCRL **-Age:** IG: 56 ±9 CG: 58 ±10 **-Length of lymphedema (in years):** range:1-15 years **-Lymphedema volume (%):** IG: 15 ±14.7 CG: 17.3 ±6.6	**52 week intervention:** Progressive RE program (supervised x 13 weeks) **Time:** 90-min session **Frequency:** 2x/ week Stretching, cardiovascular warm-up, abdominal and back exercises, and weight-lifting exercises. **Intensity:** little-to-no resistance at start. 7 Upper-body exercises 5 Lower-body exercises	Wore compression sleeve daily and during weight lifting **Characteristic of garment:** New custom-fitted compression garment provided at baseline and at 6 months **-Adherence:** (results not provided) stated no significant differences between groups	Control group: continued with their own exercises	No serious adverse events. Significant between group benefit for self-reported severity of lymphedema symptoms ($p = 0.03$) and upper- and lower-body strength ($p < 0.001$ for both comparisons) and a lower incidence of lymphedema exacerbations

McKenzie et al. 2003[50] RCT	14 women with BCRL **-Age:** 56.6 ±9 IG: 56.4 ±10.4 CG: 56.9 ±8.2 **-Length of lymphedema (in months):** not mentioned **-Lymphedema volume (%):** IG: 128.9.5 ±12.2 CG: 126.2 ±13.6	**8 weeks** supervised progressive upper-body exercise program The training sessions consisted of a 5-7 minute period of aerobic warm-up such as cycling or walking, 5 minutes, stretching for major body parts, the strength training program, the strength exercises prescribed were the seated row, bench press, latissimus dorsi pull down, one arm bent-over rowing, tricep extension, and bicep curl. After 2 weeks, added upper-body aerobic exercise, using an arm cycle ergometer	-Well fitted compression sleeve was used by each participant for all exercise sessions and daily by all participants in both groups. -Adherence: not measured	No specific exercise instruction	No between group significant differences in arm volume and QOL.
COMBINED SUPERVISED AND HOME EXERCISE PROGRAM					
Author (year) & Study Design	**Participants, Mean Age (SD)**	**Exercise Intervention**	**Compression Features and Adherence**	**Control/ Comparison**	**Result**

Kim et al. 2010[46] RCT	40 women with BCRL **-Age:** IG: 50.5 ±10.58 (27-71) CG: 50.9 ±9.15 (39-76) **-Length of lymphedema (in months):** IG: 4.35 ±12.91 (1-57) CG: 5.24 ±12.61 (0.5-68) **-Lymphedema volume(cm^3):** IG: 7913.11 ±271.88 CG: 7570.14±429.63	**8 weeks** (supervised x 2 weeks with CDPT) After the remedial exercise of the CDPT, the patients performed shoulder stretching exercises followed by RE using dumbbells for 15 minutes while wearing a compression garment or a multilayer bandage Six upper body exercises prescribed	Compression garment or multilayer bandage worn during exercise **-Adherence and Characteristic:** not reported	-The first 2 weeks: CDPT (manual lymphatic drainage, compression therapy, and remedial exercise) was led by a physical therapist once a day, 5 times a week groups. The remaining 6 weeks: continued self-administered CDPT	-No significant difference in arm volume between both groups -Significant improvements in role physical and general health in active resistance exercise compared with non-active resistance exercise group (P.<05)
McClure et al. 2010[45] RCT	32 women with BCRL **-Age:** IG: 57 ±2.9 (30.7);78) CG: 59.7 ±2.1 **-Length of lymphedema (in months):** IG: 53.3 ±813.8 (3,222) CG: 45.7 ±14.4 (2,228) **-Lymphedema volume(ml):** not mentioned	Concentric gravity-resisted arm, flexibility exercises and diaphragmatic deep breathing **Duration:** 17-weeks program **Frequency:** daily either at home or during the required 1-hr biweekly group sessions for 5 weeks followed by 3 months self-directed program. **Intensity:** Low-to-moderate intensity **Mode:** Proximal to distal	- Both group instructed to wear compression garment **-Characteristic of garment:** not mentioned -**Adherence**: included as covariate in the repeated-measures mixed model.	Standard Care "Continued with health professionals' recommendations"	Significant improvement in lymphedema measurements using BIA (p = .049) but not calculated volume measurements between groups. -Adherence to compression was not a significant factor -Significant between group improvement in total shoulder AROM (p = .034) in favour of exercise

		sequence, concentric gravity-resistive arm movements: shoulder flexion, abduction, and external rotation correspond with the inhaling breath.			-Significant between group improvement in vitality at 5-week (p= .05) in favour of exercise
HOME EXERCISE PROGRAM					
Author (year) & Study Design	**Participants, Mean Age (SD)**	**Exercise Intervention**	**Compression Features and Adherence**	**Control/ Comparison**	**Result**
Jeff et al. 2013[44] Pilot RCT	23 women with BCRL **-Age:** IG: median 66 yrs CG: median 64.5 yrs **-Length of lymphedema (months):** IG:58 CG:67.5 **-Lymphedema volume in ml (%):** IG: 410 mls (15.4%) CG: 631 mls (25.6%)	**6-month** home exercise program Standard self-care plus home-based exercise (a series of gravity resistive isotonic arm exercises in a sequence designed to simulate MLD)	**Characteristic of garment:** Flat knit: IG: 7 CG: 11 Circular knit: IG:4 CG:1 **Adherence:** IG: 91%, CG: 92% **Duration:** "greater part of each day"	Standard self-care: compression garment	No between group differences.
Irdesel et al. 2007[48] Pilot RCT	19 women with BCRL **-Age:** 51.6 ±8.8 (33-64) **-Length of lymphedema (in months):** 23.5 ±16.8 (3-60) G1: 26.6 ±17.4 G2: 20.8 ±16.6 **- Lymphedema volume(ml):** not reported	Home exercise program consisted of upper extremity ROM exercises and light resistive exercises **Duration:** 6-months **Frequency:** 3×/day	-Intervention Participants advised to wear the garments at all times expect when sleeping during duration of study. **-The compression garments feature:** 40 mmHg of pressure. **-Adherence:** not reported	Control: same exercise program, no compression	No significant between group differences.

Table 1: *Summary of included studies*

Table 2: *Compression use and characteristic*

Author (year)	Characteristic	Duration	Adherence
Bok et al. (2016)[41]	Not reported	Compression stocking or a multilayer bandage worn during PRE	Not reported
Singh et al. 2015[42]	Five participants personally-fitted with Venosan compression sleeve (23-32 mmHg). The others worn their won garments (no more details).	One session with compression and one without compression separated by at least a 6 day wash-out period.	NA
Jeff et al. 2013[44]	Characteristic of garment: Flat knit: IG 7(64%); CG: 11(92%) Circular knit: IG:4(36%) CG:1(8%)	-Duration: the greater part of each day -Both groups worn the compression garment throughout the study	- High adherence in both groups (91%IG, 92%CG)
McClure et al. 2010[45]	Not reported	Not reported	-Both group instructed to wear compression garment <50% of the time
Kim et al. 2010[46]	Not reported	Compression garment or multilayer bandage worn during exercise	Not reported
Schmitz et al. 2009[47]	New custom-fitted compression garment (Jobst, BSN Medical) provided at baseline and at 6 months	Wore compression sleeve daily and during weight lifting	The differences between the two study groups were not significant (results not shown)

Irdesel et al. 2007[48]	The compression garments with 40 mmHg of pressure.	They advised to wear the garments at all times expect when they go to sleep for the duration of the study	Not reported
McKenzie et al. 2003[50]	-Well fitted compression sleeve was used by each participant	for all exercise sessions as well as daily by all participants in both the control and exercise groups.	Not reported
Johansson K 2005[49]	-Standard type or custom-made compression sleeve of at least class II (23-32 mmHg. Most of them had a silicon top band. The sleeve was no older than 3 months.	All participants instructed to wear it at least 2 weeks before the start of the Study and during the day and night or daytime only. Compression	NA

☐ Supervised and comined program ☐ Home program ☐ Acute exercise

Table 3: *Resistance exercise program*

Author (year)	Program duration	Intensity and frequency	Equipment	Adherence	Adverse events
Bok at al. 2016[41]	8 weeks	Six exercise performed with a 0.5-kg dumbbell and repeated five times twice a day. Every week, the number of repetitions was increased by adding five additional repetitions.	Dumbbell	Not mentioned	Not mentioned
Singh et al. 2015[42]	Cross over, pre-post exercise	Intensity of the exercise was progressed throughout four familiarization sessions (two weeks prior to experimental exercise sessions) from very light (two sets of 15-20 repetitions with minimal weight) to moderate load resistance exercise session (three sets of 10-12 repetitions with two minutes rest between each set and between each exercise).	Weight (not specified)	No minor or major adverse events during the study	No minor or major adverse events during the study
Jeff et al. 2013[44]	6-months	Daily 10-15 min A series of gravity resistive isotonic arm exercises. The first three exercises incorporate deep breathing and aim to stimulate the lymphatics in the trunk and at the root of the limb; four gravity-resistive arm exercises follow to stimulate venous and lymphatic return from the arm; finally, the first three exercises are repeated in reverse order to encourage clearance of fluid stimulated by the exercise.	No equipment	Moderately high: six participants (55 %) mostly performed the exercise programme daily, four participants (36 %) performed the exercise programme 5 days per week and one participant (9 %) did the exercise programme "when I remember" which was generally every other day.	There were no reported adverse reactions to the intervention
McClure et al. 2010[45]	17 weeks	low-to-moderate intensity daily exercise, either at home or during the required 1-hr biweekly group sessions for 5 weeks followed by a 3-month self-	No weight used	Excellent adherence at 5 weeks (E = 7.9 ± 1.6, R = 8.7 ± 1.7) and	No adverse reaction

		monitored daily home program		good adherence reported at 3-month follow-up (E = 5.3 ± 1.0, R = 5.4 ± 1.1).	
Kim et al. 2010[46]	8weeks	2 sets of 10 repetitions for 8 weeks. Started with 0.5 kg in the first two weeks and progressed to 1kg in the next 6 weeks "if not too heavy"	Dumbbells	Not reported	No adverse effects
Schmitz et al. 2009[47]	52 week	90-minute session, twice weekly. Participants were taught one to three new exercises per session they increased their number of sets of each exercise per session from two to three, with 10 repetitions per set in the first 5 weeks. Resistance: increased gradually with monitoring symptoms starting from little-to-no resistance.	Community fitness Center setting: seated row, chest press, lateral or front raises, bicep curls, and tricep pushdowns, leg press, back extension, leg extension, and leg curl.	The median rates of exercise-session attendance were 96%, 88%, 81%, and 75% in the first, second, third, and final quarters of the year-long study	No serious adverse events related to the intervention
Irdesel et al. 2007[48]	6-months	Light resistive exercises 10rep./3times/day		Not reported	Not mentioned
McKenzie et al. 2003[50]	8 weeks	-Light weight and progressing as tolerated by each subject. -3times/week -Two sets of 10 repetitions for each exercise in the first week, three sets of 10 were done thereafter -After a program that began with five 1-minute bouts of cycling at a resistance of 8.3 W, the program progressed to 20 minutes of continuous cycling with a resistance of up to 25 W.	-Not mentioned -Arm cycle ergometer used for aerobic exercise	Not reported	Not mentioned

Johansson K 2005[49]	Pre-post exercise	-Long lever-arm exercises were performed with 0.5 kg weights and short lever-arm exercises with 1.0 kg weights - 5 days with two training sessions with measurement the day after. One day of rest was held between the two sessions.	Dumbbells	Not reported	-No changes in mean rating of heaviness or immediately after the exercise or the following day in both groups

Table 4: *Outcome measures*

Author (year)	Lymphedema status:	Upper extremity status and function	Quality of life	Other
Bok at al. 2016[41]	Upper limb circumference using a tape measure	The thickness of the subcutaneous tissue and muscle were measured using ultrasonography	Not measured	–
Singh et al. 2015[42]	1.Bioimpedance spectroscopy (BIS). The ratio of impedance values converted to an L-Dex score. 2.Arm circumferences 3. Visual analogue scale (VAS) to assess the severity of lymphedema-associated symptoms (pain, heaviness and tightness)	NA	NA	NA
Jeff et al. 2013[44]	1. Limb volume measurement using Perometer 350S	1.Range of shoulder abduction (frontal plane) and extension (sagittal plane) was measured using a plastic goniometer 2.QuickDASH-9 questionnaire	The lymphedema specific 28-item LYMQOL question naire	–
McClure et al. 2010[45]	1. ImpediMed (Pinkenba, Queensland, Australia) IMP™ XCA bioelectrical impedance analysis system 2. Truncated cone girth measurements, which report volume.	Shoulder AROM measurements were obtained using a standard, two-armed goniometer	Self-report SF–36 Health Survey–II	1. Weight 2. Mood was assessed using the BDI 3. 21-question self-report inventory used to measure mood and depression
Kim et al. 2010[46]	Volume changes using the circumferences of the upper limbs (proximal, distal, and total)	–	Short Form-36 version 2 question naire	–
Schmitz et al. 2009[47]	1. The proportion of participants with an absolute	Muscle strength	–	Anthropometric measures

	increase of 5 percentage points or more in the interlimb volume discrepancy (the interlimb difference over time) using water displacement 2. lymphedema exacerbation and symptoms			
Irdesel et al. 2007[48]	Circumferential measurements	Shoulder ROM: Measured with goniometry		1.Visual Analog Scale (VAS 2. Shoulder tenderness: according to the scale of 0-3
McKenzie et al. 2003[50]	1. Arm circumference measurements 2. Volume measurements using arm circumference measurements 3. Upper extremity volume using water displacement.	–	36-Item Short Form Survey (SF-36) general	Height and weight
Johansson K 2005[49]	1. Arm volume was measured with the water displacement 2. The lymphedema absolute volume (LAV) 3. The lymphedema relative volume (LRV) 4. Multiple frequency bioelectrical impedance analysis (MFBIA)	–		1. Subjective sensations: the experiences of heaviness and tightness using horizontal visual analogue scale (VAS). 2. Perceived exertion were rated on a Borg scale 3. Physical activity using questionnaire

Table 5: *Putting Evidence into Practice (PEP) level of evidence*

Intervention	Number of studies	Number of studies with low risk of bias*	Weight-of-evidence category
Single bout RE with/out compression	2	0	Effectiveness not established
Mild intensity RE (no external weight) with compression, such as gravity resistance isotonic and concentric arm exercise	3	1	Likely to be effective
Mild to moderate intensity RE (using external weight) with compression, including seated row, bench press, biceps curl, and triceps pull down	4	0	Likely to be effective

*Studies described as low risk of bias if they scored 3/5 in acute exercise (single bout) trials, or 5/7 in intervention trials and meeting low risk of bias criteria for randomization method and concealment of allocation.

CHAPTER 3: METHODS

1.12 Study Design

A randomized controlled pilot trial was conducted to determine the feasibility and preliminary efficacy of combining compression and a low-to-moderate intensity decongestive progressive resistance exercise (DPRE) training program on arm lymphedema volume in breast cancer survivors. The study compared the results of three groups: 1) Standard care (control), 2) DPRE + daytime compression sleeve (flat knit or circular knit), and 3) DPRE + advanced compression (AC) using an adjustable compression wrap. The study was carried out over a 24-week period comprising a 12-week supervised intervention and a 12-week follow-up period. The outcome measures were assessed at the baseline, 12-week, and 24-week time points. As well, lymphedema-specific outcome measures were assessed additionally at 6-week and 18-week follow-up to inform feasibility of the protocol.

A fast-track trial design was used. In this design standard care participants cross-over after the initial intervention period, and receive the experimental intervention within the study period. A fast-track design optimizes recruitment rate and completion rates in studies where participants have a strong preference for assignment to the experimental intervention. In the present study, after the 12-week randomized trial period, participants in the standard care group were fast-tracked to the supervised DPRE program and were fitted for an adjustable compression wrap to use during exercise.

1.13 Ethical Consideration

Ethical approval was obtained from the Health Research Ethics Board of Alberta: Cancer Committee. The REDCap database, a secure web application for building and managing online databases supported by the Faculty of Medicine and Dentistry at the

University of Alberta, was used for data collection. All participants were required to provide written informed consent. The consent form outlined their rights, risks, and benefits of taking part in the study as well as confidentiality. Participants were informed that they were free to withdraw from the trial at any time, for any reason. In addition, consent could be withdrawn by the oncologist, if the participant was unable to tolerate the exercise, experienced an adverse effect during or after exercising, developed a skin reaction, a blood clot or arm infection during the study period.

1.14 Eligibility Criteria

Women with BCRL were eligible for inclusion if meeting the following criteria;

(1) a female with a history of breast cancer;

(2) had undergone surgery, including sentinel lymph node biopsy or axillary lymph node dissection;

(3) had unilateral mild to moderate BCRL of at least 200 ml or 10% inter-limb volume difference and/or minimal volume difference of 100 ml or 5% in hand and forearm region[17, 57];

(4) had chronic lymphedema, defined as lymphedema that has been present for at least 3 months;

(5) was in the lymphedema maintenance phase of lymphedema treatment;

(6) used a well fitted compression sleeve (not older than 1 month) and was agreeable to wearing the sleeve for a minimum of 12 hours per day (providing a minimum of 30 mm Hg of pressure);

(7) was agreeable to discontinuing other lymphedema treatments, including manual lymph drainage and intermittent pneumatic compression during the 12-week randomized trial period of the study.

Women were excluded if the survivor met any of the following exclusion criteria:

(1) undergoing or scheduled for chemotherapy, radiotherapy or biological therapy;

(2) presented with limb infection, deep vein thrombosis, or cellulitis, or had active metastatic disease;

(3) any neurological or cognitive deficit or other uncontrolled health condition that may have interfered with assessment and/or the progressive resistance exercise training intervention;

(4) had any contraindications to wearing compression on the limb, including arterial insufficiency or degeneration, or acute heart failure.

1.15 Recruitment

Women were recruited through the Rehabilitation Medicine Department at the Cross Cancer Institute in Edmonton. Potential participants were informed about the study at their follow-up visit with their physical therapist. The physical therapist provided the woman with a pamphlet that provided further information on the study. The survivor was then required to initiate contact with the investigators if interested in taking part in the study.

1.16 Procedures

Potentially eligible participants were scheduled for an appointment to discuss the study and answer any questions about the study. Final screening for eligibility was performed and the participant was then required to provide written consent. Baseline testing was performed prior to randomization.

1.17 Randomization

An independent researcher made allocation cards using computer-generated random numbers and the cards were placed in sequentially numbered and sealed opaque envelopes. Participants were stratified by lymphedema severity (mild versus moderate as per the criteria of the International Society of Lymphology) and daytime compression sleeve type (flat knit

versus circular knit) and then randomized into one of three groups: (i) standard care, (ii) DPRE with compression sleeve, and (iii) DPRE with adjustable compression wrap.

1.18 Interventions

1.18.1 i. Standard care group

Participants in this group received standard care for lymphedema maintenance. Participants were provided with a home program of decongestive exercise (Appendix D). Participants were instructed to perform the exercise once daily for 10-15 minutes and to wear their day-time compression sleeve for at least 12 hours per day (including when performing exercise), seven days a week. After 12 weeks, participants in standard care group were fast-tracked to the combined DPRE program with AC and followed the protocol of the DPRE with AC group.

1.18.2 ii. DPRE groups

a. DPRE with daytime compression sleeve

Participants randomized to this group were required to wear their daytime compression sleeve during the DPRE program. As per standard of care, they were required to wear their compression garment for at least 12 hours per day, seven days a week. Participants took part in the supervised DPRE program twice a week for 12 weeks. Exercise sessions started with at least 5 minutes of range of motion exercises for the muscles targeted in resistance training (Appendix F.2). Exercises were individualized and offered in a group-based format with a ratio of one therapist to two-three participants. Exercises were monitored and progressed at each session by first increasing the number of repetitions (10, 12, 15 reps) and then the resistance weight was increased. Exercises commenced with deep breathing, followed by exercises involving large muscle groups of the trunk, and proximal upper and lower extremities to

stimulate lymphatic flow in the trunk and the limbs. At the end of exercise sequence (proximal to distal), the arm exercises were performed in reverse order to encourage clearance of lymphatic fluid stimulated by the exercise (Appendix F.3).

b. DPRE with Adjustable Compression Wrap

Participants randomized to this group were measured for an adjustable compression wrap and were instructed in its application by a physical therapist. Educational materials related to garment application and maintenance were provided. (Appendix E.2). The participants were required to wear their adjustable compression wrap during the DPRE program. As per standard of care, they were required to wear their compression sleeve for at least 12 hours per day, seven days a week (excluding the exercise session). Participants in this group underwent the same DPRE program as the group performing DPRE with a compression sleeve (Appendix F.3).

Exercise sessions took place at the Cancer Rehabilitation Clinic in Corbett Hall at the University of Alberta. After the 12-week intervention, participants continued with the same program (unsupervised) twice weekly for an additional 12 weeks with options for location: at Corbett Hall, in a community-based fitness center, or at home.

In addition, all participants were asked to record any additional treatments that they had received for their lymphedema. At the conclusion of study, participants were encouraged to continue with the DPRE program.

1.19 Adverse Events

Participants in the DPRE program were monitored for any adverse events such as pain, tension (congestion) and fatigue at each session. The participants were instructed to report any adverse events immediately to the study coordinator or primary investigator. In case of increased swelling or other symptoms, the resistance weight and/or repetitions were adjusted as per Table 6.

Table 6: *The protocol modification in case of adverse events*

Adverse events	If resolved within 24 hours	If not resolved after 24 hours or persists
Increases arm swelling/tension	Continue with the same weight and number of repetitions (no progression)	Decrease the number of repetitions and/or the weight
Increased Fatigue	Continue with the same weight and number of repetitions	Decrease the number of repetitions
Muscle soreness	Continue with the same weight and number of repetitions	Decrease the number of repetitions
Joint pain	Decrease the weight or continue with the previous weight	Decrease the number of repetitions and/or the weight

1.20 Blinding

An independent assessor blinded to the group assignment conducted all the study measurements. Training of the assessor was done in advance of the study start and involved the standard procedures related to the measurement protocol.

1.21 Standardized Assessment

All outcome measurements were completed following a standard protocol. Measurements were taken at close to the same time in the day at each assessment visit. Participants removed the compression sleeve only at the time point immediately prior to the lymphedema outcome measurement in order to standardize the time without compression across measurement time points.

1.22 Data Collection

Demographic characteristics were collected from the participants at baseline. Medical data (such as tumor stage, number of nodes removed) were obtained from the participant and the participant's medical record at the baseline assessment (Appendix H,I). All outcome measurements were taken at baseline (prior to randomization), at 12-weeks, and at 24-week follow-up. Lymphedema measurements were performed and exercise diaries were collected at

the additional measurement sessions of 6 weeks and 18 weeks. All objective outcome measurements were completed by the same blinded independent assessor at 12-week and 24-week follow-up sessions.

1.23 Outcomes

1.23.1 Primary outcomes

The primary outcomes related to ***feasibility*** were the study recruitment, adherence, and completion rates.

The primary outcome related to ***preliminary efficacy*** of treatment was the change of excessive arm lymphedema volume, which was calculated as follows:

Lymphedema relative volume (LAV) change will be calculated as follows[4,43]:

$$\text{LAV} = \text{affected arm volume} - \text{unaffected arm volume}$$

(1) LAV baseline – LAV follow-up

(2) unaffected arm volume

Per cent change in excess volume $= \frac{(1)}{(2)} \times 100$

Lymphedema relative volume (LRV) was calculated as follows[4,43]:

$$\frac{\text{affected arm volume} - \text{unaffected arm volume}}{\text{unaffected arm volume}} \times 100$$

Optoelectronic limb volumeter (Perometer):

Lymphedema was objectively measured using the optoelectronic limb volumeter (perometer). The perometer creates an image of the limb using infrared light technology. The perometer is a valid, reliable and sensitive method for quantifying limb volume[58-61]. The perometer is the only device that has excellent intra-rater and inter-rater reliability expressed by means of the relative differences (1.5 ± 1.4%)[59] and an ICC of 1 (95% CI: 0.99 to 1), both

of which are higher than traditional water displacement volumetry and measurements of circumference[58, 59]. The standard error of measurement using the perometer with repeated measurements is 8.9 ml, less than 0.5% of the limb volume[61]. Therefore, the perometer is considered to be the modern "gold standard" for limb volume measurement[60]. It is also quick, and easy to use, taking only 2-3 minutes to perform[60].

For the test, the participant was sitting on a stool, the arm abducted to the horizontal position and the tip of the fingers placed on the hand support. The perometer frame was moved over the limb in a slow steady motion from hand to shoulder, and back. Measurements are taken by the device every 4 mm and are used to calculate arm volume[60] (Appendix J.1).

To improve accuracy, each measurement was taken twice for each participant (both edematous and non-edematous arms at each time point) and the mean difference was calculated. If the difference between any two measurements of the same limb exceeded 1%, a third measurement was taken and the average of the two closest measures was used[62].

1.23.2 Secondary outcomes

Secondary outcomes included extracellular fluid status within the arm, muscular strength, shoulder ROM, quality of life, physical activity, body image, weight, and BMI. All the study questionnaires were sent to the participants prior each assessment session through REDCap.

Bioimpedance analysis (BIA):

Bioimpedance analysis (BIA) is specially designed to predict the extracellular fluid volume in the limb. With BIA, a small imperceivable current is passed through the body[58, 63]. Impedance to the current is inversely related to the amount of fluids in the extracellular space. BIA measures the impedance ratio of the affected and unaffected limb and the calculated index (based on the difference in limbs) provides an estimate of extracellular fluid volume[63]. A study by Moseley et al. showed that both the BIA and perometry are independently valid and reliable

in presenting data representing lymphedema reduction[64]. The BIA is a sensitive, valid, and reliable measurement method. Its validity has been measured in comparison to water volumetry and circumferential measurement[65, 66]. A study by Jain et al.[67] confirmed its validity and reliability compared to perometry with high correlation (r=0.926). Czerniec et al.[58] reported a high intra-rater reliability with ICC=0.94 (95% CI: 0.90 to 0.97) and inter-rater reliability with ICC= 0.99 (95% CI: 0.96 to 1.00) with a standard error of measurement of 0.05. BIA has been used in multiple studies as a tool to detect early lymphedema post breast cancer and to monitor treatment efficacy in those with established BCRL[63, 65-68]. The BIA is portable, easy to utilize, and takes on 2-3 minutes to perform.

BIA records impedance values for each limb and provides an index (L-Dex value) that indicates the difference between the affected and unaffected limb. L-Dex values are displayed against a normal "healthy" range. As the amount of fluid in the tissue increases, the L-Dex value gets correspondingly higher[69]. L-Dex values greater than 10 or an increase of 10 L-Dex units is considered indicative of lymphedema[69].

For the test, the participant was required to remove any jewellery or metal objects on the hands and feet and to lie in a supine position on a nonconductive plinth. The limbs were held out to the sides in a slightly abducted position with forearms pronated. Using anatomical positions, self-adhering electrodes were applied to the dorsal aspect of each hand and the right foot. Colour coded cables were connected to the BIA devices based on the manufacturer's instructions and then attached to the electrodes using metal clips (Appendix J.2). Contraindications to BIA include individuals with a pacemaker (not eligible for study), who are pregnant (not eligible for study), or have metal implanted in the arms or legs (i.e. plates from fracture or a joint replacement)[70].

To standardize all variables that might influence the BIA measurements, participants were required to limit their exercise within 2 hours of the measurement, to avoid eating or drinking immediately before measurements[63], and to empty their bladder prior to testing[70].

One-repetition maximum (1-RM):

Muscle strength was assessed with the one-repetition maximum (1-RM) method for bench press, leg press, and seated row. The 1-RM is the highest weight that can be lifted once using proper form, a smooth motion and without pain or other symptoms[71]. The 1-RM is recognized as the gold standard of assessing the muscle strength in a non-laboratory setting[71-73]. It is a simple and safe method[73-75], that requires relatively inexpensive machines.

The 1-RM is a reliable method of assessing muscle strength of trained[76] and untrained[77] individuals. Using standard equipment for resistance exercise during testing, and one session of familiarization ensures the reliability and reduces the influence of learning or systematic bias during the 1-RM test[77, 78]. The reliability of 1-RM has been assessed for different resistance exercises and muscle groups, such as leg press[71, 76], seated row, and bench press.[77] Dong-il et al.[76] reported high intra-class correlation coefficients (ICC > 0.9, r > 0.92) for the test-retest reliability of the 1-RM.

Participants were familiarized with vertical bench press, seated row, and leg press equipment at the baseline assessment. During the familiarization session, each exercise was demonstrated and participants were taught the correct movement and breathing techniques. Also, instructions were given on how to use the Borg Rating of Perceived Exertion (RPE) scale ranging from 1 (minimum) to 10 (maximum) (Appendix J.3.1). The RPE was used to quantify the exercise test intensity and to predict the subsequent repetition test weight[79, 80].

Testing was done on the same equipment that was used by participants during the exercise program[71, 73]. Each 1 RM testing session started with a 1-minute period of general warm-up. The participant's RPE was used to determine the amount of weight increase until

the 1-RM was reached. In between each attempt, a minimum of one-minute rest was given and a two-minute rest between each specific exercise. The 1-RM testing occurred in the following order: bench press, leg press, and seated row. This order was chosen to ensure adequate muscle recovery between the upper body tests (Appendix J.3.2).

Goniometer for measuring shoulder range of motion (ROM):

Shoulder range of motion (ROM) was measured using a plastic goniometer and each arm was measured separately for flexion, abduction, internal, external rotation, and horizontal abduction. The goniometer is valid and reliable for measuring shoulder ROM; it has excellent reliability (ICC≥ 0.94) when using the measurements procedures outlined by Clarkson[81] and Kolber[82].

Movements were demonstrated, and flexion, abduction, internal, and external rotation ROM were assessed while participants were seated. Horizontal abduction was performed from the supine position (Appendix J.4).

The Lymphedema Functioning, Disability and Health (Lymph-ICF):

The Lymphedema Functioning, Disability, and Health (Lymph-ICF) is a lymphedema-specific outcome questionnaire used to assess health related quality of life (HRQOL). It is a descriptive and evaluative tool consisting of 29 questions related to functional impairments, activity limitations, and participation restrictions in patients with upper limb lymphedema[83]. The questionnaire is divided into five domains: physical function, mental function, household activities, mobility activities, and life and social activities. The Lymph-ICF is valid tool with high reliability (ICC > 0.90) in women with BCRL[83]. The total score of the Lymph-ICF on the five areas ranges from 0 to 100, with a score of 0 meaning no impact and 100 linked to having the greatest negative impact for the question asked[83] (Appendix K.1).

The Rand Short Form-36 Version 2 (SF-36):

The Rand Short Form-36 Version 2 (SF-36) was used to assess general HRQOL. It is a validated self-report measure, comprised of 36 questions that aim to evaluate the following eight models of HRQOL: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality/energy, social functioning, role limitations due to emotional problems, and general mental health[83]. The test-retest reliability for the SF-36 is reported as excellent (0.80)[83]. It is easy to use and takes only a few minutes to complete (Appendix K.2).

The Godin leisure-time exercise questionnaire (GLTEQ)

The Godin leisure-time exercise questionnaire (GLTEQ) was used to assess the physical activity level. It is a valid, reliable, and sensitive tool among different populations, including breast cancer survivors[85]. The Godin questionnaire is a self-reported measure of the average duration and frequency of strenuous (heart beats rapidly), moderate (not exhausting), and mild activities (minimal effort), resistance training, and flexibility training exercise. It is simple, easy to use, as well as time and cost effective[85,86] (Appendix K.3 (modified GLTEQ with added resistance exercise and flexibility questions)).

The Body Image and Relationships Scale (BIRS)

The Body Image and Relationships Scale (BIRS) is a self-report measure of body image and relationships. It consists of 32 questions in the following three domains: bodily strength and health, relationships and social functioning, and body appearance and sexuality (Appendix K.4)[87]. The BIRS was developed and used to assess body image in strength training intervention study among participants with BCRL[47]. The BIRS has been showed to have a satisfactory test-retest reliability and internal consistency in addition to convergent and divergent validity[87].

Body height and weight were measured without shoes at each scheduled follow-up.

Adherence: Participants in DPRE group were asked to record their adherence to their assigned program using an exercise diary. The exercise diary collected details on exercise sessions performed, including sets, repetitions, and resistance weight, as well as adherence to the compression sleeve (i.e. use of the garment during exercises and number of hours per day and the number of days per week worn). Participants in the standard care group were also asked to record their adherence to their assigned program using daily diary. The daily diary collected details on exercise sessions performed, as well as adherence to the compression sleeve (i.e. use of the garment during exercise, and number of hours per day and the number of days per week worn). Participants were asked to return the completed journal at each 6-week follow-up session (Appendix G).

1.24 Data analysis plan

1.24.1 Sample size

The sample size for the study was based on an estimated 10% (SD: 17%; power: 80%; significance level: 0.05) greater reduction in arm lymphedema volume in favour of the DPRE with adjustable compression wrap group over standard care. This difference was deemed a level of clinical interest to both clinicians and women with BCRL. We anticipated that based on this estimated difference a total of 40 participants would be needed in each group for a total sample of 120 for the full randomized controlled trial. For the purpose of this feasibility pilot trial, fifteen breast cancer survivors with lymphedema were recruited.

Point estimates and measures of variability were to be used to confirm the required sample size for the multicenter RCT. If study procedures were deemed feasible, the plan was to launch the full RCT including data from participants in the pilot study.

1.24.2 Data analysis

For the purposes of analyses of the pilot study data, the two DPRE groups were collapsed into one group. Quantitative data, medical, and demographic information were analysed descriptively to compare the groups. Independent sample T-tests were used to compare the outcome measures of the two groups for the purposes of point estimates and measures of variability.

CHAPTER 4: RESULTS

1.25 Recruitment

Participant recruitment took place between May 2017 to February 2018. Figure 4 details participant flow through the trial. Approximately forty study brochures were provided to potentially eligible patients by their respective physiotherapist at the Rehabilitation Medicine Department in the Cross Cancer Institute. Seventeen women with breast cancer related lymphedema were interested and contacted the investigators. Each participant was further screened for eligibility, and all were eligible. Two women subsequently opted not to participate due to travel issues. Fifteen women consented to participate in the study and were randomly assigned to one of three groups: (standard care: n=6), (DPRE with compression sleeve: n=3), and (DPRE with adjustable compression wrap: n=6). Due to the small sample size, the data from participants in the two DPRE groups were combined in one group (DPRE: n=9), (Figure 4).

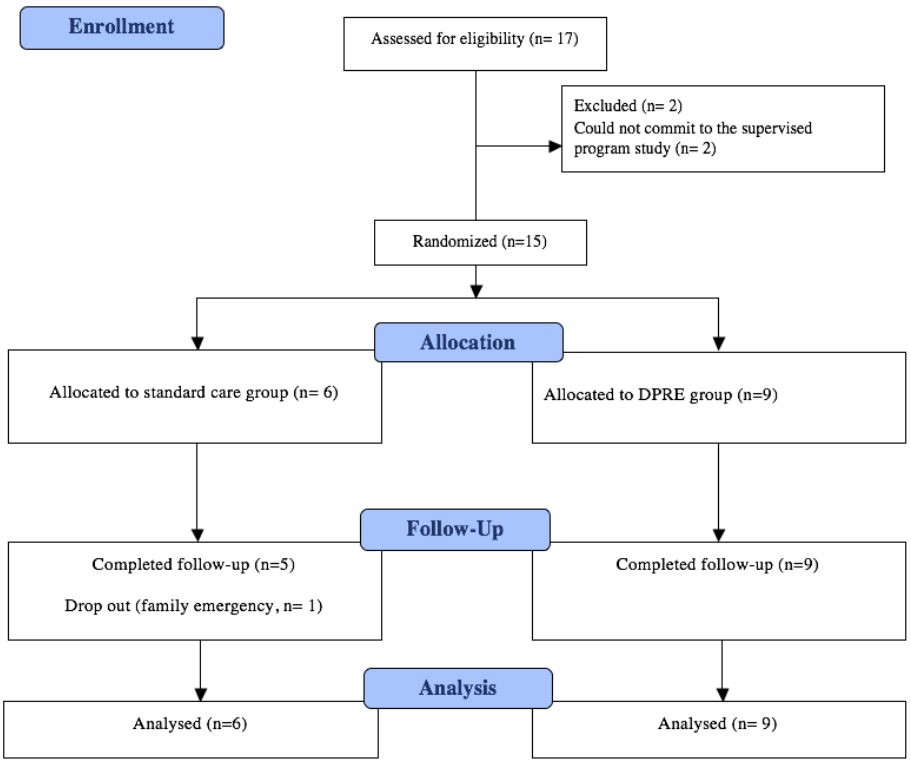

Figure 4: *Flow of participants through the trial*

1.26 Baseline Characteristics

The baseline demographic and medical characteristics for all participants are presented in Table 7 and 8. The mean age of the standard care group was 63.2 years (range: 55-68 years) and the DPRE group was 67 years (range, 57-79). The mean time since breast cancer surgery ranged between 6 months and 32.5 years, with average of 11.9 years in standard care group and 8.6 years in DPRE group. The mean number of lymph nodes removed was 18 (range, 6-21), with average of 16 in standard care group and 18 in DPRE group. Six participants (40%) reported post-surgery complications of infection and/or drainage tube issues, with three in each group.

The majority of participants in both groups were overweight or obese (standard care: 83.5%; DPRE: 77.7%), and the reported mean of physical activity minutes per week ranged from zero to 720 min/week, with average of 133 mins/week in standard care group and 18 mins/week in DPRE group. The average time since lymphedema diagnosed in the standard care group was 9.7 years and DPRE group was 7.3 years, and 67% of participants in each group had their lymphedema involving their dominant arm. Forty-seven percent of participants had a lymphedema volume difference of more than 20% (moderate to severe lymphedema: standard care: 33%; DPRE: 56%). Only 20% of the participants had less than 10% volume difference (subclinical lymphedema: standard care: 33.3%; DPRE: 11.1%), however all had greater than a 200mL volume difference between limbs. All participants were wearing a well fitted day-time compression garment, with 8 participants (53%) having a circular knit garment (three participants in standard care group and five participants in DPRE group).

Table 7: *Baseline Characteristics of Participants*

Characteristics	All (n=15) Mean (%; Range)	Standard Care (n=6)	DPRE (n=9)
Age-year	65.47(55-79)	63.17(55-68)	67(57-79)
Marital status- no(%)			
Married	10 (66.67)	6 (100)	4 (44.4)
Divorced	2 (13.33)	0	2 (22.2)
Widowed	2 (13.33)	0	2 (22.2)
Never Married	1 (6.67)	0	1 (11.1)
Education- no(%)		0	
Completed High school	4 (26.67)	2 (33.3)	2 (22.2)
Some University/College	5 (33.33)	2 (33.3)	3 (33.3)
Completed University/College	2 (13.33)	0	2 (22.2)
Some Graduate School	1(6.67)	1 (16.7)	0
Completed Graduate School	3(20)	1 (16.7)	2 (22.2)
Employment Status- no(%)			
Retired	10 (66.67)	3 (50)	7 (77.8)
Full time	1 (6.67)	0	1 (11.1)
Part time	1 (6.67)	1 (16.7)	0
Disability	2 (13.33)	1(16.7)	1 (11.1)
Homemaker	1(6.67)	1 (16.7)	0
Ethnicity- no(%)			
White	13 (86.7)	5(83.3)	8(88.9)
Black or African American	2 (13.3)	1(16.7)	1(11.1)
Smoking Status- no(%)			
Never	9 (60)	5 (83.3)	4 (44.4)
Ex-smoker	6 (40)	1 (16.7)	5 (55.6)
Drinking Status- no(%)			
Never	3 (20)	2 (33.3)	1 (11.1)
Social	5(33.3)	1 (16.7)	4(44.4)
Occasional	6(40)	3(50)	3 (33.3)
Regular	1 (6.67)	0	1 (11.1)
Resident Location- no(%)			
Edmonton	13 (86.67)	4 (66.7)	8 (88.9)
Out of Edmonton	2 (13.33)	2(33.3)	1 (11.1)
Physical Activity min/week	64.40(0-720)	132.67(0-720)	18(0-120)
Sleeve Type			
Circular-knit	8(53.33)	3 (50)	5 (55.6)
Flat-knit	7(46.67)	3 (50)	4 (44.4)

Table 8: *Medical Variable of Breast Cancer*

Variables	All (n=15)	Standard Care (n=6)	DPRE (n=9)
Cancer History no(%)			
Time since main BC surgery (months)	118.59(6-390)	142.39(10-377)	102.72(6-390)
Type-no(%)			
In situ ductal	1(6.66)	1(16.67)	0
Invasive lobular	1(6.66)	0	1(11.1)
Invasive ductal	12(80)	5(83.33)	7(77.78)
Cancer stage			
I	1(6.7)	0	1(11.1)
II	7(46.7)	3(50)	4(44.4)
III	6(40)	3(50)	3(33.3)
Unknown	1(6.7)	0	1(11.1)
Breast surgery- no(%)			
Lumpectomy	4(26.7)	1(16.7)	3(33.3)

Modified Radical Mastectomy	4(26.7)	3(50)	1(11.1)
Mastectomy	7(46.6)	2(33.4)	5(55.5)
# Nodes removed	17.71(6-33)	16.4 (6-21)	18.45(10-33)
Post surgery complications (%)			
Yes (infection and/or drainage issue)	6 (40)	3(50)	3(33.3)
No	9 (60)	3(50)	6(66.7)
Chemotherapy - no(%)			
Yes	13 (86.7)	6(100)	7(77.8)
No	2 (13.3)	0	2(22.2)
Radiation - no(%)	15(100)	6(100)	9(100)
RT Location-no(%)			
Breast	2(13.33)	0	2(22.22)
breast, axilla, and chest wall	8(53.33)	3(50)	5(55.55)
breast, axilla, chest wall, and supraclavicular nodes	5(33.33)	3(50)	2(22.22)
Hormone Therapy-no(%)			
Tamoxifen	7(46.7)	3(50)	4(44.4)
Aromatase Inhibitor	2(12.3)	3(50)	2(22.2)
Both	1(6.7)	0	1(11.1)
No	5(33.3)	0	2(22.2)
Comorbidities- no(%)			
None			
1 co-morbid condition	5(33.3)	3(50)	2(22.2)
2 co-morbid condition	3(20)	1(16.7)	2(22.2)
3 co-morbid condition	3 (20)	1(16.7)	2(22.2)
>3 co-morbid condition	4(26.7)	1(16.7)	3(33.3)
Onset of lymphedema post surgery (months)	25.58(2-82)	25.83(5-43)	25.43(2-82)
Duration of lymphedema (months)	98.28(3.17-353)	116.36(3.2-353)	86.98(3.17-308)
Lymphedema severity			
<10	3 (20)	2 (33.33)	1(11.11)
≥10 and ≤20	5(33.33)	2 (33.33)	3(33.33)
>20	7(46.67)	2(33.33)	5(55.56)
Affected arm is dominate arm- no(%)			
Yes	10(66.7)	4(66.7)	6(66.7)
No	5(33.3)	2(33.3)	3(33.3)
BMI			
Normal (18.5–24.9) - no(%)	3(20.1)	1(16.7)	2(22.2)
Overweight (25–29.9) - no(%)	3(20.1)	2(33.4)	1(11.1)
Obese (≥30) - no(%)	9(60.3)	3(50.1)	6(66.6)

1.27 Primary Outcome

1.27.1 Recruitment:

A recruitment rate of 37.5% was achieved (15 out of 40 potentially eligible participants). The intervention completion rate was 100% and the study completion rate was 93%. Fourteen of 15 participants completed the baseline, 6-week, and 12-week assessments.

1.27.2 Adherence to the program:

On average, participants in standard care group reported completion of 70.5 of the 84 scheduled sessions (84%), with a range of 40 to 80 based on daily exercise diary. Participants in DPRE group attended an average of 21.78 of the 24 supervised sessions (91%), with a range of 17 to 24 (Table 9). Participants started with an average of 30% of their 1RM at baseline for chest press and seated row and 60% of their 1RM at baseline for leg press. Over a period of 12-week, their weight progressed to an average of 73.5% of baseline 1 RM for upper limb and 88.5% of baseline 1 RM for lower limb. Exercises were done in two sets by all participants (100%) and adherence to prescribed repetitions was 97.2%. The average rating of perceived exertion was 3.8 (moderate to somewhat strong) and ranged between 2 to 7 over the course of 12-weeks.

1.27.3 Adherence to the compression garment use:

All participants in both groups reported 100% adherence to wearing their compression garment during exercise. Participants reported wearing their compression garment during the day for 12.2 and 12 hours for the standard care and DPRE groups, respectively.

Table 9: *Adherence to DPRE Protocol*

Participant	1RM result	Intensity % baseline 1RM/weight (baseline-12-week)	Repetitions 10-12-15	2 Sets	Frequency/ attendance	Overall RPE	Comment
DREAM 1	Chest press 30lbs	3.3%-83.3% (1lb-25)	92.2%	100%	100%	2.7 (2-5)	*Modified to squat exercise
	Seated row <15lbs	16.7%-233% (2.5lb-35lb)	96.3%	100%			
	*Leg press	NA	NA	NA			
DREAM 2	Chest press 95lbs	(29.5%-42%) (28lb-40lb)	100%	100%	75%	2.5 (2-5)	*modified to squat exercise for 4 sessions due to knee pain
	Seated row 120lbs	(25-37.5%) (30lb-45lb)	96.2%	100%			
	*Leg press 170lbs	(52.9%-56.5%) (90lb-96lb)	116%	100%			
DREAM 7	Chest press 40lbs	37.5%-75% (15lb-30lb)	91.9%	100%	100%	3.7 (2.5-5)	-
	Seated row 65lbs	30.8%-53.8% (20lb-35lb)	93.2%	100%			
	Leg press 100lbs	60%-80% (60lb-80lb)	67.6%	100%			
DREAM 8	Chest press 45lbs	29.4%-88.9% (13.25lb-40lb)	100%	100%	79.17%	4.7 (3-7)	-
	Seated row	30%-66.7%	100%	100%			

	60lbs	(18lb-40lb)					
	Leg press 100lbs	60%-105% (60lb-105lb)	102%	100%			
DREAM 9	Chest press 35lbs	28.6%-100% (10lb-35lb)	104.4%	100%	70.83%	4.1 (4-5)	-
	Seated row 75lbs	30%-53.3% (22.5lb-40lb)	92.8%	100%			
	Leg press 45lbs	66.7%-133.3% (30lb-60lb)	97.3%	100%			
DREAM 10	Chest press 45lbs	33.3%-88.9% (15lb-40lb)	99.4%	100%	91.67%	3.9 (3-4.5)	*modified to resistive leg raise exercise for 11 sessions due to knee pain
	Seated row 75lbs	33.3%-66.7% (25lb-50lb)	97.9%	100%			
	*Leg press 90lbs	66.7%-88.9% (60lb-80lb)	99.5%	100%			
DREAM 12	Chest press 55lbs	36.4%-81.8% (20lb-45lb)	95.3%	100%	100%	3.6 (2-5)	-
	Seated row 115lbs	34.8%-54.3) (40lb-62.5lb	97.3%	100%			
	Leg press 130lbs	50%-82.6% (65lb-95lb)	98.3%	100%			
DREAM 13	**Chest press 35lbs	28.6%-58.9% (10lb-20.6lb)	97.3%	100%	100%	4.7 (3-5)	-
	Seated row 60lbs	33.3%-51% (20lb-30.6lb)	98.3%	100%			
	Leg press 90lbs	44.4%-72.2% (40lb-65lb)	100%	100%			
DREAM 14	Chest press 30lbs	33.3%-141.7% (10lb-42.5lb)	97.3%	100%	100%	4.7 (2-6)	-
	Seated row 45lbs	33.3%-105.6% (15lb-47.5lb)	98.9%	100%			
	Leg press 95lbs	63.2%-89.5% (60lb-85lb)	97.3%	100%			

1.27.4 Adverse Events:

There were no serious adverse events. The primary minor adverse events related to the exercise program were (1) an initial increase in arm lymphedema volume reported by four participants; (2) fatigue reported by 5 participants, and (3) muscle soreness reported by 4 participants. Only one participant in the standard care group stopped exercise as a result of the increase in arm volume. Other reported adverse events were not related to the exercise program (Table 10).

Table 10: *Adverse events*

Reported adverse events	Standard Care Group (n)	DPRE Group (n)
Fatigue	2	3
muscle soreness	2	2
Arm volume increases	3 (one participant stopped exercising)	1 (due to insect bite) 1(upper arm)

Knee pain	0	2 (one post home injury, not related to exercise)
Inflammation around surgical scar, pain and discomfort under arm	0	1 (before starting exercise program)
Ankle pain and swelling	0	1 (home injury, not related to exercise)
Muscle cramp	0	1 (not related to exercise)

1.27.5 Preliminary efficacy of exercise on lymphedema volume:

Lymphedema measurements at baseline, 6-week and 12-week are presented in Table 11 and Figure 2. There were no statistically significant differences between the two groups at baseline for LAV and LRV (p=0.242, p=0.531), respectively. Twelve week follow-up assessment showed borderline significance in LRV over the time between the two groups (p=0.074) and a statistically significant difference in the mean change of arm lymphedema volume between the two groups (p=0.027) (mean, standard care: +66.9 mls; DPRE: -65.0 mls).

The descriptive statistics showed that the LAV scores of the DPRE group decreased over time from baseline (mean = 737.83, SD = 485.92) to 6 weeks (mean = 692.72, SD =516.21), and at 12 weeks (mean = 672.83, SD =502.73). Whereas the standard care group scores increased from baseline (mean = 472.33, SD =249.19) to 6 weeks (mean = 479.08, SD = 320.09), and 12 weeks (mean = 539.25, SD = 334.62). A similar trend was seen in the LRV (Table 11 and Figure 5).

Table 11: *Arm volume measurements*

	Baseline			6-Week			12-Week			Change in arm measurements		
	Standard Care Mean(SD)	DPRE Mean(SD)	P	Standard Care Mean(SD)	DPRE Mean(SD)	P	Standard Care	DPRE	P	Standard Care Mean(SD)	DPRE Mean(SD)	P
Arm Volume (mL)	469.58 (250.56)	730.61 (487.086)	0.25	480.96 (320.60)	690.72 (517.34)	.39	537.92 (335.44)	670.64 (503.56)	0.58	66.92 (138.71)	-65.00 (66.79)	0.027
Arm Volume (%)	19.70 (10.24)	25.49 (20.31)	0.53	20.40 (14.39)	23.92 (20.44)	.72	21.81 (15.46)	23.56 (20.55)	.86	2.90 (6.81)	-1.83 (2.36)	0.074
L-Dex Ratio	13.20 (16.70)	27.46_a (28.09)	0.29	19.08 (18.85)	26.88_a (27.74)	.56	19.13 (19.08)	27.22 (27.33)	.54	5.93 (7.46)	-.23 (12.06)	0.287

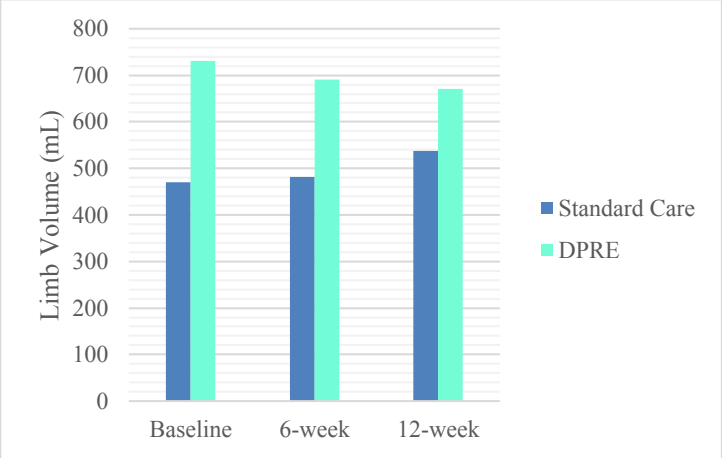

Figure 5: *Arm Volume Difference in mls*

The compression garment type and the changes in lymphedema volume:

Of nine participants in the DPRE group, six were wearing an adjustable compression wrap during exercise, two were wearing a circular knit compression sleeve, and one was wearing a flat knit compression sleeve. For daytime compression use, six participants were wearing a circular knit, and three were wearing a flat knit compression sleeve. In the standard care group, three participants were wearing a flat knit compression sleeve, and the other three were wearing a circular knit during exercise and daytime.

Despite the significant benefit from DPRE for absolute arm volume, differing patterns were seen across participants. Four participants had an initial increase in arm lymphedema volume at the 6-week time point, followed by a reduction at 12 weeks, four participants had reduction in their lymphedema volume at the 6-week follow-up with a slight increase at the 12-

week assessment point (but remained lower than baseline), and one participant had reduction in her lymphedema volume over time (Figure 6). On the other hand, two participants in the standard care group had increases in their lymphedema volume over time, two participants had slight reductions in arm lymphedema volume at the 6-week time point, followed by an increase at 12-week (to more than their baseline value), and one participant had a reduction in her arm lymphedema volume over time (Figure 7).

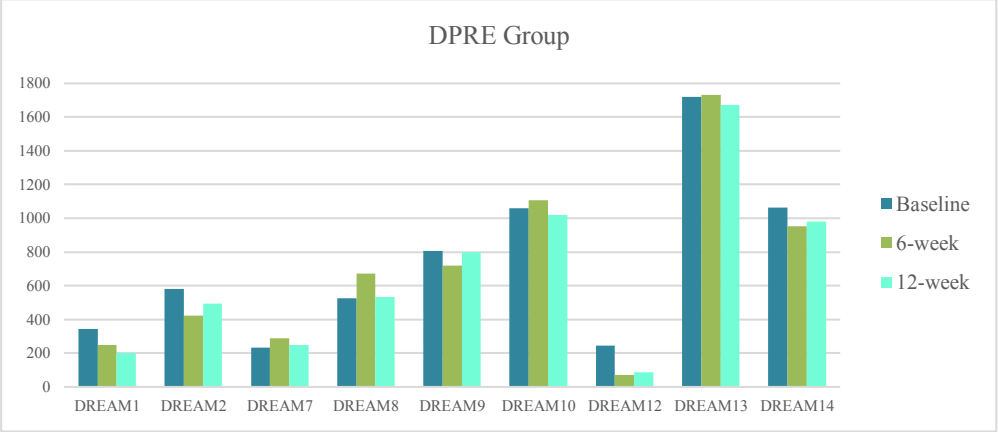

Figure 6: *DPRE group Arm Volume Measurements*

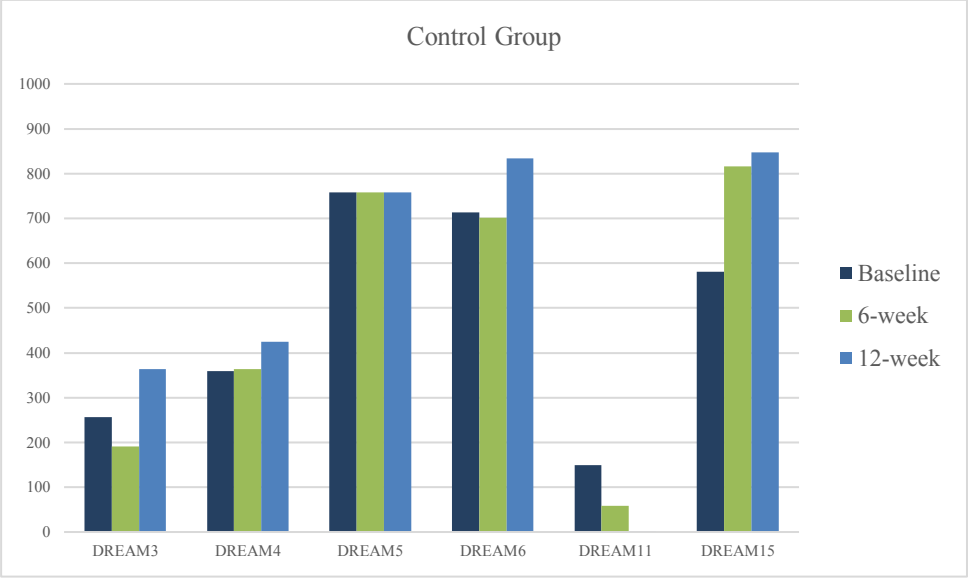

Figure 7: *Standard Care Arm Volume Measurements*

1.28 Secondary Outcome

1.28.1 L-Dex ratio:

There were no statistically significant differences between the two groups at baseline measurements of L-Dex ratio (p=0.287). The scores showed similar trends as LAV and LRV over the time with no statistical significant difference between both groups (Table 11).

1.28.2 Muscle Strength:

Muscle strength test results using 1-RM are provided in Table 12. There were no statistically significant differences between the two groups at baseline measurements of muscle strength (p>0.05). After the 12-week DPRE program, there was a significant improvement of the bench press (p < 0.048) in DPRE group compared with standard care group. No statistic significant difference was found for the seated row or leg press tests.

Table 12: *1-RM strength test*

		Baseline					12-Week					Mean change		
		Standard Care		DPRE		P Value	Standard Care		DPRE		P Value	Standard Care Mean(SD)	DPRE Mean (SD)	P Value
		N.	Mean(SD)	N.	Mean (SD)		N.	Mean (SD)	N.	Mean (SD)				
Grip Strength	**R**	6	21.5(7.20)	9	27.67(5.45)	0.08	6	21.167(9.24)	9	29.56(4.56)	0.08	-.33(4.502)	1.89(2.93)	0.27
	L	6	22.17(6.43)	9	24.44(5.934)	0.49	6	22.00(7.07)	9	26.67(4.39)	0.14	-.17(3.76)	2.22(3.93)	0.26
Bench Press		6	52.5(16.66)	9	45.56(20.22)	0.5	6	51.67(13.66)	9	76.11(24.85)	0.05	-.83(14.97)	30.56(22.84)	0.01
Leg Press		5	121(29.45)	8	102.5(35.86)	0.36	5	145.00(29.58)	8	141.88(37.98)	0.88	24.00(22.75)	39.38(22.903)	0.26
Seated Row		6	60.83(18.28)	9	68.33(35.88)	0.65	6	84.17(23.11)	9	98.33(23.32)	0.27	23.33(19.66)	30.00(25.125)	0.59
Weight		6	80.15(21.49)	9	87.88(19.36)	0.48	6	79.75(22.57)	9	87.08(18.695)	0.50	-.40(1.42)	-.80(1.23)	0.57
BMI		6	31.73(6.86)	9	33.499(7.21)	0.64	6	31.73(7.08)	9	33.18(7.02)	0.70	.002(.55)	-.32(.82)	0.42

1.28.3 Body Weight and BMI:

There were no statistically significant differences between the two groups in the weight and BMI at baseline measurements. Similarly, no significant differences were found between groups at 12-week time point (Table 12).

1.28.4 Shoulder ROM:

Shoulder ROM measures at baseline and 12-week are presented in Table 13. There were no statistically significant differences between the two groups in the shoulder ROM at baseline measurements (p>0.5). Similarly, at 12-weeks there were no significant differences between the two groups (Table 13).

Table 13: *Shoulder ROM*

		Baseline			12-Week			Mean Change		
		Standard Care Group Mean (SD)	DPRE Group Mean (SD)	P Value	Standard Care Group Mean (SD)	DPRE Group Mean (SD)	P Value	Standard Care Group Mean (SD)	DPRE Group Mean (SD)	P Value
Flexion	R	142.50(14.22)	144.44(14.89)	0.80	145.33(7.89)	145.89(11.78)	0.92	2.83(11.39)	1.44(9.34)	0.80
	L	131.33(31.12)	138.11(10.17)	0.55	137.17(29.90)	145.33(11.82)	0.55	5.83(10.65)	7.22(10.76)	0.81
Abduction	R	137.50(18.75)	132.67(29.05)	0.73	146.08(13.73)	147.33(14.85)	0.87	8.58(14.25)	14.67(19.63)	0.51
	L	125.33(45.11)	129.44(19.76)	0.81	145.50(20.54)	138.11(19.87)	0.50	20.167(47.68)	8.67(15.19)	0.74
Internal	R	39.17(5.46)	39.33(16.63)	0.98	57.00(8.41)	54.44(13.92)	0.70	17.83(11.23)	15.11(17.37)	0.96
Rotation	L	46.33(14.24)	44.78(20.23)	0.87	55.33(13.69)	53.33(14.160)	0.79	9.00(15.68)	8.56(16.82)	0.39
External	R	78.83(9.07)	67.56(17.88)	0.18	84.83(9.45)	78.44(16.90)	0.42	6.00(10.08)	10.89(10.53)	0.29
Rotation	L	68.50(24.78)	54.44(20.57)	0.25	74.67(22.39)	73.33(13.96)	0.89	6.17(10.82)	18.89(26.51)	0.29
Horizontal	R	69.83(16.20)	80.33(8.70)	0.19	75.17(13.82)	80.22(8.074)	0.38	5.33(9.33)	-.11(6.41)	0.20
Abduction	L	65.00(26.26)	79.33(9.10)	0.25	66.67(24.99)	78.89(7.42)	0.29	1.67(3.14)	-.44(10.97)	0.66

1.28.5 Lymph ICF:

Self-reported questionnaires are presented in Table 14. There was no significance difference between the groups at baseline. At 12 weeks, the mean changes of scores in both groups showed improvement. However, there was no statistical significant difference between the groups (p=0.366), (Table 14).

1.28.6 Rand SF-36 items:

Baseline data showed no significant differences between the groups. At 12 weeks, one domain, energy vitality, of SF-36 was significantly increased in the DPRE group when compared to the standard care group (p=0.01), (Table 14).

1.28.7 Body Image and Relationship Scores (BIRS):

The baseline date showed no significant differences of BIRS scores between both groups at baseline (p=0.369). No significance difference between both groups after 12- week. At 12-week follow-up, data analysis showed a trend towards significance (p=0.09). Subscale analysis of BIRS scores did not show any statistically significant differences between the groups (Table 14).

1.28.8 Godin Leisure Time Questionnaire:

There were no significant differences between the groups at baseline for physical activity. Post intervention both groups reported declines in overall physical activity (Mean difference: standard care: -9.83; DPRE: -15.20); however, there were no statically significant differences between the groups (p=0.285), (Table 14).

Table 14: *Self-reported questionnaires*

	Baseline			**12-Week**			**Mean Change**		
	Standard Care Group	**DPRE Group**	**P Value**	**Standard Care Group**	**DPRE Group**	**P Value**	**Standard Care Group**	**DPRE Group**	**P Value**
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Lymph-ICF	406.32(137.68)	379.69(152.29)	0.74	358.62(134.49)	256.32(111.40)	0.13	-47.70(85.57)	-123.37(183.36)	0.37
Rand SF-36									
Physical Function (PF)	54.167(22.89)	64.44(16.29)	0.33	62.50(15.41)	72.78(5.65)	0.17	8.33(12.11)	8.33(14.58)	1.00
Social Function (SC)	67.00(13.91)	82.89(16.60)	0.08	66.83(17.30)	91.44(13.22)	0.01	-.17(20.98)	8.56(12.02)	0.32
Mental Health (MH)	78.67(12.30)	81.33(14.97)	0.72	78.67(15.73)	89.33(6.32)	0.17	.00(13.39)	8.00(13.71)	0.28
Bodily Pain (BP)	52.00(17.01)	67.89(24.049)	0.19	66.83(18.649)	69.22(20.72)	0.82	14.83(18.05)	1.33(23.33)	0.25
Change in Health (CiH)	54.17(29.23)	47.22(23.20)	0.62	50.00(27.39)	77.78(19.55)	0.04	-4.167(43.06)	30.56(27.32)	0.08
Role limitation Physical (RLP)	4.167(10.21)	22.22(44.096)	0.27	.00(.00)	50.00(48.41)	0.02	-4.17(10.21)	27.78(42.29)	0.06
Role Limitation Mental (RLM)	5.50(13.47)	33.33(44.128)	0.11	16.67(27.97)	81.44(37.73)	0.003	11.167 (34.41)	48.11 (44.49)	0.11
Energy Vitality (EV)	53.33(7.53)	55.56(17.93)	0.78	50.83(14.29)	76.67(9.35)	0.001	-2.50(10.37)	21.11(15.77)	0.01
Health Perceptions (HP)	60.83(23.75)	71.67(14.58)	0.29	57.50(20.92)	75.56(15.50)	0.08	-3.33(8.76)	3.89(14.53)	0.3
BIRS	87.83(8.64)	79.67(23.89)	0.37	91.00(13.89)	65.44(10.83)	0.001	3.17(11.58)	-14.22(20.92)	0.09

Strength and Health	37.17(7.22)	35.77(9.35)	0.76	37.33(8.36)	27.67(5.196)	0.02	.167(11.053)	-8.11(7.77)	0.11
Social Barriers	15.50(5.01)	15.67(11.39)	0.97	20.00(4.00)	13.00(6.26)	0.03	4.50(8.36)	-2.67(13.23)	0.26
Appearance and Sexuality	34.00(10.37)	26.89(10.04)	0.21	32.33(11.72)	22.00(6.20)	0.09	-1.67(4.63)	-4.89(6.66)	0.32
Godin LSI	25.33(24.52)	17.89(15.80)	0.48	15.50(18.14)	16.22(11.68)	0.93	-9.83(15.89)	-15.20(30.74)	0.29
PA min/week	132.67(289.04)	18.89(41.366)	0.38	.00(.00)	42.33(53.24)	0.04	-15.20(30.74)	23.44(41.76)	0.10

CHAPTER 5: DISCUSSION

1.29 Hypotheses related to Feasibility:

The present study hypothesized that a DPRE program combined with compression therapy for women with BCRL would be feasible in terms of recruitment rate, program attendance, adherence, and completion rates. Overall the findings support the feasibility of the intervention and acceptability from the perspective of women with BCRL.

The findings revealed a high completion rate, with 93% of women completing the intervention and all testing sessions. Only one participant in standard care group withdrew from the study for personal reasons. These findings align with previous studies that have also shown high completion rates of 88% and higher to RE with[41, 43, 46, 47, 50] or without[44, 45, 48] external resistance weight.

The present pilot study also found high adherence in terms of the supervised DPRE program with 91% of the sessions attended and completed. All participants in the supervised program were able to follow the exercise protocol and the prescribed mild to moderate intensity. High exercise adherence to prescribed repetitions (97%) was achieved. Exercise weight and/or the number of repetitions were maintained or reduced if needed, for instance in case of pain or reporting a higher RPE.

The Home Exercise Program completed by standard care participants also achieved high adherence with 84% of participants completing the daily remedial exercise regimen. Of interest, prior to enrolment in the study, participants reported not performing any lymphedema specific exercises. High adherence to exercise was also reported by Schmitz et al. with 96% adherence to the supervised period (13-week) of a lymphedema-specific RE program[47]. Additionally, a high adherence (100%) to day-time compression was achieved in both groups

with an average of 12 hours of reported wear-time during the day. Although data are lacking on adherence to exercise and compression in previous research, the result is comparable to two trials that reported more than an 84% adherence rate to a RE program and "high" adherence to garment use[43, 44].

The recruitment rate in the present study, however, was less than optimal. Using a relatively passive method of recruiting participants (i.e. referral from the participant's physical therapist), only 37.5% of eligible participants contacted the investigators. This rate is higher than a previous study by Jeffs et al. who reported a recruitment rate of 27% to a home RE program by sending invitations to the potentially eligible participants over 4-month period[44]. Previous studies in the area, however, often used more active recruitment methods including advertisement[45], recruiting patients from the outpatient clinics[41, 46, 48], and through direct contact with previous patients[43]. One large scale RCT[47] reported using both passive and active methods of recruitment such as letters, advertisements, and interviews. In the current study, the less than optimal recruitment rate could be due to number of reasons. First, the long-time commitment (24-weeks) for the full study intervention and follow-up, as well as the requirement of attendance twice per week at the center may have been barriers to participation, especially for working women and those living far from the center. Moreover, there may have been a lack of interest in participating in the PRE intervention, especially among women who are more sedentary regardless of whether the program was home-based or supervised-based. For future studies, more than one method of recruitment may be needed to optimize enrollment numbers. This may include, for example, casting a wider net by identifying participants in outpatient clinics, targeted invitations to identified women with BCRL, and approaching potentially eligible participants after their follow up appointment. Education about the study intervention and its purpose, as well as the safety of progressive RE training for women with lymphedema may help to increase interest and enrollment of women.

Although the study recruitment was slow, this pilot study achieved high completion and adherence rate, suggesting that the combined DPRE program is feasible and tolerated by participants from different age groups (55-79 years), physical activity levels, and even in those with higher BMI. The high adherence may have resulted from the design of the RE program that was personalized to the participant's baseline strength level. Moreover, the program started with a lower percentage of 1 RM resistance weight, and was progressed overtime with modification as needed. For example, upper limb exercises were modified if an increase in limb swelling was observed and lower limb exercises were modified for participants who had lower extremity joint pain.

1.30 Hypotheses related to preliminary efficacy

1.30.1 Lymphedema volume:

We hypothesized that combining DPRE program with compression would show trends towards reduction in excessive arm lymphedema volume. The mean change of excessive arm lymphedema volume showed a statistically significant difference (p=.027) in favor of the DPRE group with a trend towards significance improvement in the percentage change of excessive arm lymphedema volume (p=.074). Although the improvements of -65mls and -1.83% are unlikely to be clinically significant, the findings are promising and indicate the need for further evaluation.

Our findings are consistent with those of two previous studies showing trends towards improvement in lymphedema volume with exercise and compression[44, 45] and an additional study showing a significant within group improvement in the distal arm measurements in the group who used a compression garment during RE[48].

The influence of DPRE protocol and compression on lymphedema:

The observational analyses indicates that high adherence to the combined DPRE program might have resulted in reduction of excessive lymphedema volume in DPRE group compared to standard care. In a study that used a combined compression and RE with the aim to stimulate the lymphatic drainage[44, 45], the results supported potential benefits for arm lymphedema volume. Another two studies used MLD[41, 46] with or without remedial exercise[46] in addition to RE, and reported improvements in the proximal[41,46] and distal[41] aspects of arm lymphedema volume within the RE group. In the current trial, the focus of the DPRE program was on therapeutic elements of exercise. Using diaphragmatic deep breathing[88] and the decongestive sequence appear to have a beneficial effect on lymphedema volume. Therefore, a large scale randomized control trial is warranted to examine the efficacy of this combined program.

Due to pilot nature of this study, we could not determine if the type of compression garment may have had an influence on the lymphedema volume changes. However, recent evidence by Hirai et al. showed that the higher stiffness compression garment such as flat-knit or short stretch may enhance the muscle pump effect during exercise compared with higher elasticity garments such as circular-knit garments[30]. Johnson et al. reported that wearing compression during and following exercise on the arm with lymphedema resulted in a smaller increase in total arm volume when compared with the unaffected arm, suggesting benefit from the addition of compression[43]. A strength of the present study is that data on compression type and time worn was collected prospectively, and with a larger sample, findings will help to answer questions over whether the type of garment worn may influence the exercise response.

1.30.2 Arm function:

We hypothesized that combining DPRE program with compression would show a trend towards improvement in the arm strength and function. The results showed significance improvement of the DPRE group in the bench press test at 12-week compared with standard care group (p=.048). No significant changes in the other upper limb strength tests (hand grip and seated row) were found. However, the descriptive data showed improvement in the DPRE group at 12 weeks when compared with standard care group. Failing to detect significance changes might be due to the small sample size and low power. Furthermore, lower limb strength test measured by leg press did not show any significant difference between both groups post intervention. This might be due to the incidence of knee pain in two participants from DPRE group who were unable to perform the test. As a result, the sample size was likely too small to show a statistical difference. Of note, the improvements in the leg press within the DPRE group were similar to a previous study examining RE for lower leg muscle strength[47].

Results from the shoulder ROM measurements did not show any significance difference between the two groups at 12 weeks. Whereas the descriptive statistics showed improvement in ROM of both groups. This result is not surprising as range of motion was a component of the exercise regimen for both DPRE and standard care programs. The improvements of the standard care group in some of the outcome measurements were not anticipated. However, given that standard care group participants were not doing any lymphedema-specific exercises before the study, improvements may have resulted high adherence to the home decongestive exercise program.

1.30.3 QOL and Body image:

We hypothesized that combining the DPRE program with compression would show trends towards improvement in quality of life, and body image compared with standard care.

This study showed that the DPRE program has the potential to improve general health QOL, using SF-36, with significant improvement in the domains of energy vitality, and trend towards improvement in change in health and role limitation due to physical problems. The mean scores were between 21.11 to 30.56 are considered clinically meaningful. Additionally, lymphedema related QOL assessed by Lymph-ICF showed a trend towards improvement in both groups. This might indicate that standard care program might be beneficial in addressing the self-reported impairments related to lymphedema. However, of note, the change scores post intervention were more than double in the DPRE group compared with standard care group.

For body image, the findings showed a trend to significance in the BIRS questionnaire in favour DPRE group post intervention compared with standard care group. Although the subscale analyses did not show any statistical significance between groups, the descriptive data showed improvements of more than double in the scores of strength and health, social barriers, appearance and sexuality in DPRE group when compared with standard care group. This finding supports our hypothesis that the DPRE program would show a trend towards improvement in body image among women with BCRL. Similar findings were reported by previous study that analyzed data from 234 women with or at risk of BCRL[89]. In the trial, the investigators found that twice-weekly strength training improved body image and social relationship among breast cancer survivors[89].

Physical activity level and BMI

The data on physical activity from this study showed that neither group were, on average, meeting the recommended physical activity guidelines of at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity per week. Interestingly, there was a decline in the physical activity reported in the standard care group at 12 weeks, and an

increase in moderate to vigorous intensity activity in the DPRE group by an average of 42.2 mins/week.

The average weekly leisure activity score index slightly exceeded the cut point of 24 (mean =25.33, SD=24.52) in the CG, meaning that on average physical activity in this group was more than the basic public health recommendations in terms of the minimal weekly volume of light-to-strenuous activities. Whereas in the DPRE group, mean physical activity levels were below the cut point of 24 and individual data showed that 78% of DPRE group were insufficiently active or inactive. At 12-week follow-up, there was a decline in weekly leisure activity index scores in both groups with an average of less than 24 indicating that physical activity was less than the public health recommendations for the minimal weekly volume of light-to-strenuous activities.

Generally, the data indicate that the overall sample in the present study were inactive. As well, the low activity among participants may explain the higher BMI, with 80% classified as overweight or obese and no significant changes in body weight were found at the 12-week follow-up. Findings from this study are supported by previous studies that found a lower level of physical activity among women with BCRL compared with those without lymphedema[90, 91], and the negative association with higher BMI[90].

1.31 Sample Size Calculation for a Future Large Scale Trial

As the intervention and procedures of the pilot trial were shown to be feasible, the next step is to conduct a full scale RCT including the present pilot study data. Using the point estimates and measures of variability derived from data from this pilot trial, we are able to estimate the sample size for a future randomized trial. To detect the minimal expected reduction of 4% (standard deviation: 5) in LRV favoring the intervention groups, (power of 80% with 0.05 significance level), the estimated overall sample size is 75 participants.

Considering a 10% loss to follow-up/ withdrawal, and 3 levels of stratification, an additional 20 participants would be added for a total sample of 95.

1.32 Limitations and Future Directions

The present pilot study has several limitations, including small sample size and slower than anticipated recruitment rate. Furthermore, due to small sample size, the two DPRE groups were collapsed into one group which did not allow for comparisons across the originally three groups that were planned. Another limitation of this study is that the analysis included only two time points (6- and 12-week follow-up) within the randomized controlled trial portion of the study. The maintenance period of the study was not included in the current analyses. Hence, information about the long-term effect of the program and adherence were lacking.

In the current study, we measured the arm volume using the perometer and extracellular fluids using the L-Dex ratio. A limitation of the present pilot study is that we do not know whether the RE program resulted in arm composition changes such as muscle hypertrophy or reduced subcutaneous fat tissue. Bok et at.[41] measured the muscle mass of the arm using ultrasonography and reported that at baseline the muscle thickness of the affected arm was significantly less than the unaffected arm. After 8-week of progressive RE program, they found significant increase in the muscle thickness of the arm, along with a reduction in distal and proximal circumference within the RE group[41]. This suggests that exercise may result in positive tissue changes that may not be captured by volume measurements. Another study reported a trend towards a reduction of fat mass in the upper arm in both affected and unaffected side (p=.067) following a 12-week home progressive RE program[43]. It is not clear whether the fat reduction was in the arm only as there was no reported change in the body weight among the participants, and the MRI did not show an increase in muscle mass or water. Therefore, to better understand the impact of exercise on limb tissue composition, future studies should

consider the addition of imaging to better examine the effect of combined compression and RE on muscle and subcutaneous fat mass as well as extracellular fluid.

1.33 Future Research

Given the promising findings of the combined DPRE program with compression on BCRL, future research with a larger sample is warranted. Additionally, more active recruitment methods will need to be explored to potentially increase the recruitment rate. We will also consider implementing an imaging method to measure the effect of DPRE program on muscle mass, subcutaneous fat tissue and extracellular fluid. A longer duration study intervention program may be helpful to increase overall physical activity behaviours. Moreover, further research is needed examining the impact of low physical activity and high BMI levels on BCRL, and investigate whether an improvement in lymphedema may in turn result in increased physical activity participation.

1.34 Clinical Implication

This study provides promising results of combining a DPRE program and compression on lymphedema arm volume, arm function, QOL and body image. Moving forward, the data collected will help to inform the development of a step-by-step protocol for survivors to facilitate implementation of lymphedema-specific exercise programming in the clinical and community settings.

1.35 Conclusion

The present pilot study demonstrated that a twice weekly supervised DPRE program is feasible in women with BCRL, indicated by high completion rate (93%), adherence rate (91%), and preliminary evidence of benefit for reducing lymphedema arm volume. The preliminary data is promising and will guide us in performing a more definitive large scale trial. The larger

trial will allow for higher power to detect differences, control of confounding factors such as BMI, and subgroup analysis based on compression type and lymphedema severity. Moreover, we will plan to assess adherence and benefits from the intervention over a longer follow-up time period.

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Appendix A

Systematic Review Search Terms and each Database Results

Breast cancer or breast neoplasm*

Lymphoedema OR lymphedema OR lymphatic edema

Compression or bandag* (won't search for this because this may not show up in abstract)

Resist* exercise* or weight training or resist* training or strength training or weightlifting or (lift* n4 weight*) or gravity resistive or isotonic or isometric

Reduce swelling and arm volume, muscle strength, quality of life

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to 2018 April 16
Results: 72
Date: April 16, 2018
Search term used:
1. exp Breast Neoplasms/
2. (breast cancer* or breast neoplasm* or masectom*).mp.
3. 1 or 2
4. Resistance Training/
5. Weight Lifting/
6. (Resist* exercise* or weight train* or resist* training or strength train* or weightlifting or (lift* adj4 weight*) or gravity resistive or isotonic or isometric).mp.
7. 4 or 5 or 6
8. lymphedema/ or breast cancer lymphedema/
9. Lymphangiosarcoma/
10. (Lymphoedema or lymphedema or lymphatic edema).mp.
11. 8 or 9 or 10
12. 3 and 7 and 11
13. remove duplicates from 12

Embase 1974 to 2018 April 16
Results: 138
Date: April 16, 2018
Search term used:
1. exp breast tumor/
2. (breast cancer* or breast neoplasm* or masectom*).mp.
3. 1 or 2
4. Resistance Training/
5. Weight Lifting/
6. (Resist* exercise* or weight train* or resist* training or strength train* or weightlifting or (lift* adj4 weight*) or gravity resistive or isotonic or isometric).mp.

7. 4 or 5 or 6
8. lymphedema/ or breast cancer lymphedema/
9. Lymphangiosarcoma/
10. (Lymphoedema or lymphedema or lymphatic edema).mp.
11. 8 or 9 or 10
12. 3 and 7 and 11
13. remove duplicates from 12

CINAHL
Results: 62
Date: April 16, 2018
Search term used:
((MH "Breast Neoplasms+") or breast cancer* or breast neoplasm* or masectom*) AND ("Resist* exercise*" or "weight train*" or "resist* training" or "strength train*" or weightlifting or (lift* n4 weight*) or "gravity resistive" or isotonic or isometric) AND (Lymphoedema or lymphedema or lymphatic edema or lymphangiosarcoma)

SportDiscus
Results: 22
Date: April 16, 2018
Search term used:
(breast cancer* or breast neoplasm* or masectom*) AND ("Resist* exercise*" or "weight train*" or "resist* training" or "strength train*" or weightlifting or (lift* n4 weight*) or "gravity resistive" or isotonic or isometric) AND (Lymphoedema or lymphedema or lymphatic edema or lymphangiosarcoma)

Pedro
Results: 58
Date: April 16, 2018
Search term used:
Abstract & Title: lymphedema
Therapy: Strength training
Results: 47
Abstract & Title: lymphoedema
Therapy: Strength training
Results: 11

ALL: 352
Duplicate: 172
After removing duplicate: 180

Appendix B

Study Pamphlet

What will my participation involve?

If you take part in this study, you will have the **following tests and procedures** done: 1)We will take measurements along both your arms using a **perometer.** These measurements will help us to determine the size difference between your arms; 2) We will take measures of your arms using **bioimpedance analysis.** This device provides information on how much fluid is in your arm; 3)We will measure your upper limb and lower limb **muscle strength;** 4)We will measure your **shoulder range of movement;** 5) You will also be asked to complete a **self-administered questionnaire** that asks about the function of your arm, your physical activity, and overall quality of life. 4) We will measure your **height and weight.** 5) You will be asked to fill out a daily **journal** recording the amount of time you have worn compression each day.

"The above tests will be done at the beginning of the study, at 12, and 24 weeks of the study and additional lymphedema test will be done also at 6 and 18 weeks as well."

What else should I know?

IF YOU WOULD LIKE TO KNOW MORE ABOUT THE STUDY, PLEASE CONTACT US:

MONA: 780-492-6007
ALONAZI@UALBERTA.CA

DR.MARGIE: 780-248-1531
MMCNEELY@UALBERTA.CA

The DREAM Study

Decongestive Progressive Resistive Exercise with Advanced Compression for Breast Cancer Related Lymphedema Management

Investigators:
Mona AlOnazi
Dr. Margie McNeely
Dr. John Mackey

What is the DREAM study?

The DREAM study is a lymphedema treatment study. The study is taking place at the at the Cancer Rehabilitation Clinic in Corbett Hall at the University of Alberta.

What is the purpose of the study?

The purpose of this study is to see if using different type of compression garments during decongestive progressive resistance exercise (DPRE) will help in reducing lymphedema. We also want to see its effect on arm movement, strength, and different aspects of quality of life.

Who is eligible for the study?

You are eligible for the study if you:
have mild to moderate swelling in your arm that has occurred as a result of your breast cancer treatment;
are in maintenance phase of lymphedema treatment.
Finished all of your cancer treatment
Your compression sleeve not older than 1 month

WHAT TREATMENT IS PROVIDED IN THE STUDY?

Once you have agreed to enter the study, you will be randomly assigned to one of three groups. Random assignment is similar to a toss of a coin and is done so that each group has a similar mix of patients of different ages and state of health. You will have an equal chance of being assigned to any of the following 3 treatments groups:

1

STANDARD CARE

If you are randomized into this group, you will be provided with a home program of active, non-resistive motion exercise. You will perform the exercise once daily which takes about 10 minutes for 12 weeks.
*After 12 weeks, you will be fitted for a ready-wrap compression garment and You will be required to wear it during the DPRE program. DPRE program will be supervise, twice a week for 12 weeks. You will be required to wear your daytime compression sleeve for at least 12 hours daily.

2

DPRE WITH DAYTIME COMPRESSION SLEEVE

If you are randomized into this group, You will attend a DPRE program and you will be required to wear your daytime compression sleeve during the exercise. DPRE program will be twice a week and supervise for 12 weeks followed by additional 12 weeks for the same program at community-based fitness center or at home. You will continue wearing your compression sleeve for at least 12 hours per day, each day of the week.

3

DPRE WITH ADJUSTABLE COMPRESSION WRAP

If you are randomized into this group, you will be fitted for a Adjustable Compression Wrap garment and You will be required to wear the it during the DPRE program and you will continue wearing your daytime compression sleeve for at least 12 hours per day, each day of the week. DPRE program will be twice a week and supervise for 12 weeks followed by additional 12 weeks for the same program at community-based fitness center or at home.

Appendix C

Consent Form

Informed Consent Form for Participation in a Research Study

Decongestive Progressive Resistance Exercise with Advanced Compression for Breast Cancer Related Lymphedema Management (DREAM): A Pilot Randomized Control Trial

(A study to see whether combining compression with strength training will result in improved arm swelling in breast cancer survivors)

Protocol ID: HREBA - CC 16-1026

Principal Investigator: Dr. Margaret McNeely, PT, PhD
Department of Physical Therapy/ Department of Oncology
University of Alberta & Cross Cancer Institute
Phone: 780-248-1531

Sponsor/Funder(s): University of Alberta

Emergency Contact Number (24 hours / 7 days a week):
Cross Cancer Institute Telephone Triage Nurse:
780-432-8919 or 1-877-707-4848 (toll free)

You are being invited to participate in a research study because you have arm swelling as a result of breast cancer treatment. This consent form provides detailed information about the study to assist you with making an informed decision. Please read this document carefully and ask any questions you may have. All questions should be answered to your satisfaction before you decide whether to participate.

The study staff will tell you about timelines for making your decision. You may find it helpful to discuss the study with family and friends so that you can make the best possible decision within the given timelines.

Taking part in this study is voluntary. You may choose not to take part or, if you choose to participate, you may leave the study at any time without giving a reason. Deciding not to take part or deciding to leave the study will not result in any penalty or any loss of medical or health-related benefits to which you are entitled.

The principal investigator, who is one of the researchers, will discuss this study with you and will answer any questions you may have. If you do consent to participate in this study, you will need to sign and date this consent form. You will receive a copy of the signed form.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

Lymphedema is a swelling in the arm, chest wall and breast on the side of the breast cancer. You have developed arm lymphedema as a result of your breast cancer surgery and/ or radiation therapy. Compression therapy and exercise are commonly prescribed treatment to help reduce the arm swelling and to maintain the result. The exercise prescribed is called decongestive exercise. It is active, non resistive movements that follow a specific order from the truck to the limb and then repeat them in reverse order to increase muscle pump and to remove (decongest) fluid away from the swollen arm to non affected regions.

There are different types of compression garments that have the potensial to reduce swelling when women are exercising. The daytime compression sleeve with high elastic fabric (circular knit) or with less elastic fabric (flat-knit). The other garment, the "Adjustable Compression Wraps" has an adjustable elastic compression system that aims to help reinforce the compression on the arm. Recent research suggests that these specialized garments enhance the muscle pump effect on lymphedema; however, no research has been conducted to test whether this results in improved arm lymphedema in breast cancer survivors.

Resistance exercise training helps to improve arm flexibility, strength, function, and quality of life in breast cancer survivors. Recent evidence based guidelines have shown that breast cancer survivors with lymphedema, can safely perform resistance training (strength training) without causing their swelling to get worse. Women in these studies also wore a compression garment during exercise; however, the type of compression garment worn and details on adherence with garment use were not reported. Similarly, step-by-step recommendations on how to start resistance exercise are not available. As a result, survivors with lymphedema do not know the best way to start exercising. Also, there is no study have been performed combining all potential therapeutic approaches for lymphedema management: resistance exercise, decongestive exercise order, and compression. The proposed decongestive progressive resistance exercise in this study is following a specific sequence from trunk to the arm in order to improve the fluid drainage and reduce lymphedema.

The Health Research Ethics Board of Alberta – Cancer Committee (HREBA-CC), which oversees the ethical acceptability of research involving humans, has reviewed and granted ethics approval for this study.

WHY IS THIS STUDY BEING DONE?

The purpose of this pilot study is to investigate the feasibility of using these two different types of specialized compression garments with a decongestive progressive resistance exercise (DPRE) program for breast cancer survivors with lymphedema. Because there will only be a small number of participants, it is not expected to give complete answers to the research questions and will not prove effectiveness. If women with breast cancer related lymphedema are interested and able to take part in this pilot study, the results will be used to guide a larger study.

WHAT ARE OTHER OPTIONS IF I DECIDE NOT TO PARTICIPATE IN THIS STUDY?

You do not have to take part in this study, in order to receive continued medical care. Your physiotherapist will discuss with you other treatment options. The standard care of lymphedema at the Cross Cancer Institute involves receiving two weeks of daily compression bandaging for your arm lymphedema followed by maintenance treatment using a day-time compression sleeve and home exercise.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 24 women with breast cancer related lymphedema will take part in this study.

WHAT WILL HAPPEN DURING THIS STUDY?

ASSIGNMENT TO A GROUP

If you decide to participate then you will be "randomized" into one of the three groups described below. In this study, you will receive one of three treatments. Randomization means the treatment to which you are assigned is determined by chance. It is like flipping a coin. You will have an equal chance of being assigned to group 1,2 or 3. Neither you, the study staff, nor the study investigator can choose what group you will be in.

This is a single-blinded study, which means that you will know which group you are in, but the study assessor who will perform the measurements of your arm will not know.

STUDY INTERVENTION

Group 1 (Standard care group):

If you are randomized into this group, you will receive the usual care for lymphedema maintenance. You will be provided with a home program of therapeutic (decongestive) exercise, which will include active, non-resistive motion of the involved limb. Exercises will follow a specific order that aims to stimulate lymphatic flow in your trunk and arm. You will perform the exercise once daily for about 10 minutes and you will be required to wear your compression sleeve for at least 12 hours per day, each day of the week for 12 weeks. After 12 weeks, you will start a supervised PRE program twice a week for 12 weeks at the Cancer Rehabilitation Clinic in Corbett Hall at the University of Alberta. You will be fitted for an adjustable compression wrap and you will be required to wear it during the DPRE program. Exercise session will take approximately 60-90 minutes. Each session will start with at least 5 minutes of stretching and deep breathing, followed by a progressive resistance training program offered in a group-based format. Exercises will follow a specific order that aims to stimulate lymphatic flow in your trunk and arm. You will continue wearing your usual compression sleeve at least 12 hours per day, each day of the week. You will be seen at 6, 12, 18 and 24 weeks from the start of the study for follow-up assessment.

Group 2 (DPRE group with compression sleeve):

If you are randomized into this group, You will attend a supervised DPRE program twice a week for 12 weeks at the Cancer Rehabilitation Clinic in Corbett Hall at the University of Alberta. you will be required to wear your daytime compression sleeve during the DPRE program and you will continue wearing your compression sleeve for at least 12 hours per day, each day of the week. Exercise session will take approximately 60-90 minutes. Each session will start with at least 5 minutes of stretching and deep breathing, followed by a progressive resistance training program offered in a group-based format. Exercises will follow a specific order that aims to stimulate lymphatic flow in your trunk and arm. After 12 Weeks, you will continue the same program twice weekly for an additional 12 weeks in a community-based fitness center or at your home.

Group 3 (DPRE group with Adjustable Compression Wrap):

If you are randomized into this group, you will be fitted for an adjustable compression wrap. You will be required to wear the adjustable compression wrap during the DPRE program and you will continue wearing your usual compression sleeve at least 12 hours per day, each day of the week. You will attend a supervised PRE program twice a week for 12 weeks at the Cancer Rehabilitation Clinic in Corbett Hall at the University of Alberta. Exercise session will take approximately 60-90 minutes. Each session will start with at least 5 minutes of stretching and deep breathing, followed by a progressive resistance training program offered in a group-based format. Exercises will follow a specific order that aims to stimulate lymphatic flow in your trunk and arm. After 12 Weeks, you will continue the same program twice weekly for an additional 12 weeks in a community-based fitness center or at your home.

STUDY PROCEDURES

Established Procedures

The following established procedures will be done as part of this study. Some of these procedures may be done as part of your standard care, in which case the results may be used. Some may be done more frequently than if you were not taking part in this study. Some of these procedures may be done solely for the purpose of the study. If the results show that you are not able to continue participating in the study, the principal investigator will let you know.

- Height and weight: we will measure your high and weight at the start of the study, and your weight at the follow-up sessions at 6, 12, 18 and 24 weeks. These measurements will take less than 1 minute.
- Arm volume measurements – we will measure your arm using a Perometer. The perometer is an opto-electric volumeter which provides information on the size of your arms. This measurement will help us to identify the volume difference between your arms with and without lymphedema and to detect any changes during and following the treatment program. The Perometer measurements takes 2-5 minutes.
- Arm fluid – we will measure your arm fluid using Bioimpedance analysis (BIA). BIA is a technology that measures the resistance to a very small electrical signal applied to the arm. Bioimpedance is able to detect even small differences in fluid levels between your arms, which may

go unnoticed with the other measurement methods. Electrodes will be placed on the back of your hands, your wrists and on the top of one foot. A small harmless electrical signal will be passed through the electrodes in your arms. You will not be able to feel the signal passing through your arms. Bioimpedance is painless and measurements can be taken within 2-3 minutes.

- Muscle strength – we will use the one repeatition maximum strength test of your arms with bench press and seated row and of your legs with the leg press. This test will help us to identify your muscle strength level before the study and your progression during (12 weeks) and after the study (24 weeks).
- Range of motion of the shoulder – we will measure the range of your shoulder movement with a plastic goniometer for movements overhead, out to the side and when rotating the arm. These measurements will help us to identify any limitation in your shoulder movement.

Arm volume and arm fluids measurements will be taken at the start of the study and at 6, 12, 18 and 24 weeks follow-up appointments. The other tests will be performed only at the start of the study, and at 12 and 24-week follow-up appointments to see what effect the treatment has on your arm lymphedema.

Questionnaires

You will be provided with questionnaires (electronic or paper copy) before starting this study, at 12 weeks and at 24 weeks. The purpose of the questionnaire is to understand how the treatment impacts your function and quality of life.

- Lymphedema-related Quality of Life – We will assess your quality of life using this specific lymphedema questionnaire. It contains 29 questions related to functional impairments, activity limitations, and participation restrictions due to arm swelling. This questionnaire will take about 7 minutes to complete.
- Health-related Quality of Life – We will assess your general health- related quality of life the Rand Short Form-36 (SF-36). It involves 36 questions about your mental health, physical health, social health, function, pain, vitality/energy, health perceptions. It is easy to use and takes only 8 minutes to complete.
- Physical activity level – We will assess your physical activity level using the Godin leisure-time exercise questionnaire. It will ask you about the average, intensity, duration, and frequency of your physical activity. This questionnaire will take about 2-3 minutes to complete.

The information you provide is for research purposes only and will remain strictly confidential. Some of the questions are personal; you may choose not to answer them.

Even though you may have provided information on a questionnaire, these responses will not be reviewed by individuals not involved in this study, e.g., your health care practitioner/team. If you would like them to know this information, please bring to their attention.

Participant Diaries

You will be asked to keep a diary of your exercise and compression garment use. You will be required to record the exercise sessions performed each day (including sets, repetitions and

resistance weight). You will also record the compression garment use during exercise, and number of hours per day you used the compression sleeve. You will be asked to return the diary for each each follow-up appointment at 6, 12, 18 and 24 weeks to the cancer rehabilitation clinic in Corbett Hall, University of Alberta or submit an electronic copy to the researchers.

OPTIONAL RESEARCH

The researchers doing this study are interested in doing additional optional research. You will be given a separate optional study consent form(s) to read and sign if you wish to give permission to this. You may decide not to participate in the "optional" study and still participate in this main study.

WHAT ARE THE POTENTIAL SIDE EFFECTS FROM PARTICIPATING IN THIS STUDY?

You may experience side effects from participating in this study. Some side effects are known and are listed below, but there may be side effects that are not expected. You should discuss these with the principal investigator. The risks and side-effects of the standard or usual treatment will be explained to you as part of your standard care. These risks are not included in this consent form.

The main side effect that you may experience is muscle soreness and fatigue from muscle strength testing and resistance training. Muscle soreness or pain is usually associated with resistance training especially in the first week. Arm swelling is also one of the temporary side effects of the resistance training and it will resolve within 24 hours after the exercise. These symptoms will improve as your progress with the exercise. Also, we will individualize the exercise program and modified it as needed if you have muscle fatigue or extreme muscle soreness.

If you experience any side effects, you should call the study investigator immediately.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

Participation in this study may or may not be of personal benefit to you. The expected benefit from taking part in this study include reduced arm volume, improved muscle strength and quality of life but there is no guarantee that the intervention may be of direct benefit to you. However, based on the results of this study, it is hoped that in the long-term, patient care can be improved.

WHAT ARE MY RESPONSIBILITIES AS A STUDY PARTICIPANT?

If you choose to participate in this study, you will be expected to:

- Tell the study investigator about your current medical conditions;
- Tell the study investigator about all prescription and non-prescription medications and supplements, including vitamins and herbals, that you may be taking and check with the study doctor before starting, stopping or changing any of these. This is for your safety as these may interact with the intervention you receive on this study;
- Tell the study investigator if you are thinking about participating on another research study;
- Attend all scheduled study visits and undergo all of the procedures described above and complete the questionnaires;

- Return any diaries taken home to complete;
- Tell the study investigator of any injuries, side effects or health problems that you may be experiencing;
- Before each follow-up testing session, try to limit your exercise, avoid eating or drinking because this might influence the arm fluid measurements.

HOW LONG WILL I BE PARTICIPATING IN THIS STUDY?

The study program will last for about 24 weeks. If you assigned to group 1 or 2, you will be asked to come twice a week for 12-week. Generally, you will be requested to come back to the Cancer Rehabilitation Clinic in Corbett Hall at the University of Alberta for follow-ups at 6, 12, 18 and 24 weeks. Each follow-up testing session will take around an hour (60 minutes) to complete.

WILL THERE BE ANY LONG-TERM FOLLOW-UP INVOLVED WITH THIS STUDY?

No matter which group you are randomized to, and even if you stop receiving the study intervention early, we would like to keep track of your health for up to 24 weeks to look at the long-term effects of your participation on the study. We would do this by having you come back to the Rehabilitation Clinic in Corbett Hall at the University of Alberta for the follow-ups assessments at 12-weeks and 24 weeks.

In the event it is necessary to further evaluate the feasibility and efficacy of the intervention program, it may be necessary to have access to additional information about your health status. The study team may attempt to obtain study-related information about your health from you or from other private sources, including your care physician. This may include contacting you again by phone or letter, but only if you have not withdrawn your consent for future contact. However, contacting you, your care physician or using other private sources of information, is optional, please indicate your decision using the check boxes below.

You give permission to the study doctor or member of the study team to attempt to obtain study-related information about your health status to further evaluate the feasibility and efficacy of the intervention program. This may include contacting your care physician, or by contacting you by phone or letter (i.e., future contact).

☐ Yes ☐ No Participant's Initials: _____

Name/phone number of care physician: _____

CAN I CHOOSE TO LEAVE THIS STUDY EARLY?

You can choose to end your participation in this research (called early withdrawal) at any time without having to provide a reason. If you choose to withdraw early from the study without finishing the intervention, procedure or follow-up, you are encouraged to contact the principal investigator or study staff. You may be asked questions about your experience with the study intervention.

You may withdraw your permission to use information that was collected about you for this study at any time by letting the principal investigator know. However, this would also mean that you withdraw from the study. Information that was recorded before you withdrew will be used by the researchers for the purposes of the study, but no additional information will be collected or sent to the sponsor after you withdraw your permission.

CAN MY PARTICIPATION IN THIS STUDY END EARLY?

The principal investigator may stop your participation in the study early, and without your consent, for reasons such as:

- You are unable to tolerate the exercise;
- You experience an adverse effect during or after exercising;
- The treatment causes your lymphedema to become worse;
- You develop a skin reaction, a blood clot or arm infection during your treatment.
- You are unable to complete all required study procedures;
- Your doctor no longer feels this is the best treatment for you;
- The sponsor decides to stop the study;
- A regulatory authority (for example, Health Canada) or the research ethics board withdraws permission for the study to continue.

If this happens, it may mean that you would not receive the study intervention for the full period described in this consent form. If you are removed from the study, the principal investigator will discuss the reasons with you and plans will be made for your continued care outside of the study.

HOW WILL MY PERSONAL INFORMATION BE KEPT CONFIDENTIAL?

If you decide to participate in this study, the principal investigator and study staff will only collect the information they need for this study.

Records identifying you, including information collect from your medical files/records, such as your Electronic Medical Records (EMR), Netcare, charts, etc., will be kept confidential to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in this consent document.

Authorized representatives of the following organizations may look at your identifiable medical/clinical study records at the site where these records are held for quality assurance purposes and/or to verify that the information collected for the study is correct and follows proper laws and guidelines:

- Members of the Regulatory/Audit team at at the Cross Cancer Institute, for quality assurance purposes;
- The Health Research Ethics Board of Alberta – Cancer Committee, which oversees the ethical conduct of this study;

- Health Canada, which oversees the use of natural health products/drugs/devices in Canada and the conduct of clinical trials;
- Other regulatory agencies that have oversight of this study;

Authorized representatives of the above organizations may **receive** information related to the study from your medical/clinical study records that will be kept confidential in a secure location and may be used in current or future relevant health research. Your name or other information that may identify you will not be provided (i.e., the information will be de-identified). The records received by these organizations will be coded with a number. The key that indicates what number you have been assigned will be kept secure by the researchers directly involved with your study and will not be released. To protect your identity, the information that will be on your assessment forms and questionnaires will be limited to your study ID and initials.

Any disclosure of your identifiable health information will be done in accordance with federal and provincial laws including the Alberta Health Information Act (HIA). The organizations listed above are required to have organizational policies and procedures to protect the information they see or receive about you, except where disclosure may be required by law. The principal investigator will ensure that any personal health information collected for this study is kept in a secure and confidential location AHS facility as also required by law.

If the results of this study are published, your identity will remain confidential. It is expected that the information collected during the study will be used in analyses and will be published and/or presented to the scientific community at meetings and in journals, but your identity will remain confidential. This information may also be used as part of a submission to regulatory authorities around the world to support the approval of this intervention.

Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated. Every effort will be made to keep your identifiable information confidential, and to follow the ethical and legal rules about collecting, using and disclosing this information.

Data collected will be entered into the secure RedCap server held at the University of Alberta and data will only be used for research purposes.

Studies involving humans sometimes collect information on race and ethnicity as well as other characteristics of individuals because these characteristics may influence how people respond to different interventions. Providing information on your race or ethnic origin is voluntary.

WILL MY HEALTHCARE PROVIDER(S) BE INFORMED OF MY PARTICIPATION IN THIS STUDY?

Your family doctor/health care provider will be informed that you are taking part in a study so that you can be provided with appropriate medical care. If you do not want your family doctor/health care provider to be informed, please discuss with your study team to find out your options.

WILL THERE BE ANY COSTS INVOLVED WITH PARTICIPATING IN THIS STUDY?

You will not have to pay for the compression garment and exercise program you receive in this study. We will provide a parking pass to cover your parking costs at the University of Alberta when you come for any exercise sessions, tests, or procedures associated with the study. There may be additional costs to you for taking part in this study such as:

Taking part in this study may result in added costs to you. For example:

- transportation,
- snacks/meals during the study;
- babysitting, etc.

Possible Costs After the Study is Complete

You may not be able to receive the study intervention after your participation in the study is completed. There are several possible reasons for this, some of which are:

- Your caregivers may not feel it is the best option for you;
- You may decide it is too expensive and insurance coverage may not be available;
- The intervention, even if approved in Canada, may not be available free of charge.

The principal investigator will discuss these options with you.

WILL I BE COMPENSATED FOR PARTICIPATING IN THIS STUDY?

You will not be paid for taking part in this study. However, in the case of research-related side effects or injury, as a direct result of participating in this research, you will receive all medical treatments or services recommended by your doctors.

Although no funds have been set aside to compensate you in the event of injury or illness related to the study treatment or procedures, you do not give up any of your legal rights for compensation by signing this form.

WHAT ARE MY RIGHTS AS A PARTICIPANT IN THIS STUDY?

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study. You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of these results, please contact the principal investigator.

The results of this study will be available on a clinical registry; refer to the section titled "Where can I find online information about this study?". Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form, you do not give up any of your legal rights against the hospital, investigators, sponsor, involved institutions for compensation or their agents, nor does this form relieve these parties from their legal and professional responsibilities.

IS THERE CONFLICT OF INTEREST RELATED TO THIS STUDY?

There are no conflicts of interest declared between the principal investigator and sponsor of this study.

WHAT IF RESEARCHERS DISCOVER SOMETHING ABOUT ME AS A RESEARCH PARTICIPANT?

During the study, the researchers may learn something about you that they didn't expect. For example, the researchers may find out that you have another medical condition.

If any clinically important information about your health is obtained as a result of your participation in this study, you will be given the opportunity at that time to decide whether you wish to be made aware of that information.

WHERE CAN I FIND ONLINE INFORMATION ABOUT THIS STUDY?

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

The study registration number to use this website is: [XXXXXXXXXXX]

WHO DO I CONTACT FOR QUESTIONS?

If you have questions about taking part in this study, or if you suffer a research-related injury, you should talk to the principal investigator. These person(s) are:

Mona AlOnazi, PT	780-492-6007
Name	Telephone
Dr. Margaret McNeely, PT,PhD	780-432-8716 or 780-248-1531
Name	Telephone

Dr. Margaret McNeely can also be paged through the Cross Cancer Institute Switchboard at 780-432-8771

If you have questions about your rights as a participant or about ethical issues related to this study and you would like to talk to someone who is not involved in the conduct of the study, please contact the Office of the Health Research Ethics Board of Alberta – Cancer Committee at:

Telephone: 780-423-5727 Toll Free: 1-877-423-5727

SIGNATURES

Part 1 - to be completed by the potential participant.

	Yes	No
Do you understand that you have been asked to take part in a research study?	☐	☐
Do you understand why this study is being done?	☐	☐
Do you understand the potential benefits of taking part in this study?	☐	☐
Do you understand the risks of taking part in this study?	☐	☐
Do you understand what you will be asked to do should you decide to take part in this study?	☐	☐
Do you understand the alternatives to participating in this study?	☐	☐
Do you understand that you are free to leave the study at any time, without out having to give reason and without affecting your future health care?	☐	☐
Do you understand who will see your records, including health information that identifies you?	☐	☐
Do you understand that by signing this consent form you are giving us permission to access your health information and specimens if applicable?	☐	☐
Do you understand that by signing this consent form that you do not give up any of your legal rights?	☐	☐
Do you understand that your family doctor/health care provider will/may be informed of your participation in this study?	☐	☐
Have you had enough opportunity to ask questions and discuss this study?	☐	☐

By signing this form I agree, or allow the person I am responsible for, to participate in this study.

_____	_____	_____
Signature of Participant /Substitute Decision-Maker	PRINTED NAME	Date

(As a Substitute Decision-Maker, you are being asked to provide informed consent on behalf of a person who is unable to provide consent for him/herself. If the participant gains the capacity to consent for him/herself, your consent for them will end.)

Part 2 - to be completed by the principal investigator or designee who conducted the informed consent discussion. Only compete this section if the potential participant has **agreed** to participate.

I believe that the person signing this form understands what is involved in the study and has freely decided to participate.

Signature of Person Conducting the Consent Discussion	PRINTED NAME	Date

Part 3 - to be completed only if the participant is unable to read or requires assistance of an oral translator/interpreter.

- The informed consent form was accurately explained to, and apparently understood by the participant/substitute decision maker.
- Informed consent was freely given by or on behalf of the participant.

Signature of Impartial Witness/Interpreter	PRINTED NAME	Date

**You will be given a copy of this signed and dated consent form prior to participating in this study. **

Appendix D

Remedial Exercise Protocol for Standard Care Group

Lymphedema Remedial Exercise involves active, repetitive, non-resistive motion of the involved body part.

D.1 -Decongestive Exercises for the Upper Extremity Instructions:

- Exercises should be performed wearing compression sleeves
- Tight or restrictive clothing (tight underwear or bra, heavy breast prosthesis) should not be worn while performing the exercises
- Exercises should be performed twice daily for about 10-15 minutes.
- Movements should be performed in a slow and controlled manner, and the musculature should be relaxed between each individual exercise. The relaxation phase should last at least as long as the time spent during the exercise
- Exercises are performed in a supported position: sitting on stool or a chair without leaning back, or performed lying on the floor. Proper breathing techniques should be used throughout the session.

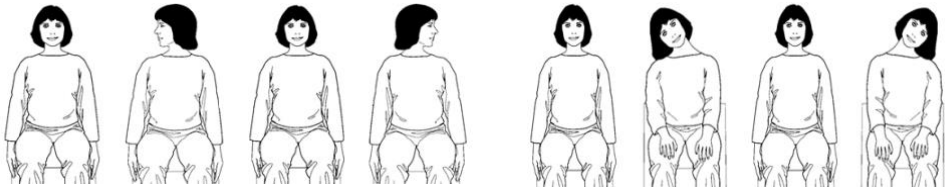
D.2 Remedial Exercises Program and Instructions

1. **Abdominal Breathing**

- Lie on your back on a flat surface or in bed, with your knees bent and your head supported
- Place both hands on your belly
- Inhale slowly and deeply through your nose into your belly (feel how you breathe against your hands)
- Tighten your abdominal muscles, letting them fall inward as you exhale through pursed lips
- Continue for 10 repetitions

2. **Neck Exercises** (2-3 repetitions each)

- Turn your head slowly and look to the right and return to normal position. Do not use force; turn gently; repeat on the left side
- Bend your head to the right and try to touch the shoulder with your ear (do not shrug your shoulder). Return to the starting position and repeat for left side
- Slowly and smoothly draw chin toward chest, raise head and look toward ceiling. Repeat gently



3. **Shoulder circles (**5 repetitions each)

- Roll your shoulders forward in a circle
- Roll your shoulders backwards in a circle
- Relax.

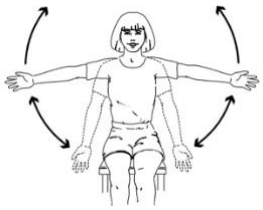
4. **Massaging the arm pit** (5 repetitions)

Massage the arm pit on your normal side for 30 seconds.

5. **Shoulder flexion (**5 repetitions)

- Start with your arms at your side.
- With your palms facing each other, raise your arms in front of you as far as you can
- Return to the starting position.

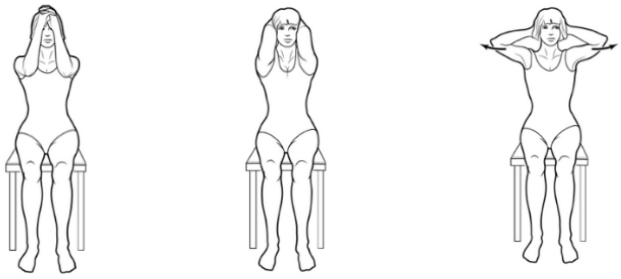
6. **Shoulder abduction/adduction (lateral shoulder arm raises)** (5 repetitions)



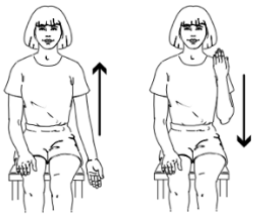
- Extended your arms out to the side
- Slowly raise your arms above your head
- Return to the starting position.

7. **Shoulder external rotation (**5 repetitions)

- Start by slowly raising your hands over your head until you reach the back of your neck
- Spread your elbows as far apart as possible
- Hold for 5 seconds.
- Return to the starting position.



8. **Elbow extension and flexion (**5 repetitions)

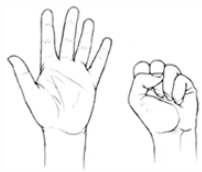


- Start with your arms at your sides, with your palms facing forward
- Bend at your elbow so that your palm touches your shoulder.
- Return to the starting position.
- Repeat the exercise with your other arm.

9. **Wrist extension and flexion (**5 repetitions)

- Place your arms on a supported surface such as a table or desk, leaving

10. **Full Fist (**5 repetitions)



- Straighten your wrist and point your fingers and thumb upward
- Make a fist by bringing your fingers to the middle of your palm and place your thumb against your index and middle fingers
- Hold for a count of one then repeat

***Repeat all exercises in reverse order, starting with #10 and ending with node clearing and breathing exercise.**

Appendix E

Advanced compression's Use and Care

E.1 Enhanced compression or (Ready Wrap low-elastic medical binders)

Enhanced compression or (Ready Wrap low-elastic medical binders) are alternative or supplement to elastic compression hosiery. The low-stretch materials work with the venous and lymphatic systems to naturally improve fluid movement, enhancing natural muscle pump and producing low resting and high working pressures. Ready Wrap's easy Velcro closure system also allows for easy donning and doffing, especially for individuals who have difficulty donning elastic compression garments. There are various manufactures provides a flat-knitted compression garments such as Solaris, Medi, ...etc.

E.1.1 Arm:

-Double-sewn liner allows for easy, one-handed donning and doffing.
-Features a padded wrist and elbow to eliminate compression hot spots and provide additional comfort.
-Bilateral design contours to both left and right arms.
-Provides coverage from the wrist to MCP and overlaps the Ready Wrap arm garment to reduce gapping.
-Left/Right specific design contours more naturally to the hand.
-Built in padding for palm and dorsum helps provide consistent compression over bony prominences.
- Pocket design allows for foam pads to provide additional support.

Figure 3: solarismed.com

E.2.2 Gauntlet:

-Provides coverage from the wrist to MCP and overlaps the Ready Wrap arm garment to reduce gapping.
-Left/Right specific design contours more naturally to the hand.
-Built in padding for palm and dorsum helps provide consistent compression over bony prominences.
-Pocket design allows for foam pads to provide additional support.

Figure 4: solarismed.com

E.3.1 Measuring Landmarks for ready wrap garments

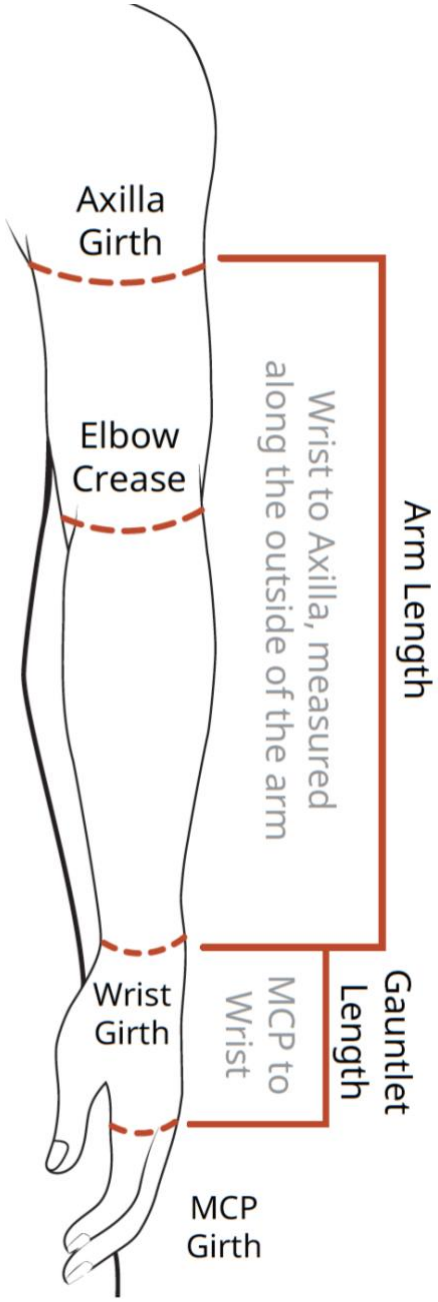


Figure 5: solarismed.com

E.2.4 Upper Extremity Donning Instructions:

➢Arm:

1. Slide your arm through the inner liner. Adjust so the seam of the elbow pad is directly over the bony prominence of your elbow.
2. Fasten the strap with white hook over your wrist. Fasten the remaining straps in order from light blue to dark blue, adjusting for comfort as needed.

➢Gauntlet:

1. Open the wrist strap of your arm unit. Place your hand in the gauntlet, keeping your thumb in a relaxed position. Fasten the white tab to the palm of your gauntlet.

2. Fasten the light blue wrist strap so it overlaps the arm liner. Then fasten the dark blue palm strap. Adjust the thumb strap and refasten the wrist strap of your arm garment.

E.2.5 Care Instructions:

Washing

- Hand wash only
- Use warm water with a drop of mild detergent or dish soap
- Do not use bleach, fabric softeners, or other additives.

Drying

- Lay flat to dry
- Do not machine dry and do not iron
- Drying time can be shortened by laying the garment on a towel and rolling it inside the towel to collect excess water.

Appendix F

Intervention Protocol for DPRE groups

F.1 General Guidelines:

1. Exercise will be stopped for pain, discomfort, or signs of lymphedema exacerbation (flare-up).
2. Participants will receive information that will enable them to spot worsening of their lymphedema, and to know how to respond.
3. Participants will attend a supervised PRE program twice per week for 12 weeks, followed by 12 weeks unsupervised PRE program
4. Exercise will start gradually, increased gradually.
5. Participants in DPREG will always wear well fitted adjustable compression garment or flat-knitted compression sleeve (based on the assigned group) during exercises.
6. Participant will be encouraged to maintain a proper posture and breath fully during exercises and throughout the day.
7. Participants should maintain a regular breathing pattern that includes exhaling during concentric contraction and inhaling during eccentric contraction
8. Each exercise will be done with correct technique in a slow and controlled motion, with 2 seconds count lifting (concentric contraction) and 2 seconds count lowering (eccentric contraction)
9. Exercise session will start with the following order: warm up, resistive exercises, cool down and stretching
10. Exercises will start with deep breathing and big muscle groups of the trunk and proximal extremity
11. At the end of exercise set, the exercises will be done in reverse order to encourage clearance of fluid stimulated by the exercise.
12. All exercises will be performed on the unaffected side first and then the affected side
13. Borg rate of perceived exertion (BRPE) scale will be used to measure the exercise effort
14. Each exercise will be progressed first by increasing the number of repetitions (10, 12, 15 reps) and then the resistance weight.

F.1.2 Components of PRE

▶Warm-up phase

Exercise sessions should start with a 5-10-minute low-intensity exercise incorporating light stretching exercises. This should be followed by warming up for the specific exercise to be undertaken.

▶Progressive resistive exercise:

Exercises should be done in a circuit in the following order:

1. Diaphragmatic breathing exercise, **2.** Bench press/Chest press, **3.** Seated row, **4.** Shoulder shrug, **5.** Front raises,
6. Overhead shoulder Press, **7.** Triceps pushdowns, **8.** Wrist extension, **9.** Ball squeezing, **10.** Leg press, **11.** Leg curl, **12.** Ball squeezing, **13.** Wrist flexion, **14.** Bicep curls, **15.** Front raises, **16.** Shoulder shrug **17.** Diaphragmatic breathing exercise

▶Cool-down with Light stretching exercise

F.2 Table1: Targeted Muscle Group[1,2,3,4]

Exercise	Purpose	Muscle groups	Starting/Finish position
Chest press	To strengthen chest, anterior shoulder, and posterior arm muscles	Pectoralis major, anterior deltoid, triceps	Lying supine on weight bench. From the Start/Finish position of comfortable stretch, the dumbbells will be raised vertically without rotation.
Seated row	Strengthen rhomboids to compensate for weakened or absent middle trapezius	Rhomboid	Sitting with a dumbbell in each hand with palms facing each other. Bending slightly forward at the hips.
Shoulder shrug	Strengthen upper trapezius	Upper trapezius, levator scapulae (synergists) and erector spinae (stabilizer)	Standing with arms extended by the sides and and palms facing in and shoulder. The weights will be raised by slowly lifting the shoulders in a shrugging motion.
Front raises	To strengthen shoulder girdle, stabilize spine and improving functional abilities, such as lifting a heavy objects	Deltoid (anterior) serratus anterior, biceps brachii and clavicular portions of the Pectoralis major.	Standing with feet shoulder width apart and one foot staggered slightly forward. Hand position is thumbs upward, knuckles outward
Overhead shoulder press	To strengthen shoulder, upper back and arm muscles	Deltoids and triceps brachii	Sitting or standing with weight supported at shoulder level with overhand grip
Triceps pushdowns	Stabilize spine; strengthen elbow extensors and scapular stabilizer	Triceps	Standing and gripping the bar with an overhand grip, hands slightly less than shoulder width apart. The bar will be pulled down until the forearms are parallel to the floor with the elbows close to the body and wrists locked in a straight position. This is staring point.
Wrist extension	To strengthen the wrist extensor muscles	Extensor carpi radialis and ulnaris	Sitting with the arm supported on a bench or table, with the palm facing downwards allowing the wrists to flex until a comfortable stretch.
Ball squeezing	To strength the grip	The extensor: digitorum; the flexors: digit minima brevis, pollicis longus, digitorum	Holding a soft ball in the palm of the hand with the palm facing up**,** right elbow bent at 90 degrees and tucked in by the side

		superficialis digitorum profundus; and the intrinsic muscles: adductor pollicis, interossei and lumbricals	
Leg press	To strengthen lower body muscles in the hips, buttocks, legs and improve functional ability in walking and squatting	Gluteus maximums, quadriceps, and hamstrings	Sitting with knees flexed about 80 to 90 degrees.
Leg curl	To strengthen knee flexors	Hamstrings	Sitting with knees extended
Wrist Flexion	To strengthen the wrist flexor muscles	Flexor carpi radialis and ulnaris	Sitting with the arm supported on a bench or table, with the palm facing upwards allowing the wrists to extend until a comfortable stretch.
Bicep curls	To increase upper arm strength for performing everyday activities involving pulling motions	Biceps	Standing with feet shoulder width and one foot slightly in front of the other. With dumbbells in the patient's hands, the elbows slowly extend until she feels a comfortable stretch in her arms.

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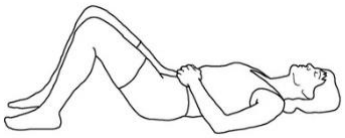
1. Ash, Werlinger, Exercises for Health Promotion: A Prescriptive Approach. First ed. Aspen publishers, Inc.1997; 231p.
2. Pollock ML, Wilmore JH. Exercise in Health and Disease: Evaluation and Prescription for Prevention and Rehabilitation. Second ed. Saunders; 1999; 741p.
3. Whaley, M., ed. ACSM's Guidelines for Exercise Testing and Prescription. Seventh ed. American College of Sports Medicine. 2006, Lippincott, Williams and Wilkins: Baltmore, MD.
4. William D. Bandy BS. Therapeutic Exercise for Physical Therapist Assistants. Third ed.; 2013. 458 p.

F.3 Progressive Resistance Exercises Program and Instructions

1. **Abdominal Breathing**

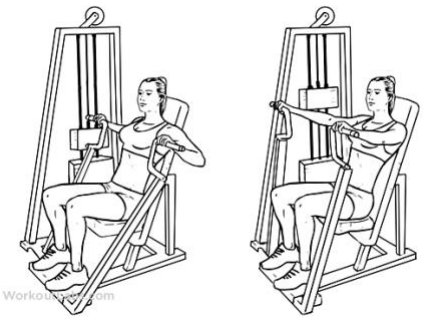
- Lie on your back on a flat surface or in bed, with your knees bent and your head supported
- Place both hands on your belly
- Inhale slowly and deeply through your nose into your belly (feel how you breathe against your hands)
- Tighten your abdominal muscles, letting them fall inward as you exhale through pursed lips
- Continue for 10 repetitions



2. **Vertical bench press/ or chest press:**

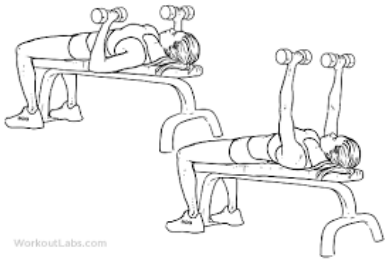
Vertical bench press

- Sit down on a machine bench press
- Position the bar arm so the handles are just out from your chest
- Grab the bar handles with an overhand grip. This is the starting position.
- Press the bar handles out away from your body slowly as you exhale until your arms are fully extended. This is the ending position.
- Return to the starting position as you inhale slowly and deeply



Chest press

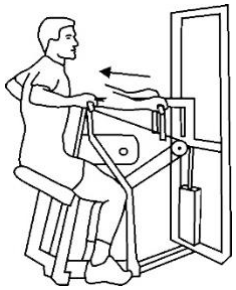
- Lie on a flat or inclined bench or bed with knees bent
- Hold a dumbbell in each hand with an overhand grip
- Start with the dumbbells placed at your chest and your elbows out. Your palms should be facing forward.
- Exhale slowly as you push the weights up towards the ceiling until your arms are straight. Hold for a count of one
- Inhale slowly and deeply as you lower the dumbbells by slowly bending your elbows back to the starting position
- Repeat the movement



*Be sure to concentrate on a balanced movement when lifting the dumbbells. Use both arms equally spaced and moving at the same speed.

3. **Seated row:**

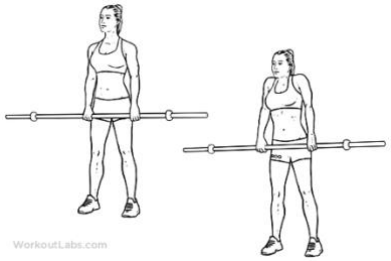
- Ensure the seat is at the correct height with your thighs parallel to the floor
- Sit on the seat and reach forward to grasp the handles and return to the correct seated position, with spine neutral and chest pad in the center of the chest
- Pull back your shoulder and raise the chest. The hips should be directly under the shoulders
- Tighten your abdominal muscles and exhale as you pull the handles by drawing the elbows back. During the pull, squeeze the shoulder blades together to ensure full back engagement.
- Hold for a count of one



- Inhale as you return to the start position extend the arms fully in a smooth movement and then pull back again in a slow and controlled motion for the next repeatition
- Repeat the movement

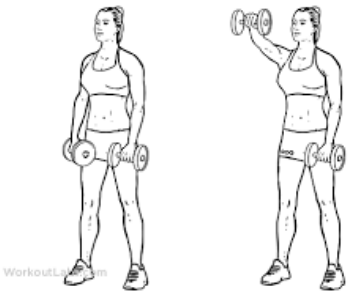
4. Shoulder shrug:

- Stand with your feet shoulder width apart and grasping the weight bar with both hand
- Keep your arms extended and by your sides and with your palms facing in. Relax your shoulders so they hang as low as possible.
- Exhale as you raise the weights by slowly lifting your shoulders in a shrugging motion. Hold for a count of one.
- Inhale as you slowly relax your shoulders to return to the start position
- Repeat the movement



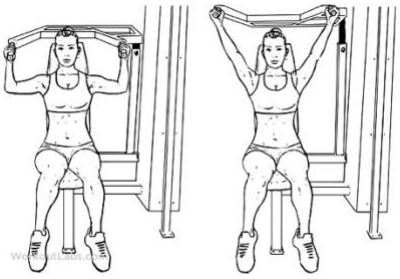
5. Front raises:

- Stand straight with your feet shoulder width apart
- Start with the dumbbells on front of your thighs at arms length and the palms of the hand facing your thighs
- While maintaining upright posture throughout the movement (without swinging), exhale as you lift the dumbbell in the affected arm to the front with a slight bend on the elbow and the palms of the hands always facing down
- Continue to go up until you arm is slightly above parallel to the floor
- Hold for a second at the top
- Inhale as you lower the dumbbell back down slowly to the starting position
- Lift the other dumbbell
- Continue alternating in this way until all of the recommended amount of repetitions have been performed for each arm



6. Overhead shoulder Press:

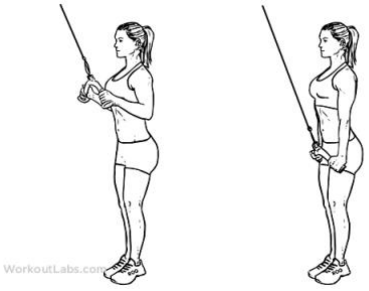
- Ensure the seat is at the correct height so that the handles are aligned with or above your shoulder height
- Keep a tight core and flat back throughout the movement
- Look straight ahead as you hold on to the handles.
- Exhale and slowly, press the handles up above your head. Do not lock out your elbow.
- Inhale and slowly bring the handles back down but do not let the weight stack touch.
- Repeat the movement



7. Triceps pushdowns:

- Grip the bar with an overhand grip, with your hands slightly less than shoulder width apart
- Stand straight, position your feet shoulder width apart, with knees slightly bent for stability, and tighten your abdominal muscles

- Pull the bar down until your forearms are parallel to the floor with your elbows close to your body and your wrists locked in a straight position. This is your staring point.
- Moving only your forearms, push the bar down towards the floor as you exhale until your arms are fully extended and you feel a stretch in your triceps. Hold for a count of one
- Inhale as you return to the start position by moving your forearms only. Hold for a count of one then repeat



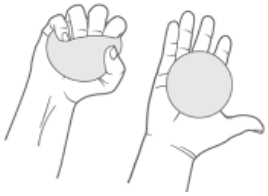
*Do not move your elbows or swing your hips for momentum during this movement

8. Wrist extension:

- Perform this movement from seated position with your forearm resting on table or on your thighs
- Your grasp is overhand (pronation) and hand spacing is approximately shoulder width
- Lower the dumbbells by allowing your wrists to flex until you feel a comfortable stretch. This is the Start/Finish position.
- The movement is performed by extending your wrists fully. Concentrate on the full range of motion.
- Repeat the movement for both hands

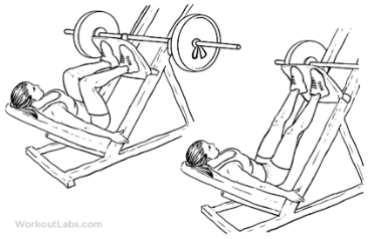
9. Ball squeezing

- Hold a soft ball in the palm of your hand with your palm facing up
- Your right elbow should be bent at 90 degrees and tucked in by your side
- Slowly squeeze the ball with your fingers and hand as if you're trying to make the ball more compact while you exhale
- Hold for 5 seconds
- Release your grip with the same controlled movement while you inhale
- Repeat the movement for both hands



10. Leg press:

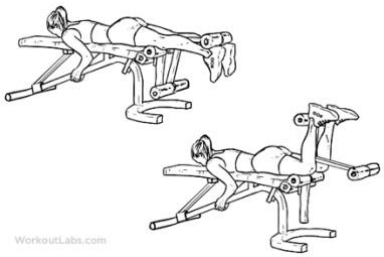
- Sit down on a leg press machine and place your legs on the platform directly in front of you at shoulder width.
- Your knees bent about 80 to 90 degrees
- Take deep breathing and Exhale as you Press the platform through the heels of your feet, engaging your quadriceps until your legs are fully extended without locking your knees
- concentrate on pushing equally with both legs
- Inhaling, slowly lower the weight to starting position. Pause for a count of one
- Continue in a slow, controlled motion between lifting and lowering the weight



11. Leg curl:

- Lie face down on a leg-curl machine and hook your heels under the roller pad

- Your legs should be stretched out straight so that the pads rest on the back of your ankles
- Grasp the handles under the bench for support
- As you exhale, curl your legs up until your hamstrings are fully contracted
- As you exhale, release and lower the weight slowly back to the starting position.
- Remaining flat on the bench, repeat the movement



12. Ball squeezing

- Repeat exercise number **9**

13. Wrist Flexion:

- Perform this movement from seated position with your forearm resting on table or on your thighs
- Your grasp is underhand (supination) and hand spacing is approximately shoulder width
- Lower the dumbbells by allowing your wrists to extend until you feel a comfortable stretch. This is the Start/Finish position
- The movement is performed by flexing your wrists fully. Concentrate on the full range of motion.
- Repeat the movement for both hands

14. Bicep curls:

- Ensure the seat is at the correct height so that your arms are level with the top of the pads
- Rest your arms against the pads and extend them fully
- Grasp the bar underhand (palms facing up) and as you exhale pull it towards your upper arm
- Pause for a moment and then as you inhale, slowly lower the bar back to starting position
- Repeat the movement

15. Front raises:

- Repeat exercise number **5**

16. Shoulder shrug:

- Repeat exercise number **4**

17. Abdominal Breathing (10 repetitions)

- Repeat exercise number **1**

Appendix G

Participants Diary

G.1 Standard Care Group Home Program Diary

STUDY ID: _____INITIALS: _____ DATE: _____ Page____of 12

	1	2	3	4	5	6	7
Did you complete your exercise training program?							
Did you wear your exercise compression during resistive exercise?							
Is there any exercise you did not do?If yes, what is the exercise(s)? Why?							
Did you experience any adverse events such as pain, tension, and fatigue? If yes, what did you have? What was the duration?							
How many hours you wear your day-time compression sleeve per day?							

G.2 DPRE Exercise Diary **STUDY ID: ----------** **NAME: ----------**

Warm up: shoulder range of motion with stick, butterfly, knee flexion

1. Abdominal Breathing **10 reps**

	Date																
AFTER LAST SESSION	**Did you experience any symptoms such as fatigue, muscle soreness/ pain, tension, increased swelling?**																
How many days per week, you wear your compression sleeve?																	
How many hours per day, you wear your compression sleeve?																	
Exercise/ Machine	**Position**	wgt	sets /rep	wgt	sets /rep	wgt	sets /rep	wgt	sets /rep	wgt	sets /rep	wgt	sets /rep	wgt	sets /rep	wgt	sets /rep
2. Vertical bench **(#6)**	-Arms by sides -Exhale as you press		2x		2x		2x		2x		2x		2x		2x		2x
3. Seated row **(#2)**	-Hands holding handles -Exhale as you pull		2x		2x		2x		2x		2x		2x		2x		2x
4. Shoulder shrug* **(#4)**	-Arms extended by sides -Exhale as you lift		1x		1x		1x		1x		1x		1x		1x		1x
5. Front raises* **OR** Overhead shoulder Press* **(#1)**	-Exhale as you lift -Exhale as you lift -Exhale as you press handles up		1x		1x		1x		1x		1x		1x		1x		1x
6. Triceps push down **(#5)**	-Exhale as you pull the handle down		2x		2x		2x		2x		2x		2x		2x		2x

7. Wrist extension	-Palm down		2x		2x		2x		2x		2x		2x		2x		2x
8. Hand grip	Hold for 5 seconds		2x		2x		2x		2x		2x		2x		2x		2x
9. Leg press **(#8)**	-Exhale as you Press		2x		2x		2x		2x		2x		2x		2x		2x
10. Leg curl **(#10)**	-Exhale as you lower the weight slowly		2x		2x		2x		2x		2x		2x		2x		2x
11. Ball Squeeze	Hold for 5 seconds		2x		2x		2x		2x		2x		2x		2x		2x
12. Wrist Flexion	Palm up		2x		2x		2x		2x		2x		2x		2x		2x
13. Bicep curls **(#4)**	-As you exhale pull the handle towards your upper arm		2x		2x		2x		2x		2x		2x		2x		2x
14. -Front raises* **OR** -Overhead Shoulder Press* **(#1)**	-Exhale as you lift -Exhale as you press handles up		1x		1x		1x		1x		1x		1x		1x		1x
15. Shoulder shrug* **(#4)**	-Arms extended by sides -Exhale as you lift		1x		1x		1x		1x		1x		1x		1x		1x
The Borg Rating (RPE)																	
POST SESSION: fatigue, muscle soreness, pain, tension, increased swelling																	

*one set on

16. Abdominal Breathing **10 reps**

Cool down: Neck, shoulder and arm stretch

Appendix H

BASELINE DEMOGRAPHIC VARIABLES

Name: _____ Initials: _____
Preferred Name: _____

Home phone: _____ Cell: _____
Business: _____ Email: _____ Other: _____

Preferred method of contact: _____
Best time to reach you: _____

---

1. Date of Birth: ___ _____ _____ Age: _____
Day Month Year

2. Marital Status: Never Married _____ Married _____ Common Law _____
Separated _____ Widowed _____ Divorced_____

3. Education (check highest level attained):
Some High School _____ Completed High School _____
Some University/College _____ Completed University/College _____
Some Graduate School _____ Completed Graduate School _____

4. Annual Family Income: < 20,000 _____ 20-39,999 _____ 40-59,999 _____
60-79,999 _____ 80-99,999 _____ > 100,000 _____

5. Current Employment Status: Disability _____ Retired _____ Part Time _____
Homemaker _____ Full Time _____ Temporarily Unemployed _____

6. Location of residence/ home? _____

7. Ethnic origin or ancestry? _____ (or underline all that apply)

- British, Western European, Eastern European, French, Northern European, Southern European, Aboriginal, East and Southeast Asian, Southern Asian, Western Asian, Pacific Islands, Arab, Latin/Central and South American, Caribbean, African, Other)

8. Smoking status:
___Never Smoked ___Ex-Smoker ___Occasional Smoker ___Regular Smoker (smoke every day)

9. Drinking status:
___Never Drank ___Ex-Drinker ___Social Drinker ____Regular Drinker (drink every day)

Appendix I

MEDICAL VARIABLES

1. Date of initial diagnosis of breast cancer: _____
Day Month Year

2. Type of breast cancer: in situ_____ invasive_____
lobular_____ ductal_____ other_____
Histopathological details: _____
Stage: T____; N____; M____ Overall stage_____

SURGERY:

3. Anatomic location of breast cancer: **right side_____ left side**_____

4. Date of main surgery for breast cancer: _____
Day Month Year

5. Type of surgery: mastectomy_____ Breast-conserving surgery_____

6. Axillary node dissection_____ Sentinel node biopsy_____

7. Number of nodes removed: _____ Number of positive nodes:_____

8. Post surgical complications: infection_____ drainage issues: _____ seroma_____ hematoma_____

Systemic Therapy: **yes____ no____**

9. CT type_____ Dosage_____ Dates: _____
Day Month Year
Biological Therapy _____ Dosage: _____Dates: _____

RADIATION THERAPY: **yes____ no____**

10. Breast_____ Axilla_____ Supraclavicular nodes_____ other: _____
11: Dosage: _____ Dates: _____

MEDICAL HISTORY:

12. Relevant past medical history: _____
13. Co-morbid/ concurrent conditions: _____
_____
14. Medications:

Medication	Indication/reason	Dosage/ frequency	Date started

LYMPHEDEMA: date of onset: _____ **Known cause:** _____
Day Month Year

Appendix J

Measurements Procedures

J.1 *Perometer Volume Measures:*

1. Each participant will have a file under her study ID number and device measurements information such as device height and length.
2. Participants will be asked to take off the watches, bracelets and any item of clothing as the compression sleeve
1. Participant will be seated on a chair at the edge of perometer with back straight and shoulder back
2. The arm will be horizontally abducted with elbow straight and the tip of the fingers placed on the hand rest of the perometer with the thumb tucked into the palm.
3. Participant should keep their arm and wrist extended during measurements.
4. The device frame will be moved in slow and steady speed towards the shoulder and returned
5. Participants will be asked to 180-degree in order to measure the other arm and the same procedure (3-6) will be repeated for the other arm,
6. Measurements will be taken 2-3 times for each arm.

J.2 *Bioimpedance analysis (BIA):* *the measurement protocol based on Cornish[19] (2006) study and L-Dex ration manufacture's instructions.*

1. Participants' height (in cm) and weight (in Kg) will be entered and saved in the device before measurements
2. At each visit, participant will be asked if she has metal implants, pacemakers or if she is pregnant. If so, the measurements will not be taken
3. Participant will be requested to take off, shoes and socks, watches and any metal jewelry on both hands and feet
4. The dominant/affected side information will be checked before measurement.
5. Participant will be asked to lie down on her back on a non-metallic surface with arms on the sides of the body, palm of the hand facing down and both feet shoulder apart. *See figure (5)*

Figure 5: L-Dex® www.impedimed.com

6. Clean the dorsum aspect of wrist and hand of each arm and the ankle of the right foot then, carefully place the electrodes in their positions without pressing too firmly. *See figure (6)*

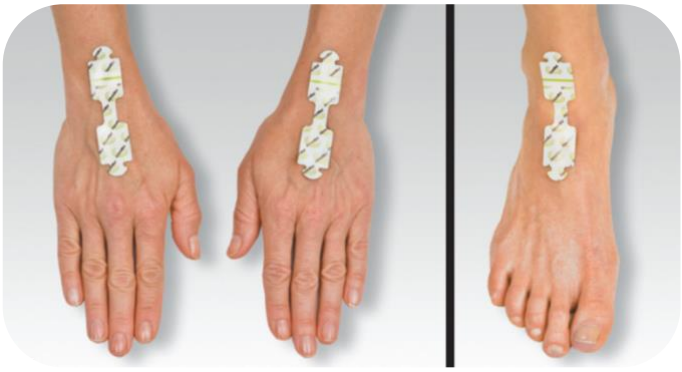


Figure 6:L-Dex® www.impedimed.com

7. Hands' electrodes position: the proximal end, with the green line will be placed on the midline of the wrist between ulnar and radial process ulnar styloid process, and the the distal end will run down towards the fingers.
8. Foot's electrodes position: the proximal end, with the green line will be placed on the ankle,

between the medial and lateral malleolus bones, and the distal end will run down towards the toes.

9. The color coded clips will be attached to the tab of the electrodes.
10. Right arm measurement, the yellow coded clip will be attached at the wrist of the right arm and the red toward the fingers of the right hand. The blue will be at the wrist of the left hand and the black at end of the electrode closest to the toes of the toes. *See figure (7)*

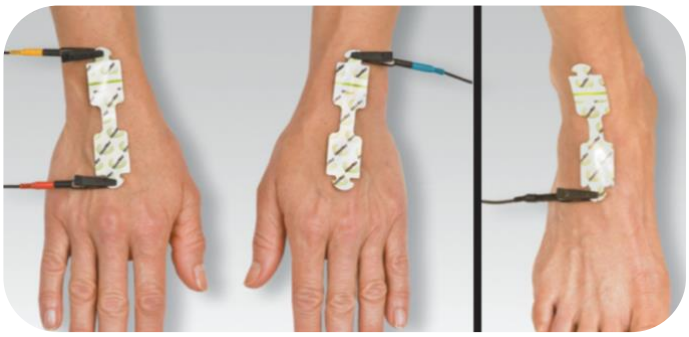


Figure 7: L-Dex® www.impedimed.com

11. Left arm measurement, the yellow coded clip will be attached at the wrist of the left arm and the red toward the fingers of the left hand. The blue will be at the wrist of the left hand and the black at end of the electrode closest to the toes of the toes. *See figure (8)*

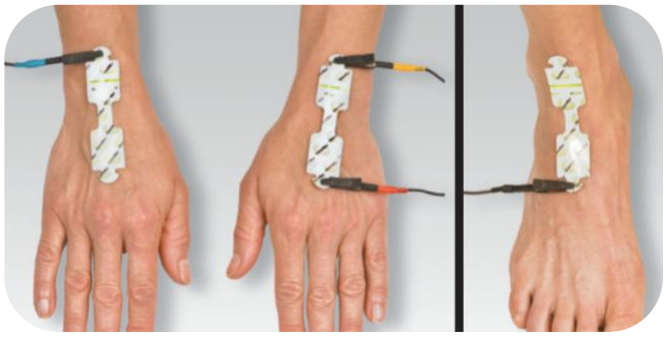


Figure 8: L-Dex® www.impedimed.com

J.3 *One-repetition maximum (1-RM) test*

J.3.1 The Borg rating of perceived exertion (RPE) scale

Borg rating of perceived exertion Scale (1-10)

Rating	How Hard you are Exercising
1	Very light
2	Very, very light
3	Moderate
4	Somewhat strong
5	Strong
6	
7	Very very sever hard
8	
9	Extremely hard
10	Maximal Exertion Hard

J.3.2 One-repetition maximum (1-RM) test procedure:

- Start with general warm-up of 3-5 minutes of light activity involving pectoralis major, anterior deltoid, triceps, rhomboid, gluteus maximums, quadriceps, and hamstrings
- Followed by stretching exercises for the the same muscles
- Each exercise will be demonstrated and participant should be taught the correct lifting and breathing techniques
- Two-minutes rest will be given between each specific exercise.
- **1-RM testing will start with the following order:**

J.3.1 -Bench Press:

1. Ask participant to sit down on the machine bench press and grab the bar handles with an overhand grip Ask participant to start by holding the dumbbells slightly wider than shoulder width apart above the shoulders, with palms facing forward.
2. If you do not know the estimated 1-RM, start with light weight and ask the participant to slowly Press the bar handles out away from her body as she exhale until her arms are fully extended.
3. Ask the participant to return to the starting position as she inhale slowly and deeply
4. Ask the participant to rate the weight using Borg rating of perceived exertion (PRPE) to measure the intensity and predict the following test weight.
5. Estimate the following test weight based on on the rated PRPE and repeat the test
6. You will increase the weight based on PRPE until the point of failure occurred
7. Give 1-minute rest between each set will be given
8.

J.3.2 -Leg press:

1. Ask participant to lie down on the leg press machine and place her legs in 90 degree knee flexion on the platform directly in front of her at shoulder width.
2. If you do not know the estimated 1-RM, start with light weight and ask the participant to press the platform through the heels of her feet, engaging her quadriceps as she exhale until her legs are fully extended without locking her knees
3. Ask the participant to slowly lower the platform until the upper and lower legs form a 90-degree angle with inhalation
4. Ask the participant to rate the weight using PRPE
5. Estimate the following test weight based on on the rated PRPE and repeat the test
6. You will increase the weight based on PRPE until the point of failure occurred
7. Give 1-minute rest between each set will be given

J.3.3 -seated row

1. Ask participant to sit down at the station and place her feet on the foot pads and to lean forward toward chest support while keeping her back straight and neck straight
2. If you do not know the estimated 1-RM, start with light weight and ask participant to hold the handles with her arms fully extended
3. Ask participant to pull the handles back towards her while squeezing her back muscles and hands reach her abdomen. Ask participant to exhale as she perform this movement and to hold for a count of one.
4. Ask the participant to inhale as she return to the start position in a smooth movement.
5. Ask the participant to rate the weight using PRPE

6. Estimate the following test weight based on on the rated PRPE and repeat the test
7. You will increase the weight based on PRPE until the point of failure occurred
8. Give 1-minute rest between each set will be given

J.4 Goniometer for measuring shoulder active range of motion (AROM):

-The measurements for AROM will be in the following order: flexion, abduction, internal rotation, and external rotation
-Participant will be asked to maintain the position at end range in order to take the measurement.
-Each movement will be demonstrated passively once

J.4.1 - Shoulder flexion:

1. Participant will be seated on a chair with back support in upright position and both arms at the side and palm facing medially
2. **Goniometer axis** will be placed at the lateral aspect of the center of the humeral head, about 2.5cm inferior to the lateral aspect of acromion process; **stationary arm**, will be parallel to the lateral midline of the trunk; and **moveable arm** will be placed parallel to the longitudinal axis of the humerus, pointing towards the lateral epicondyle of the humerus.
3. The participant will be asked to move the arm upward to the end range of elevation in sagittal plane.
4. Record the ROM at end range.

J.4.2 -Shoulder abduction:

1. Participant will be seated on a chair with back support in upright position and both arms at the side in adduction and external rotation.
2. **Goniometer axis** will be placed at midpoint of the anterior or posterior aspect of the glenohumeral joint, about 1.3cm inferior and lateral to the coracoid process; **stationary arm**, will be parallel to the sternum; and **moveable arm** will be placed parallel to the longitudinal axis of the humerus.
3. The participant will be asked to to move the arm laterally and upward to the end range in coronal plane with the thumb pointed up toward the ceiling.
4. Record the ROM at end range.

J.4.3 -Shoulder Internal rotation:

1. Participant will be sitting and the shoulder in 90 degree of abduction, the elbow is flexed to 90 degree and the forearm is in mid-position.
2. **Goniometer axis** will be placed on the olecranon process of the ulna; **stationary arm**, will be perpendicular to the floor; and **moveable arm** will be placed parallel to the longitudinal axis of the ulna, pointing towards the ulnar styloid process.
3. The participant will be asked to to move the palm of the hand towards the floor until the end range of internal rotation achieved (70 degree).
4. Record the ROM at end range.

J.4.4 -Shoulder External rotation:

1. Participant will be seated on a chair with back support in upright position and the shoulder in 90 degree of abduction, the elbow flexed to 90 degree and the forearm is mid-position. This starting position is contraindicated if the participant has a history of anterior dislocation of glenohumeral joint.
3. **Goniometer axis** will be placed on the olecranon process of the ulna; **stationary arm**, will be perpendicular to the floor; and **moveable arm** will be placed parallel to the longitudinal axis of the ulna, pointing towards the ulnar styloid process.
4. The participant will be asked to to move the dorsum of the hand towards the floor until the end range of external rotation achieved
5. Record the ROM at end range.

J.4.5 -Horizontal abduction:

1. Participant will be lying down in supine position and the arm is at the side in abduction and external rotation with elbow flexed and both hands under the head. This starting position.
2. **Goniometer axis** will be placed at midpoint of the anterior aspect of the glenohumeral joint, about 1.3cm inferior and lateral to the coracoid process; **stationary arm**, will be parallel to the sternum; and **moveable arm** will be placed parallel to the longitudinal axis of the humerus.
3. The participant will be asked to to move the arm laterally and upward until the end range

Appendix K

Questionnaires

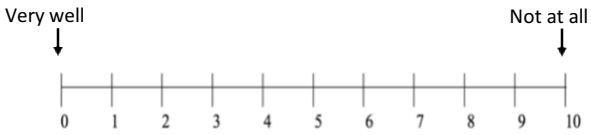
K.1 LYMPHOEDEMA FUNCTIONING, DISABILITY AND HEALTH (LYMPH-ICF) QUESTIONNAIRE

Lymphedema of the arm and/or hand can cause physical and mental complaints, as well as activity restrictions and problems participating in social life.

This questionnaire consists of 29 questions and is constructed from information given by subjects suffering from this condition.

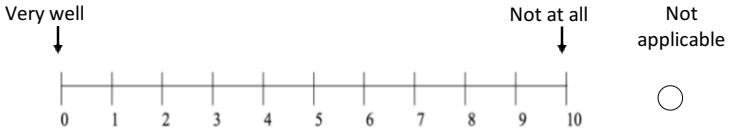
Next to each question there is a horizontal line of 10cm. At the end of the line you see the words 'not at all' and 'very much' or 'very well'. Please put a **small vertical line** on each horizontal line to indicate the degree of complaint or activity restriction due to your lymphedema.

For example:
1. Does your arm hurt?



If you do not feel any pain at all in your arm, put a small vertical line at the far left hand-side of the horizontal line.

2. Are you able to iron?

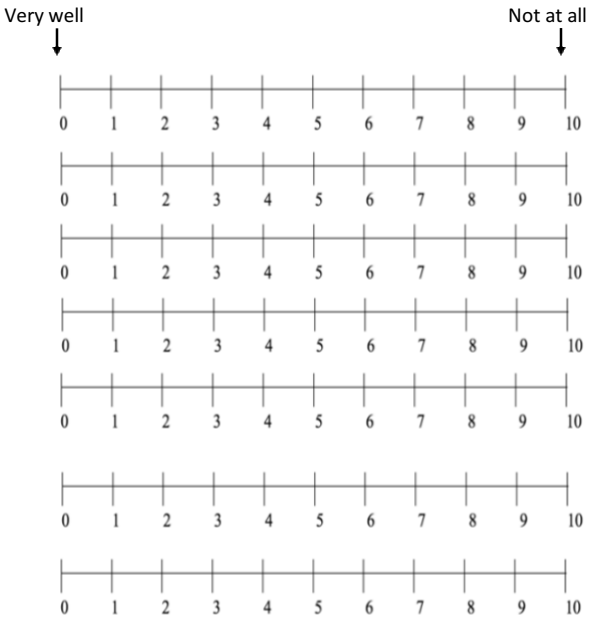


If you can hardly iron, you put a little vertical line at the right side of the horizontal line.
I you have never ironed, because you have a domestic help or you iron with your other arm, you put a cross in the little circle '⊗ _not applicable' next to the horizontal line.

Choose an answer according to your **symptoms over the last 2 weeks**. Try not to think too long about answering a certain question. Please do not leave any questions unanswered.
This is a **personal questionnaire**, to be filled in by you alone. Do not discuss these items with others in your immediate surroundings.

Pain, skin sensations, and functions of the immunologic and movement systems

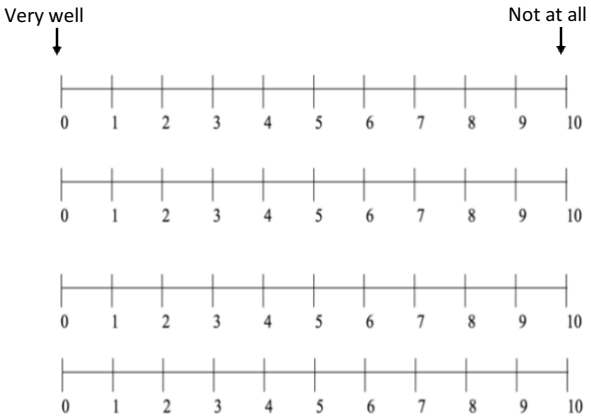
Does your arm:



1. Feel heavy?
2. Feel stiff?
3. Feel swollen?
4. Feel like it has lost strength?
5. Tingle?
6. Hurt?
7. Have a tensed skin?

Mental functions

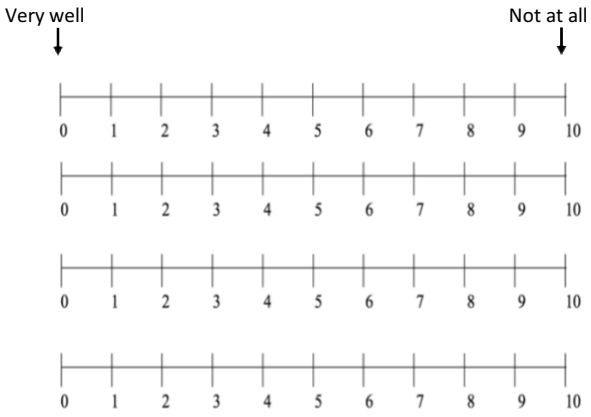
Due to your arm problems:



8. Do you feel sad?
9. Do you feel discouraged?
10. Do you have a lack of self-confidence?
11. Do you feel stressed?

Household activities

How well are you able to:

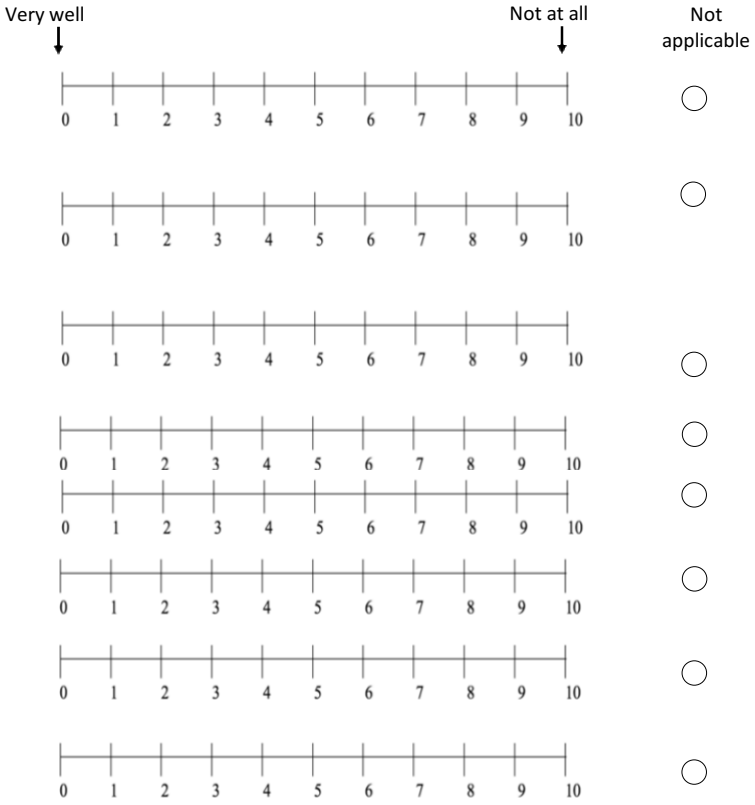


Not applicable

12. Clean (scrub, vacuum, mop)? ○
    Cook? ○
13. Iron? ○
14. Work in the garden? ○

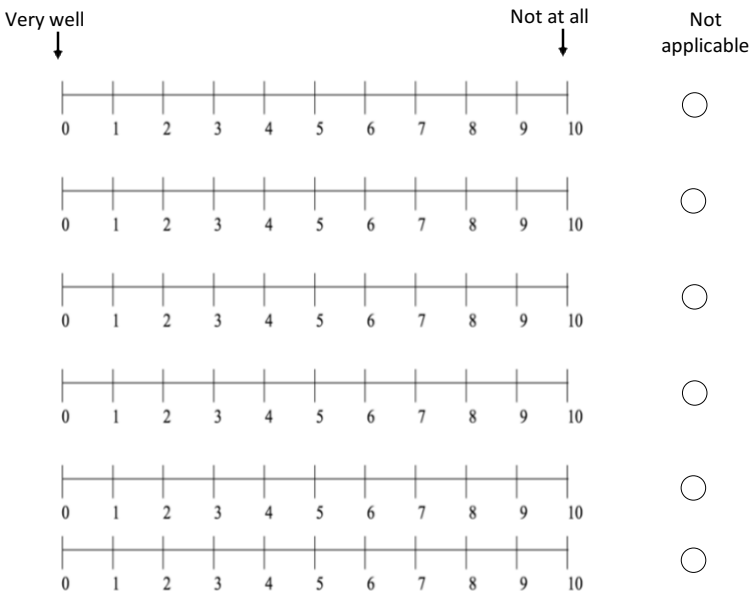
Mobility activities

How well are you able to:



Life and social activities

How well are you able to:



K.2 RAND 36-Item Short Form Health Survey (SF-36)

Question #	Question	Answer	Score (for MD use)
Example	**In general, would you say your health is:** Excellent (1) Very good (2) Good (3) Fair (4) Poor (5)	**4**	**25**

1	**In general, would you say your health is:** Excellent (1) Very good (2) Good (3) Fair (4) Poor (5)		
2	**Compared to one year ago, how would your rate your health in general now?** Much better now than one year ago (1) Somewhat better now than one year ago (2) About the same (3) Somewhat worse now than one year ago (4) Much worse now than one year ago (5)		

Question #	Question	Answer	Score (for MD use)
The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?			
3	**Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports** Yes, Limited a Lot (1) Yes, Limited a Little (2) No, Not limited at All (3)		
4	**Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf** Yes, Limited a Lot (1) Yes, Limited a Little (2) No, Not limited at All (3)		
5	**Lifting or carrying groceries** Yes, Limited a Lot (1) Yes, Limited a Little (2) No, Not limited at All (3)		
6	**Climbing several flights of stairs** Yes, Limited a Lot (1) Yes, Limited a Little (2) No, Not limited at All (3)		
7	**Climbing one flight of stairs** Yes, Limited a Lot (1) Yes, Limited a Little (2) No, Not limited at All (3)		
8	**Bending, kneeling, or stooping** Yes, Limited a Lot (1) Yes, Limited a Little (2) No, Not limited at All (3)		

Question #	Question	Answer	Score (for MD use)
9	**Walking more than a mile** Yes, Limited a Lot (1) Yes, Limited a Little (2) No, Not limited at All (3)		
10	**Walking several blocks** Yes, Limited a Lot (1) Yes, Limited a Little (2) No, Not limited at All (3)		
11	**Walking one block** Yes, Limited a Lot (1) Yes, Limited a Little (2) No, Not limited at All (3)		
12	**Bathing or dressing yourself** Yes, Limited a Lot (1) Yes, Limited a Little (2) No, Not limited at All (3)		
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?			
13	**Cut down the amount of time you spent on work or other activities** Yes (1) No (2)		
14	**Accomplished less than you would like** Yes (1) No (2)		
15	**Were limited in the kind of work or other activities** Yes (1) No (2)		

Question #	Question	Answer	Score (for MD use)
16	**Had difficulty performing the work or other activities (for example, it took extra effort)** Yes (1) No (2)		

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

17	**Cut down the amount of time you spent on work or other activities** Yes (1) No (2)		
18	**Accomplished less than you would like** Yes (1) No (2)		
19	**Didn't do work or other activities as carefully as usual** Yes (1) No (2)		
20	**During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?** Not at all (1) Slightly (2) Moderately (3) Quite a bit (4) Extremely (5)		

Question #	Question	Answer	Score (for MD use)
21	**How much bodily pain have you had during the past 4 weeks?** None (1) Very mild (2) Mild (3) Moderate (4) Severe (5) Very severe(6)		
22	**During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?** Not at all (1) Slightly (2) Moderately (3) Quite a bit (4) Extremely (5)		
	These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.		
23	**Did you feel full of pep?** All of the Time (1) Most of the Time (2) A Good Bit of the Time (3) Some of the Time (4) A Little of the Time (5) None of the Time (6)		

Question #	Question	Answer	Score (for MD use)
24	**Have you been a very nervous person?** All of the Time (1) Most of the Time (2) A Good Bit of the Time (3) Some of the Time (4) A Little of the Time (5) None of the Time (6)		
25	**Have you felt so down in the dumps that nothing could cheer you up?** All of the Time (1) Most of the Time (2) A Good Bit of the Time (3) Some of the Time (4) A Little of the Time (5) None of the Time (6)		
26	**Have you felt calm and peaceful?** All of the Time (1) Most of the Time (2) A Good Bit of the Time (3) Some of the Time (4) A Little of the Time (5) None of the Time (6)		

Question #	Question	Answer	Score (for MD use)
27	**Did you have a lot of energy?** All of the Time (1) Most of the Time (2) A Good Bit of the Time (3) Some of the Time (4) A Little of the Time (5) None of the Time (6)		
28	**Have you felt downhearted and blue?** All of the Time (1) Most of the Time (2) A Good Bit of the Time (3) Some of the Time (4) A Little of the Time (5) None of the Time (6)		
29	**Did you feel worn out?** All of the Time (1) Most of the Time (2) A Good Bit of the Time (3) Some of the Time (4) A Little of the Time (5) None of the Time (6)		
30	**Have you been a happy person?** All of the Time (1) Most of the Time (2) A Good Bit of the Time (3) Some of the Time (4) A Little of the Time (5) None of the Time (6)		

Question #	Question	Answer	Score (for MD use)
31	**Did you feel tired?** All of the Time (1) Most of the Time (2) A Good Bit of the Time (3) Some of the Time (4) A Little of the Time (5) None of the Time (6)		
32	**During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?** All of the time (1) Most of the time (2) Some of the time (3) A little of the time (4)		
How TRUE or FALSE is each of the following statements for you?			
33	**I seem to get sick a little easier than other people.** Definitely true (1) Mostly true (2) Don't know (3) Mostly false (4) Definitely false (5)		
34	**I am as healthy as anybody I know.** Definitely true (1) Mostly true (2) Don't know (3) Mostly false (4) Definitely false (5)		

Question #	Question	Answer	Score (for MD use)
35	**I expect my health to get worse.** Definitely true (1) Mostly true (2) Don't know (3) Mostly false (4) Definitely false (5)		
36	**My health is excellent.** Definitely true (1) Mostly true (2) Don't know (3) Mostly false (4) Definitely false (5)		

K.3 GODIN LEISURE TIME EXERCISE QUESTIONNAIRE

We would like you to recall your *average weekly exercise* over the *past month*. How many times per week on average did you do the following kinds of exercise over the past month?
When answering these questions please remember to:
Consider your average weekly exercise over the past month
Only count exercise sessions that lasted *15 minutes or longer* in duration
Only count exercise that was done during free time (i.e. do not included occupation or housework)
Note the main difference between the three categories is the intensity of the exercise
Write the average frequency on the first line and the average duration on the second line
STRENUOUS EXERCISE (Heart beats rapidly, sweating)
(e.g., running, jogging, hockey, soccer, squash, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling, vigorous aerobic dance classes, heavy weight training)
In an average week I was involved in strenuous exercise _____ times/week for an average duration of _____ minutes/each session.
MODERATE EXERCISE (Not exhausting, light perspiration)
(e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)
In an average week I was involved in moderate exercise _____ times/week for an average duration of _____ minutes/each session.
MILD EXERCISE (Minimal effort, no perspiration)
(e.g., easy walking, yoga, archery, fishing, bowling, lawn bowling, shuffleboard, horseshoes, golf, snowmobiling)
In an average week I was involved in mild exercise _____ times/week for an average duration of _____ minutes/each session.
RESISTANCE TRAINING EXERCISE
(e.g. exercises with dumbbells, body weight, bands, such as squats, bicep curls, etc.)
In an average week I perform resistance training activities_____ times/ week for an average duration of _____ minutes/session.
FLEXIBILITY TRAINING EXERCISE
(e.g. yoga, stretching)
In an average week I perform flexibility training activities_____ times/ week for an average duration of _____ minutes/session.

K.3.1 Godin Leisure Time Exercise Questionnaire SCORING

Step 1

A. STRENUOUS EXERCISE (Heart beats rapidly, sweating)

In an average week I was involved in strenuous exercise _____ times/week for an average duration of _____ minutes/each session.

SCORING: [number] times/week **multiplied by** [number] minutes/each session

B. MODERATE EXERCISE (Not exhausting, light perspiration)

In an average week I was involved in moderate exercise _____ times/week for an average duration of _____ minutes/each session.

SCORING: [number] times/week **multiplied by** [number] minutes/each session

C. MILD EXERCISE (Minimal effort, no perspiration)

In an average week I was involved in mild exercise _____ times/week for an average duration of _____ minutes/each session.

SCORING: [number] times/week **multiplied by** [number] minutes/each session

Step 2

TOTAL SCORE: [total number strenuous exercise**] multiplied by two** and then **added to** [total number moderate exercise]

*Note: Mild exercise is not included in Total Scoring calculation

Step 3

ACHIEVE RECOMMENDATIONS: If [Total Score] is greater than or equal to 150 then answer is **Yes**. If [Total Score] is less than 150 then answer is **No**.

K.3 The Body Image and Relationships Scale (BIRS)

Instructions

For the following statements, please indicate whether you: Strongly Disagree, Disagree, Neither Agree nor Disagree, Agree or Strongly Agree

During the past month:		Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree	N/A
1	My body felt natural to me.						
2	My body felt healthy to me.						
3	My body felt whole to me.						
4	I felt confident I could make myself stronger.						

During the past month:		Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree	N/A
5	I felt like I had some control over how healthy I was						
6	The things that determined my health felt beyond my control.						
7	I felt physically powerful.						
8	I felt physically fit.						

During the past month:		Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree	N/A
9	I felt physically capable of all the things I wanted to do.						
10	I felt uncomfortable or embarrassed because I was out of shape.						
11	Being out of shape prevented me from doing things I wanted to do.						
12	My body was strong.						

During the <u>past month</u>:		Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree	N/A
13	I restricted my social activities because of physical symptoms that I attribute to my breast cancer treatment (surgery, chemotheraphy, radiation).						
14	I was uncomfortable with or embarrassed by physical symptoms that I attribute to my breast cancer treatment (surgery, chemotherapy, radiation).						
15	Physical symptoms from breast cancer treatment (surgery, chemotherapy, radiation) prevented me from doing things I wanted to do.						
16	I was comfortable with the appearance of my body.						

During the <u>past month</u>:		Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree	N/A
17	I was uncomfortable with or embarrassed by the appearance of my body.						
18	I restricted my social activities because of my physical appearance.						

NOTE: for the following 2 questions, if you have not used the locker room of a fitness facility in the past month, please answer how you think you would have felt if you had used the locker room of a fitness facility.

During the <u>past month</u>:		Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree	N/A
19	I was comfortable changing clothes and showering in the women's locker room of a fitness facility.						
20	I was comfortable changing clothes and showering in the women's locker room of a fitness facility.						

19	Physical symptoms from breast cancer treatment (surgery, chemotherapy, radiation) prevented me from doing things I wanted to do.						
20	I was comfortable with the appearance of my body.						

During the <u>past month</u>:		Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree	N/A
21	I was embarrassed by my hot flashes.						
22	I restricted my social activities because of my hot flashes						
23	Hot flashes prevented me from doing things I wanted to do.						

During the <u>past month</u>:		Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree	N/A
24	I was embarrassed by changes in my physical appearance that I attribute to my breast cancer surgery						
25	I restricted my social activities because of changes in my physical appearance that I attribute to my breast cancer surgery.						
26	Changes in my physical appearance that I attribute to my breast cancer surgery prevented me from doing things I wanted to do.						
27	I had enough energy to do the things I wanted to do.						

During the <u>past month</u>:		Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree	N/A
28	I was uncomfortable with or embarrassed by my lack of energy.						
29	My lack of energy prevented me from doing things I wanted to do.						
30	I have been satisfied with my sex life.						
31	Sexual activity was an important part of my life.						
32	I have felt sexually attractive.						

Appendix L

Follow-Up Assessment Form

1. Since the last assessment did the participant receive any lymphedema therapy different from or in addition to the prescribed program of the Study? No ☐ Yes ☐

If yes, please describe/ provide details: _____

_____

2. Since the last assessment, indicate how many days per week, on average, the participant wore their compression garment?

☐ 7 days ☐ 6 days ☐ 5 days ☐ 4 days ☐ 3 days

☐ 2 days ☐ 1 day ☐ 0 days (specify reason: _____)

3. Since the last assessment, indicate how many hours per day, on average, the participant wore their compression garment?

☐ 4 hours or fewer ☐ 5-8 hours ☐ 9-12 hours ☐ > 12 hours

4. Since the last assessment, did the participant change her daytime compression sleeve?
No Yes

If yes, please describe/ provide details: _____

4. Since the last assessment, has the participant been diagnosed with any of the following?

a) New or recurrent cancer or other major health issue:

☐ No ☐ Yes: if yes, provide details (including dates)

_____

b) Infection in the affected limb:

☐ No ☐ Yes: if yes, provide details (including dates): _____

_____

c) Thrombosis in the affected limb:

☐ No ☐ Yes: if yes, provide details (including dates): _____

_____

d) Other adverse event not listed above:

☐ No ☐ Yes: if yes, provide details (including dates): _____

_____

Appendix M

Demographic and outcome variables

M.1 Demographic and Medical Variables

Variable	Data type	Descriptive Statistic	Inferential Statistic
Age (years and months)	Continuous: ratio	Mean and Standard Deviation	Independent sample T-test
Weight (Kilograms and grams)	Continuous: ratio	Mean and Standard Deviation	Independent sample T-test
Body mass index (BMI): -Normal (18.5–24.9) -Overweight (25–29.9) -Obese (30-40)	Categorical: ordinal	Percentage	chi-square (X^2)
BMI	Continuous	Mean and Standard Deviation	Independent sample T-test
Ethnicity: -White -Black -Other	Categorical: nominal	Percentage	chi-square (X^2)
Employment: -Professional/managerial -Clerical/service/administration -Homemaker, student, or unemployed -Other -Retired	Categorical: nominal	Percentage	chi-square (X^2)
Activity level: -Active -Sedentary	Categorical: ordinal	Percentage	chi-square (X^2)
Cancer stage: Stage I Stage II Stage III	Categorical: ordinal	Percentage	chi-square (X^2)
Lumpectomy	Discrete	Percentage	chi-square (X^2)
Modified radical mastectomy (MRM)	Discrete	Percentage	chi-square (X^2)
MRM and reconstruction	Discrete	Percentage	chi-square (X^2)
No. of nodes removed	Discrete	Mean and Standard Deviation	Independent sample T-test
Chemotherapy	Nominal	Percentage	chi-square (X^2)
Radiation	Nominal	Percentage	chi-square (X^2)
Hormonal therapy	Nominal	Percentage	chi-square (X^2)
Months since cancer diagnosis	Discrete	Mean and Standard Deviation	Independent sample T-test
Months since lymphedema diagnosis	Discrete	Mean and Standard Deviation	Independent sample T-test
Lymphedema Grade:	Categorical: ordinal	Percentage	chi-square (X^2)

-Grad I (≥10% interlimb volume difference -Grade II (>10% and ≤ 30%)			
Lymphedema measures: -Excess volume (%) -Lymphedema absolute volume (LAV) ml - Lymphedema relative volume (LRV) % -Tissue fluid (ratio)	Continuous	Mean and Standard Deviation	Independent sample T-test
Lymphedema in dominant limb	Discrete	Percentage	chi-square (X^2)

M.1 Outcome Variables (results of treatment)

Variable	Data type	Descriptive Statistic	Inferential Statistic
Recruitment rate/month	Discrete	Mean and Standard Deviation	chi-square (X^2)
Lymphedema volume: -Change in lymphedema excessive volume -LAV(ml) -LAV(ml) -Tissue fluid	Continuous: ratio	Mean and Standard Deviation	Independent sample T-test
Muscle Power: -Bench Press -Leg Press -Seated row	Continuous: ratio	Mean and Standard Deviation	Independent sample T-test
Shoulder AROM: -Flexion -Abduction -Internal rotation -External rotation	Continuous	Mean and Standard Deviation	Independent sample T-test
Quality of Life (QOL): -Lymph-ICF scores -SF-36	Discrete	Mean and Standard Deviation	Independent sample T-test
Godin			
Adherence to: -Exercise -Compression during exercise -Compression sleeve during the day	Discrete	Mean and Standard Deviation	Independent sample T-test
Physical activity Godin scores	Discrete	Mean and Standard Deviation	Independent sample T-test
Adverse events	Discrete	Percentage	chi-square (X^2)
Weight change	Continuous: ratio	Mean and Standard Deviation %	Independent sample T-test
BMI	Continuous	Mean and Standard Deviation	Independent sample T-test