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Decongestive Progressive Resistance Exercise with an Adjustable Compression Wrap for Breast Cancer Related Lymphedema [DREAM]: Protocol for a Multi-centre Randomized Controlled Trial

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ABSTRACT

Introduction: Lymphedema is a chronic swelling in the arm on the side of the breast cancer surgery, affecting one in five women. Recent studies in breast cancer-related lymphedema (BCRL) have demonstrated that resistance exercise can improve symptoms and quality of life without worsening lymphedema. No studies have explored whether combining the principles of progressive resistance exercise training with therapeutic strategies of compression therapy and the decongestive lymphatic exercise sequence are beneficial in reducing arm lymphedema volume. The aim of this 3-arm multi-centre randomized controlled trial is to determine the efficacy of a 12-week decongestive progressive resistance exercise (DPRE) program in combination with the one of two types of compression garments compared to standard care.

Methods and analysis: Sixty women with BCRL will be recruited and randomly assigned to one of the following three groups: (i) Standard care, (ii) DPRE with use of a daytime compression garment during exercise, and (iii) DPRE with use of an adjustable compression wrap during exercise. The primary outcome is the percentage reduction in arm lymphedema volume. Secondary outcomes include upper and lower body muscle strength, shoulder range of motion, physical activity level, and health-related quality of life. Exploratory outcomes include evaluating changes in arm tissue composition using Magnetic Resonance Imaging and examining outcomes between the two DPRE experimental groups. We estimated a mean reduction of 18% (+/- 16%) in lymphedema in favour of the intervention groups when compared to standard care. The primary analysis will compare changes between the groups from baseline to week 12.

Ethics and dissemination: The trial has received ethics approval from the Health Research Ethics Board of Alberta: Cancer Committee. This trial will answer important practical questions on the benefit of compression garment use during exercise.

Trial registration number: NCT02992782

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Strengths and limitations of this study

- Evaluation of the benefit of a combined program involving a specialized decongestive resistance exercise program and use of compression on arm lymphedema volume.
- Prospective collection of data on compression garment type and wear-time during exercise and throughout the day.
- Exploratory analyses on the benefit of the program on arm tissue composition through Magnetic Resonance Imaging.
- Use of a fast-track design was chosen to enhance the recruitment rate and retention; however, this design limits comparison of the originally assigned groups at 24-week follow-up.
- Data collection may be impacted by restrictions related to COVID-19.

INTRODUCTION

Background and rationale

Breast cancer-related lymphedema (BCRL), swelling in the arm, breast and chest wall on the side of the breast cancer, results from damage to the lymphatic system due to cancer or cancer treatment.[1] It occurs in an estimated 21% of cases of breast cancer.[2] To date, it is incurable, progressive, and a chronic disabling condition requiring lifelong management.[3] As a result, lymphedema is one of the most distressing and debilitating complications that may follow breast cancer treatment. Impairments associated with lymphedema include pain, fatigue, and heaviness and tightness in the extremity; and lymphedema may negatively impact shoulder range of motion, strength and function of the upper extremity.[1, 3] Not surprisingly, survivors with BCRL have been found to have a poorer health-related quality of life compared with those without the condition.[4]

There is currently no cure for lymphedema; therefore, management of the condition involves conservative interventions aiming to reduce the swelling, prevent cellulitis and optimize the survivor's function and quality of life (QOL). The initial phase of treatment is a 2-4-week course of intensive decongestive therapy, comprising skin care, manual lymphatic drainage (MLD), bandaging using multilayered bandaging, decongestive exercises, and self-care. The aim of this phase is to reduce the swelling.[5] The second phase of treatment, called the maintenance phase, involves daily use of a compression garment and a home program involving a specialized decongestive exercise program.[5-7]

Using a compression garment is essential to maintain the volume reduction during the maintenance phase.[5] There are two main types of compression garments; standard daytime compression garments and adjustable compression wraps. The standard daytime compression garments are available as ready-to-wear (off-shelf) or can be custom-made. Survivors with BCRL are told to wear their daytime compression garments during waking hours each day for 10-12 hours. Adjustable Compression Wraps, available on the market, are made of soft, non-elastic material, with an additional Velcro wrapping system allowing adjustment of compression for exercise and activity.

The principle of the decongestive exercise program is to enhance lymph drainage from the edematous area through the use of the skeletal-muscle contraction to promote

venous and lymphatic return, and the program involves active exercises without external resistance.[7,8] Recent evidence supports the safety of other types of general exercise such as aerobic and resistance exercise for BCRL. Progressive resistance exercise programs, using free weights and weight machines[8], have been found to improve symptoms and reduce the frequency of relapses (i.e. flares) in lymphedema.[9-11] High adherence to use of a compression garment and decongestive exercises during the maintenance phase is positively associated with long-term lymphedema control.[12, 13]

To date, no studies have been performed combining all potential therapeutic approaches to address lymphedema: i) use of the decongestive exercise sequence to enhance venous and lymphatic return, ii) progressive resistance exercise training to improve symptoms and prevent relapses in arm volume, and iii) use of daytime compression both during exercise and during the day to improve long-term control of the lymphedema.[11, 14-17] Figure 1 illustrates the theoretical concept for a combined program titled Decongestive Progressive Resistance Exercise (DPRE).

We recently completed a pilot randomized control trial (RCT) to examine the feasibility the DPRE program. Twenty participants were enrolled, and 19 completed the study. Feasibility data demonstrate high study completion (95%), exercise attendance (94%) and adherence to the prescribed protocol of DPRE program (97%). All participants reported 100% adherence to wearing their assigned compression garment during exercise (either using a daytime sleeve or adjustable compression wrap), and a daily average of 12 hours of wear-time. There were no minor or severe adverse events during the program. The proposed RCT will follow the same protocol, with the *a priori* planned inclusion of patient data from the pilot study.

We hypothesis that combining DPRE with either a compression garment or adjustable compression wrap will result in a larger lymphedema relative volume reduction when compared to standard care. We will explore the mean difference between the two experimental groups performing DPRE to see if there is a difference between use of a daytime sleeve or adjustable compression wrap; however, we hypothesis that the difference between groups will fall inside the equivalence interval of +/- 10% in lymphedema relative volume change. We will also explore the benefits of using Magnetic

Resonance Imaging (MRI) in informing the effect of the intervention on arm tissue composition.

Objectives

The primary objectives are the following:

1. To examine the efficacy of DPRE with use of adjustable compression wrap compared to standard care on percentage change in arm lymphedema volume.
2. To examine the efficacy of DPRE with use of a daytime compression sleeve compared to standard care on the percentage change in arm lymphedema volume.

Secondary objectives include examining the effect on arm tissue composition, shoulder range of motion (ROM), upper and lower muscle strength, physical activity, body image, QOL, and adherence.

METHODS AND ANALYSIS

Study Design

The DREAM study is a multicenter randomized controlled fast-track trial. Participants will be recruited from the Cross Cancer Institute (CCI) in Edmonton, and Tom Baker Cancer Center (TBCC) in Calgary, Canada. The study will compare the results of three groups: A) Standard care (control), B) DPRE + daytime compression garment, and C) DPRE + adjustable compression wrap. The study will be conducted over 24 weeks comprising a 12-week supervised intervention and a 12-week follow-up period. Outcome measures will be assessed at baseline, 12 and 24 weeks. See Figure 2. After 12 weeks, the standard care group participants will be fast-tracked to Group C (DPRE + adjustable compression wrap experimental intervention). The randomized fast-track trial design (with a delayed assignment of the standard care group to the experimental intervention) was chosen given the strong preference for assignment to the DPRE + adjustable compression group identified by our patient representatives. Moreover, this design, used in the pilot study, will serve to optimize recruitment as well as retention of participants in the standard care group.

Setting and Participants

Potential participants will be identified through outpatient physical therapy clinics at the Cross Cancer Institute and Holy Cross Centre. Patients will be provided with an

information pamphlet. Eligible patients will be required to initiate contact with the investigators if interested in taking part in the study.

Eligibility Criteria

A survivor will be included based on the following criteria:

- Is a female with a history of breast cancer;
- Has undergone surgery, including sentinel lymph node biopsy or axillary lymph node dissection;
- Has unilateral mild to moderate BCRL of at least 200 ml inter-limb volume difference, or regional lymphedema: defined as a minimal volume difference of 100 ml in a segment of the arm (e.g. hand and forearm region, elbow and upper arm)
- Has chronic lymphedema, defined as lymphedema that has been present for at least three months;
- Has completed intensive reduction treatment, and is in the lymphedema maintenance phase of conservative treatment;
- Uses a well-fitted daytime compression garment (not older than one month) and is agreeable to wear the garment for a minimum of 12 hours per day (providing a minimum of 30 mm Hg of pressure);
- Is agreeable to discontinuing other lymphedema treatments beyond standard care, including MLD and intermittent pneumatic compression during the 12-week RCT period of the study.

A survivor will be excluded if she:

- Is undergoing or scheduled to receive chemotherapy, radiotherapy or biological therapy;
- Presents with limb infection/ cellulitis, deep vein thrombosis, or has active metastatic disease;
- Has any neurological or cognitive deficit, is pregnant, uses a pacemaker, or has any other uncontrolled health condition that may interfere with assessment and/or the exercise training intervention;
- Has any contraindications related to use of compression on the limb, such as arterial insufficiency or congestive heart failure.

Randomization Procedure

Participants will be stratified by center (Edmonton versus Calgary) and lymphedema severity (mild: < 20% versus moderate: 20-40%), and randomized using a computer-generated randomization module within the Trial's REDCap database. Randomization will occur following baseline testing, with participants will be assigned on a 1:1:1 basis to one of the three groups.

Blinding

Independent assessors, who will be blinded to the group assignment, will carry out all objective measurements. Training and intra-rater reliability for objectively measured outcomes will be conducted prior to study onset.

Intervention

As per standard of care, participants in all groups will be required to wear their daytime compression garments (during non-exercise times) for at least 12 hours per day, seven days a week.

Group A: Standard care group

Participants in this group will receive standard care for lymphedema maintenance that involves a home exercise program involving the lymphedema decongestive exercise regimen. Participants will be instructed to perform the exercise sequence once daily for 10-15 minutes. From weeks 13 to 24 of the study, participants in this group will fast-track to the experimental protocol as per Group C below.

Group B: DPRE and daytime compression garment group

Participants will take part in the supervised in-person or virtual DPRE program twice a week for 12 weeks and will be required to wear their daytime compression garment during each DPRE session. Sessions will be offered in a group-based format with a ratio of one therapist to two-three participants. Exercise sessions will start with 5 minutes of warm-up exercises. Exercises will commence with deep breathing and progress in the sequence of the decongestive regimen from proximal to distal. The exercises will then be performed in reverse order (distal to proximal) to encourage clearance of lymphatic fluid stimulated by the exercise. Response to sessions will be monitored and the program will be progressed as indicated by first increasing the number of repetitions (10, 12, 15 reps) and then the resistance weight.

Group C: DPRE and adjustable compression garment group

Participants in this group will follow the same in-person or virtual DPRE protocol as per Group B; however, they will be assigned to wear an adjustable compression wrap when performing the DPRE program.

After the 12- week intervention, women in Group B and C will continue the same program (unsupervised) twice weekly for an additional 12 weeks in a community-based fitness center or at home.

Primary Outcome

Lymphedema Arm Volume. Lymphedema will be objectively measured using the optoelectronic limb volumeter (perometer). The perometer is a valid, reliable and sensitive method for quantifying limb volume.[18-20]

Secondary outcomes

Extracellular Fluid Volume. Bioimpedance analysis (BIA) is specially designed to estimate extracellular fluid volume in the limb. BIA measures the affected and unaffected limb's impedance ratio, and the resulting calculated index provides an estimate of extracellular fluid volume.[21] The BIA is a sensitive, valid, and reliable measurement method.[22-25]

Muscle Strength. Muscle strength will be assessed with the one-repetition maximum (1-RM) method for bench press, leg press, and seated row. The 1-RM is the maximal weight that can be lifted once using proper form, a smooth motion and without pain or other symptoms.[26]

Grip Strength. The Jamar hydraulic hand dynamometer will be used to measure grip strength, a reliable and valid tool when standardized positioning and instructions are used.[27, 28]

Shoulder Range of Motion (ROM). Shoulder active and passive ROM will be measured using a standard goniometer, and each arm will be measured separately for flexion, abduction, internal, external rotation, and horizontal abduction. The goniometer is a valid and reliable method for measuring shoulder ROM; with excellent reliability (ICC≥ 0.94)[29 30]

Health-related Quality of Life. The Lymphedema Functioning, Disability, and Health (Lymph-ICF) is a lymphedema-specific outcome questionnaire that will be used to assess

HRQOL. It is a valid tool with high reliability (ICC > 0.90) in women with BCRL.[31] The Rand Short Form-36 Version 2 (SF-36) will be used to assess general HRQOL. It is a validated self-report measure with excellent test-retest reliability.[32]

Body Image. The Body Image and Relationships Scale (BIRS) is a self-report measure of body image and relationships.[11, 33] The BIRS has been shown to have a satisfactory test-retest reliability and internal consistency in addition to convergent and divergent validity.[33]

Physical Activity. The Godin leisure-time exercise questionnaire (GLTEQ) will be used to assess the physical activity level. It is a valid, reliable, and sensitive tool among different populations, including breast cancer survivors.[34, 35]

Body Mass Index (BMI). Body height and weight will be measured, and BMI will be calculated.

Adherence. Participants will be asked to record their adherence to their assigned exercise and compression intervention program using a daily diary.

Adverse Events. We will monitor adverse events as well as any additional treatments required to manage any exacerbations of lymphedema.

Exploratory Outcomes

The Difference in Mean Outcomes Between DPRE Groups. We will explore differences between groups B and C to inform future research.

Arm Tissue Composition Volume. Magnetic resonance imaging (MRI) will be used to determine differences in arm muscle mass, fat and extracellular fluid between limbs over time. An approach called chemical shift encoded (CSE) MRI will be used to separate the signal sources from water and fat. Additionally, the water environments will be further characterized using a method called T_1-mapping. The T_1 time (longitudinal relaxation time constant) is an MRI property of the water that reflects the local environment, where water within healthy skeletal muscle has T_1 values of ~1400ms. Increased T_1 values reflect edema and fibrosis within the muscle tissue with values reaching ~3000ms for free water pools, such as those contained within subcutaneous fat. A combined CSE and T_1-mapping approach will be used to quantify volumes of muscle and fat and to characterize the water environment in all tissues.[36] Multiple axial slices (4 mm slice thickness, 0.5 mm in-plane resolution) will provide full three-dimensional coverage of the arm. See

Figure 3. MRI is a reliable method that has been used in lymphedema for diagnosis and treatment evaluation. [14, 37, 38]

COVID-19 accommodations: in the event of limitations related to, or suspension of in-person testing, objective testing will be conducted virtually and will include the following minimal dataset:

- Self-Circumference Measurements[39] will replace arm volume measurements;
- Sit-to-Stand test;[40]
- Flexion and Abduction Shoulder ROM.

STATISTICAL CONSIDERATIONS

Sample Size

The sample size for the study was based on the findings of the pilot trial. Using the point estimates and measures of variability derived for LRV, we estimated a mean reduction of 18% in lymphedema (SD: 16%) in favour of the intervention groups. The estimated sample size of 51 participants or 17 per group achieves about 86% power (significance level: $p = 0.01$). Considering a 5% loss to follow-up/ withdrawal, and two levels of stratification, an additional 9 participants will be added for a total sample size of 60 including the 20 participants from the pilot study. Thus, 40 more participants will be recruited to the trial.

Statistical Analysis Plan

Baseline medical and demographic characteristics, arm dominance relative to the lymphedematous arm, and adverse events of the three groups will be compared using one-way ANOVA for continuous data and Pearson's Chi-square tests for categorical data. The primary analysis will compare changes between the groups from baseline to week 12 with regard to percent change in arm lymphedema volume, arm tissue composition, arm function, physical activity, QoL, body image, and adherence-related outcomes. The comparisons over time (baseline, 12-week and 24-week follow-ups) will be conducted using repeated measures ANOVA and between groups comparisons will be conducted using one-way ANOVA on change scores. Generalized linear models (GLM) will be used to evaluate the treatment effect in subgroups defined by the strata adjusting for centre and lymphedema severity (mild or moderate).

Analyses of primary outcomes will be performed at the end of the RCT portion of the trial using an intention to treat analysis. Within-group analyses will also be conducted for primary and secondary outcomes from weeks 13 to 24 following completion of all follow-up measures. If missing data is greater than 30%, multiple imputation techniques will be used. Appropriate sensitivity analysis will be performed to determine the type of missing data, and statistical methods accounting for the type of missing data will be used. All statistical analysis will be conducted using SAS (SAS Institute Inc., Cary, NC) version 9.3 software.

Data management and quality control

The Clinical Trials Unit of the Cross Cancer Institute will be responsible for trial oversight. Storing and processing of all patient data will occur in compliance with institutional guidelines. A REDCap database will be used for data collection and monitoring. For quality control, the objective data of participants will be entered by the independent assessor and will be checked by a second independent research assistant. Hard copy data regarding the trial participants will be stored in a secure location in a locked cabinet at the respective centre that can only be accessed by study personnel. Data will be anonymized and stored according to participant number. A linking log is stored separately from the data. On trial completion, data will be accessible through the University of Alberta Libraries Dataserve Network.

Patient and public involvement

The idea for this study was born from patients' input. Women with BCRL often report a worsening of the swelling with exercise, and a need for better support for exercise. A patient representative actively participated in the design of the study. Findings will be disseminated to study participants and other survivors of breast cancer through workshops and presentations. Study findings will be dissemination through stakeholder groups including the Canadian Lymphedema Framework (CLF), Canadian Physiotherapy Association, and the International Lymphedema Framework (ILF) to the broader lymphedema stakeholder community.

ETHICS and DISSEMINATION

Ethical and safety Consideration:

Ethical approval was obtained from the Health Research Ethics Board of Alberta: Cancer Committee. All participants will be required to provide written informed consent and will be free to withdraw from the trial at any time, for any reason.

Dissemination Plan:

This trial will answer key questions on the effect of a combined exercise and compression intervention on arm lymphedema volume and tissue composition. The study results will be disseminated through scientific peer-reviewed publications, and presented at national and international conferences, and other media portals. The program protocol will be presented to healthcare professionals and shared with patient groups through clinical workshops and webinars.

Figure Legends:

Figure 1: Schematic of the Theoretical Concept - Combined Decongestive Progressive Resistance Exercise and Compression Therapy

Figure 2: Study Schema

Figure 3: Magnetic Resonance Imaging - one sample slice

Authors' contributions: MMA and MLM created the concept of the study. MMA, KLC, RBT, JRM and MLM developed the study concept, the exercise program and protocol. SG assisted in the statistical analysis plan and sample size calculation. All authors will oversee the implementation of the protocol and contribute to the acquisition, analysis and interpretation of data. All authors were involved in drafting and revising the protocol manuscript. All authors read and approved the final manuscript.

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This funding body had no role in the design of this study and will not have any role in its execution, analyses, interpretation of the data, or decision to submit results.

Competing interest statement. None declared.

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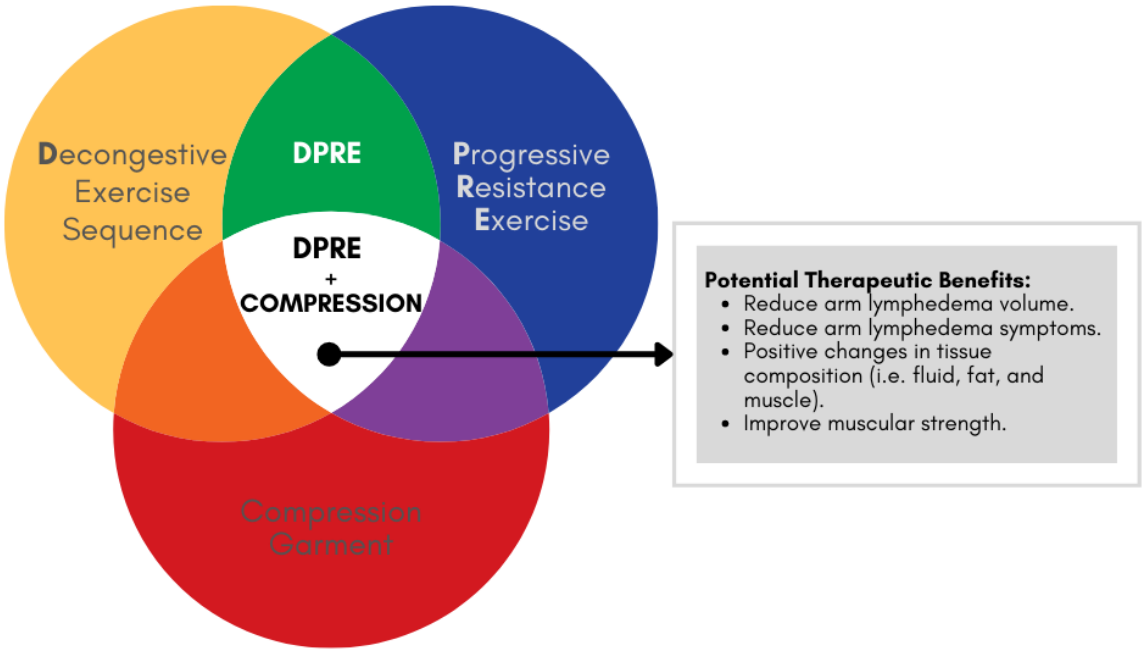

Figure 1: Schematic of DPRE and Compression Theoretical Concept

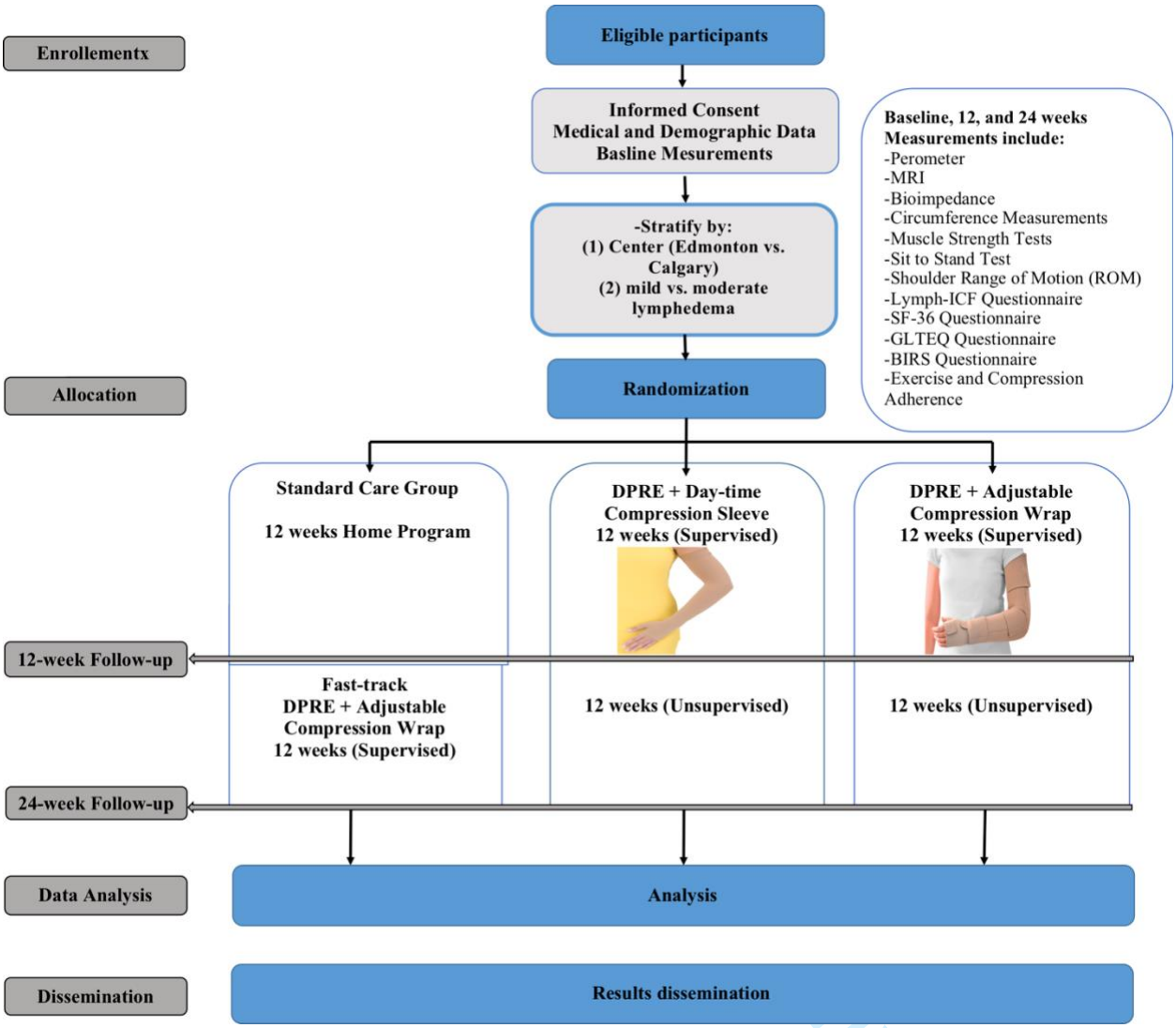

Figure 2. Study Schema

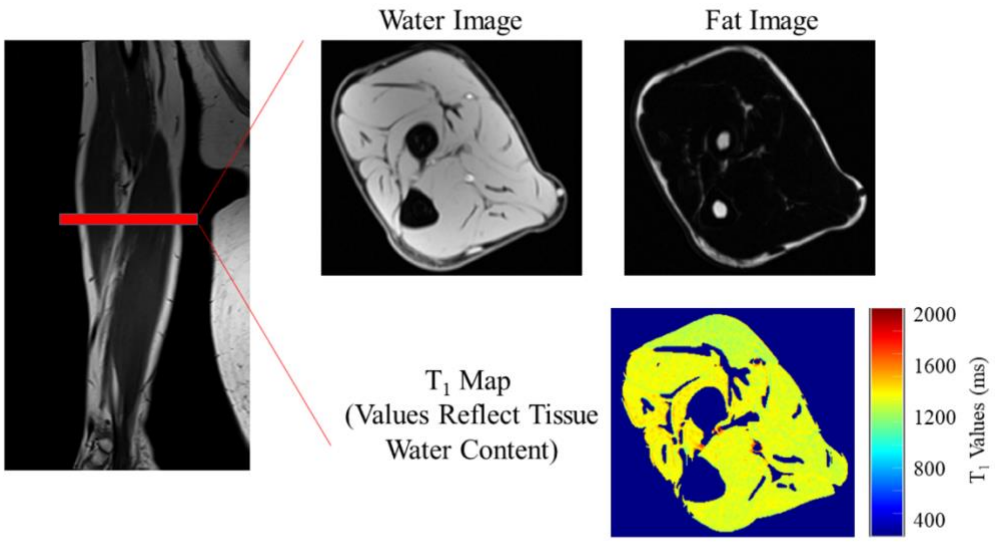

Figure 3. Magnetic Resonance Imaging - one sample slice

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Decongestive Progressive Resistance Exercise with an Adjustable Compression Wrap for Breast Cancer Related Lymphedema [DREAM]: Protocol for a Randomized Controlled Trial

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Decongestive Progressive Resistance Exercise with an Adjustable Compression Wrap for Breast Cancer Related Lymphedema [DREAM]: Protocol for a Randomized Controlled Trial

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ABSTRACT

Introduction: Breast cancer-related lymphedema (BCRL) is a chronic swelling in the arm on the side of the breast cancer surgery, affecting one in five women. Recent studies in BCRL have demonstrated that resistance exercise can improve symptoms and quality of life without worsening lymphedema. No studies have explored whether combining the principles of progressive resistance exercise training with therapeutic strategies of compression therapy and the decongestive lymphatic exercise sequence are beneficial in reducing arm lymphedema volume. The aim of this 3-arm, two-site, randomized controlled trial is to determine the efficacy of a 12-week decongestive progressive resistance exercise (DRE) program in combination with the one of two types of compression garments compared to standard care.

Methods and analysis: Sixty women with BCRL will be recruited and randomly assigned to one of the following three groups: (i) Standard care, (ii) DRE with use of a daytime compression garment during exercise, and (iii) DRE with use of an adjustable compression wrap during exercise. The primary outcome is the percentage reduction in arm lymphedema volume. Secondary outcomes include muscular strength, shoulder range of motion, physical activity level, and health-related quality of life. Exploratory outcomes include evaluating changes in arm tissue composition using Magnetic Resonance Imaging and examining outcomes between the two DRE experimental groups. The primary analysis will compare changes between the groups from baseline to week 12 reflecting the end of the randomized control trial period.

Ethics and dissemination: The trial has received ethics approval from the Health Research Ethics Board of Alberta: Cancer Committee. This trial will answer important practical questions on the benefit of compression garment use during exercise.

Trial registration number: NCT02992782

Protocol version: April 15, 2021
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Strengths and limitations of this study

- Evaluation of the benefit of a combined program involving a specialized decongestive resistance exercise program and use of compression on arm lymphedema volume.
- Prospective collection of data on compression garment type and wear-time during exercise and throughout the day.
- Exploratory analyses on the benefit of the program on arm tissue composition through Magnetic Resonance Imaging.
- Use of a fast-track design was chosen to enhance the recruitment and retention; however, this design limits comparison of the originally assigned groups at 24-week follow-up.
- Data collection may be impacted by restrictions related to COVID-19.

INTRODUCTION

Background and rationale

Breast cancer-related lymphedema (BCRL), swelling in the arm, breast and chest wall on the side of the breast cancer, results from damage to the lymphatic system due to cancer or cancer treatment.[1] It occurs in an estimated 21% of cases of breast cancer.[2] To date, it is an incurable, progressive, distressing, and debilitating condition requiring lifelong management.[3] Impairments associated with lymphedema include pain, fatigue, and heaviness and tightness in the extremity; and lymphedema may negatively impact shoulder range of motion, strength and function of the upper extremity.[1, 3] Not surprisingly, survivors with BCRL have been found to have a poorer health-related quality of life compared with those without the condition.[4]

There is currently no cure for lymphedema; therefore, management of the condition involves conservative interventions aiming to reduce the swelling, prevent cellulitis and optimize the survivor's function and quality of life (QOL). The initial phase of treatment is a 2-4-week course of intensive decongestive therapy, comprising skin care, manual lymphatic drainage, bandaging using multilayered bandaging, decongestive exercises, and self-care. The aim of this phase is to reduce the swelling.[5] The second phase of treatment, called the maintenance phase, involves daily use of a compression garment[6, 7] and a home program involving a specialized decongestive exercise program.[5-7]

Using a compression garment is essential to maintain the volume reduction during the maintenance phase.[5] There are two main types of compression garments; standard daytime compression garments and adjustable compression wraps. The standard daytime compression garments are available as ready-to-wear (off-shelf) or can be custom-made. Survivors with BCRL are told to wear their daytime compression garments during waking hours each day for 10-12 hours. Adjustable Compression Wraps, available on the market, are made of soft, non-elastic material, with an additional Velcro wrapping system allowing adjustment of compression for exercise and activity.

The principle of the decongestive exercise program is to enhance lymph drainage from the edematous area through the use of the skeletal-muscle contraction to promote venous and lymphatic return, and the program involves active exercises without external

resistance.[7,8] Recent evidence supports the safety of other types of general exercise such as aerobic and resistance exercise for BCRL. Progressive resistance exercise programs, using free weights and weight machines[8], have been found to improve symptoms and reduce the frequency of relapses (i.e. flares) in lymphedema.[9-11] High adherence to use of a compression garment and decongestive exercises during the maintenance phase is positively associated with long-term lymphedema control.[12, 13]

To date, no studies have been performed combining all potential therapeutic approaches to address lymphedema: i) use of the decongestive exercise sequence to enhance venous and lymphatic return, ii) progressive resistance exercise training to improve symptoms and prevent relapses in arm volume, and iii) use of daytime compression both during exercise and during the day to improve long-term control of the lymphedema.[11, 14-17] Figure 1 and (Supplementary Material: Table S1) illustrate the theoretical concept and provide the rationale for a combined program titled Decongestive Progressive Resistance Exercise (DRE) respectively.

We recently completed the vanguard phase of the randomized control trial (RCT) that aimed to examine the feasibility the DRE program. Twenty participants were enrolled, and 19 completed the study (95%). Feasibility data also demonstrate high exercise attendance (94%) and excellent adherence to the prescribed protocol of DRE program (97%). All participants reported 100% adherence to wearing their assigned compression garment during exercise (either using a daytime sleeve or adjustable compression wrap), and a daily average of 12 hours of wear-time. There were no minor or severe adverse events during the program. The proposed RCT will follow the same study methods and intervention as per the vanguard phase, with inclusion of patient data from this phase (Supplementary material: Appendix 1).

We hypothesize that combining DRE with either a compression garment or adjustable compression wrap will result in a larger lymphedema relative volume reduction when compared to standard care. We will explore the mean difference between the two experimental groups performing DRE to see if there is a difference between use of a daytime sleeve or adjustable compression wrap; however, we hypothesize that the difference between groups will fall inside the equivalence interval of +/- 10% in lymphedema relative volume change. We will also explore the benefits of using Magnetic

Resonance Imaging (MRI) in informing the effect of the intervention on arm tissue composition.

Objectives

The primary objectives are the following:

1. To examine the efficacy of DRE with use of adjustable compression wrap compared to standard care on percentage change in arm lymphedema volume.
2. To examine the efficacy of DRE with use of a daytime compression sleeve compared to standard care on the percentage change in arm lymphedema volume.

Secondary objectives include examining the effect on arm tissue composition, shoulder range of motion (ROM), upper and lower muscle strength, physical activity, body image, QOL, and adherence.

METHODS AND ANALYSIS

Study Design

The DREAM study is a multi-center randomized controlled fast-track trial. Participants will be recruited from the Cross Cancer Institute (CCI) in Edmonton, and Tom Baker Cancer Center (TBCC) in Calgary, Canada. The study will compare the results of three groups: A) Standard care (control), B) DRE + daytime compression garment, and C) DRE + adjustable compression wrap. The study will be conducted over 24 weeks comprising a 12-week supervised intervention and a 12-week follow-up period. Outcome measures will be assessed at baseline, 12 and 24 weeks. See Figure 2. The primary time point for the trial is 12 weeks. From week 13 to 24, the standard care group participants will be fast-tracked to Group C (DRE + adjustable compression wrap experimental intervention). The randomized fast-track trial design (with a delayed assignment of the standard care group to the experimental intervention) was chosen given the strong preference identified by our patient representatives for assignment to the DRE + adjustable compression group. Moreover, this design, used in the vanguard phase, will serve to optimize recruitment as well as retention of participants in the standard care group."

Setting and Participants

Between November 2021 and December 2022, potential participants will be identified through outpatient physical therapy clinics at the Cross Cancer Institute and Holy Cross Centre, as well as local and provincial lymphedema patient support groups and organizations. Patients will be provided with an information pamphlet, and if interested in taking part they will be required to initiate contact with the investigators.

Eligibility Criteria

A survivor will be included based on the following criteria:

- Is a female with a history of breast cancer;
- Has undergone surgery, including sentinel lymph node biopsy or axillary lymph node dissection;
- Has unilateral mild to moderate BCRL of at least 200 ml or 10% inter-limb volume difference (as per the criteria of the International Society of Lymphology),[18] or regional lymphedema: defined as a minimal volume difference of 100 ml or 5% in a segment of the arm (e.g. hand and forearm region, elbow and upper arm);[18-20]
- Has chronic lymphedema, defined as lymphedema that has been present for at least three months;[21]
- Has completed intensive reduction treatment, and is in the lymphedema maintenance phase of conservative treatment;
- Uses a well-fitted daytime compression garment (not older than one month) and is agreeable to wear the garment for a minimum of 12 hours per day (providing a minimum of 30 mm Hg of pressure);
- Is agreeable to discontinuing other lymphedema treatments beyond standard care, including manual lymphatic drainage and intermittent pneumatic compression during the 12-week RCT period of the study;
- Is able to read and understand English.

A survivor will be excluded if she:

- Is undergoing or scheduled to receive chemotherapy, radiotherapy or biological therapy;
- Presents with limb infection/ cellulitis, deep vein thrombosis, or has active metastatic disease;
- Has any neurological or cognitive deficit, is pregnant, uses a pacemaker, or has any other uncontrolled health condition that may interfere with assessment and/or the exercise training intervention;
- Has any contraindications related to use of compression on the limb, such as arterial insufficiency or congestive heart failure.

Randomization Procedure

Participants will be stratified by centre (Edmonton versus Calgary) and lymphedema severity (mild: < 20% versus moderate to severe: ≥ 20% inter-limb difference in limb), and then randomized using a computer-generated randomization module within the Trial's REDCap database. Randomization will occur following baseline testing, and participants will be assigned on a 1:1:1 basis to one of the three groups.

Blinding

A single independent assessor, who will be blinded to the group assignment, will carry out all objective measurements. Independent assessor training will be conducted and intra-rater reliability will be established for the primary outcome measure prior to trial continuation.

Intervention

As per standard of care, participants in all groups will be required to wear their daytime compression garments (during non-exercise times) for at least 12 hours per day, seven days a week.

Group A: Standard care group

Participants in this group will receive standard care for lymphedema maintenance that involves a home exercise program involving the lymphedema decongestive exercise regimen. Participants will be instructed to perform the exercise sequence once daily for 10-15 minutes. From weeks 13 to 24 of the study, participants in this group will be fast-track to the experimental protocol as per Group C below.

Group B: DRE and daytime compression garment group

Participants will take part in the supervised DRE program either in-person or virtually twice a week for 12 weeks and will be required to wear their daytime compression garment during each DRE session. Sessions will be offered in a group-based format with a ratio of one therapist to two-three participants. Exercise sessions will start with 5 minutes of warm-up exercises.

The intervention program involves upper and lower limb exercise and will commence with deep breathing and follow the principles of the decongestive lymphatic sequence from proximal to distal, and then will be performed in reverse order. A two-minute rest period will be observed between exercises. The resistance exercise program will use weight machines, free weights and resistance bands (RB). Participants will be familiarized with the exercises, weight machines and resistance bands prior to the start of the training. We will determine the starting weight and the progression using a standardized protocol (Supplementary material: Table S2). The exercise program will be individualized to the respective participant and the resistance intensity will be tailored based on their baseline assessment and response to exercise in terms of lymphedema symptoms.

The exercise intensity will be monitored and adjusted, as needed, based on the participant's reported rate of perceived exertion (RPE) ranging on a scale from 1 (very light) to 10 (maximal exertion/ hard). Responses to exercise sessions will also be monitored for each lymphedema symptom (Supplementary material: Table S3). Participants will be asked prior to exercise and after each session to rate their perceived exertion and to report if they experienced any increase in fatigue, or negative changes in lymphedema symptoms. If the symptoms are stable, and the participant's exercise perceived exertion falls within the recommended mild to moderate intensity range (2-5 on RPE), the exercise program will be progressed. This will be done by first increasing the number of repetitions (10, 12, 15 reps) and then the resistance weight.

Group C: DRE and adjustable compression garment group

Participants in this group will follow the same supervised DRE protocol as per Group B; however, they will be assigned to wear an adjustable compression wrap when performing the DRE program.

After the 12- week intervention, women in Group B and C will continue the same program (maintenance exercise period) twice weekly for an additional 12 weeks with the option of continuing in-person or virtually.

Primary Outcome

Lymphedema Arm Volume. The primary outcome will be the percentage change in arm lymphedema volume (Supplementary material: Table S4: calculation formula). Lymphedema will be objectively measured using the optoelectronic limb volumeter (perometer). The perometer is a valid, reliable and sensitive method for quantifying limb volume.[22-24]

Secondary outcomes

Extracellular Fluid Volume. Bioimpedance analysis (BIA) is specially designed to estimate extracellular fluid volume in the limb. BIA measures the affected and unaffected limb's impedance ratio, and the resulting calculated index provides an estimate of extracellular fluid volume.[25] The BIA is a sensitive, valid, and reliable measurement method.[26-29]

Muscle Strength. Muscle strength will be assessed with the one-repetition maximum (1-RM) method for bench press, leg press, and seated row. The 1-RM is the maximal weight that can be lifted once using proper form, a smooth motion and without pain or other symptoms.[30]

Grip Strength. The Jamar hydraulic hand dynamometer, a valid and reliable tool, will be used to measure grip strength [31, 32] Participants will be tested using standardized procedures. Participants will be standing with their arm slightly abducted and elbow extended, and will be asked to squeeze the handle of the dynamometer as hard as possible for five seconds. Two measurements will be taken for each hand and the highest value will be recorded.

Shoulder Range of Motion (ROM). Shoulder active and passive ROM will be measured following standardized procedures[33,34] using a traditional goniometer. Each arm will be measured separately for the following movements: flexion, abduction, internal, external rotation, and horizontal abduction. Active ROM will be assessed with the participant in a sitting position with their back in an upright position to prevent compensation by trunk

muscles. Passive shoulder ROM and horizontal abduction will be performed in the supine position.

Health-related Quality of Life. The Lymphedema Functioning, Disability, and Health (Lymph-ICF) is a lymphedema-specific outcome questionnaire that will be used to assess HRQOL. It is a valid tool with high reliability (ICC > 0.90) in women with BCRL.[35] The Rand Short Form-36 Version 2 (SF-36) will be used to assess general HRQOL. It is a validated self-report measure with excellent test-retest reliability.[36]

Body Image. The Body Image and Relationships Scale (BIRS) is a self-report measure of body image and relationships.[11, 37] The BIRS has been shown to have a satisfactory test-retest reliability and internal consistency in addition to convergent and divergent validity.[37]

Physical Activity. The Godin leisure-time exercise questionnaire (GLTEQ) will be used to assess the physical activity level. It is a valid, reliable, and sensitive tool among different populations, including breast cancer survivors.[38, 39]

Body Mass Index (BMI). Body height and weight will be measured, and BMI will be calculated.

Adherence. Participants will be asked to record their adherence to their assigned exercise and compression intervention program using a daily diary. The adherence diary will collect details on exercise sessions performed each day, including sets, repetitions, and resistance weight, as well as use of the assigned compression sleeve (i.e. use of the garment during exercises and number of hours per day and days per week the compression sleeve is worn). Adherence is considered to be high if participants report 80% or greater adherence to the exercise program and the compression use.

Adverse Events. We will monitor adverse events as well as any additional treatments required to manage any exacerbations of lymphedema.

Exploratory Outcomes

The Difference in Mean Outcomes Between DRE Groups. We will explore differences between groups B and C to inform future research.

Arm Tissue Composition Volume. Magnetic resonance imaging (MRI) will be used to determine differences in arm muscle mass, fat and extracellular fluid between limbs over time. An approach called chemical shift encoded (CSE) MRI will be used to separate the

signal sources from water and fat. Additionally, the water environments will be further characterized using a method called T_1-mapping. The T_1 time (longitudinal relaxation time constant) is an MRI property of the water that reflects the local environment, where water within healthy skeletal muscle has T_1 values of ~1400ms. Increased T_1 values reflect edema and fibrosis within the muscle tissue with values reaching ~3000ms for free water pools, such as those contained within subcutaneous fat. A combined CSE and T_1-mapping approach will be used to quantify volumes of muscle and fat and to characterize the water environment in all tissues.[40] Multiple axial slices (4 mm slice thickness, 0.5 mm in-plane resolution) will provide full three-dimensional coverage of the arm. See Figure 3. MRI is a reliable method that has been used in lymphedema for diagnosis and treatment evaluation. [14, 41, 42]

COVID-19 accommodations: in the event of limitations related to, or suspension of in-person testing, objective testing will be conducted virtually and will include the following minimal dataset:

- Self-Circumference Measurements[43] will replace arm volume measurements

STATISTICAL CONSIDERATIONS

Sample Size

The sample size for the study was based on the findings of the pilot vanguard trial phase. Using the point estimates and measures of variability derived for LRV of the 12-week post intervention, we estimated a mean reduction of 18% in lymphedema (SD: 16%) in favour of the combined data from the intervention groups. As a result of the interim analyses, an alpha adjustment was required to preserve the overall Type I error rate. Thus, the value for the level of significance for this study was revised from 0.05 to 0.01. The estimated sample size of 51 participants or 17 per group achieves about 86% power (significance level: p = 0.01). Considering a 5% loss to follow-up/ withdrawal, and two levels of stratification, an additional 9 participants will be added for a total sample size of 60 including the 20 participants from the pilot study. Thus, 40 more participants will be recruited to the trial

Statistical Analysis Plan

Baseline medical and demographic characteristics, arm dominance relative to the lymphedematous arm, and adverse events of the three groups will be compared using one-way ANOVA for continuous data and Pearson's Chi-square tests for categorical data. The primary analysis will compare changes between the groups from baseline to week 12 with regard to percent change in arm lymphedema volume, arm tissue composition, arm function, physical activity, QoL, body image, and adherence-related outcomes. The comparisons over time (baseline, 12-week and 24-week follow-ups) will be conducted using repeated measures ANOVA and between groups comparisons will be conducted using one-way ANOVA on change scores. Generalized linear models (GLM) will be used to evaluate the treatment effect in subgroups defined by the strata adjusting for centre and lymphedema severity (mild or moderate-severe).

Analyses of primary outcomes will be performed at the end of the RCT portion of the trial using an intention to treat analysis. Within-group analyses will also be conducted for primary and secondary outcomes from weeks 13 to 24 following completion of all follow-up measures. If missing data is greater than 30%, multiple imputation techniques will be used. Appropriate sensitivity analysis will be performed to determine the type of

missing data, and statistical methods accounting for the type of missing data will be used. All statistical analysis will be conducted using SAS (SAS Institute Inc., Cary, NC) version 9.3 software.

Data management and quality control

The Clinical Trials Unit of the Cross Cancer Institute will be responsible for trial oversight. Storing and processing of all patient data will occur in compliance with institutional guidelines. A REDCap database will be used for data collection and monitoring. For quality control, the objective data of participants will be entered by the independent assessor and will be checked by a second independent research assistant. Any hard copy data involving the trial participants will be stored in a secure location in a locked cabinet at the respective centre that can only be accessed by study personnel. Data will be anonymized and stored according to participant number. A linking log is stored separately from the data. On trial completion, data will be accessible through the University of Alberta Libraries Dataserve Network.

Patient and public involvement

The idea for this study was born from patients' input. Women with BCRL often report a worsening of the swelling with exercise, and a need for better support for exercise. A patient representative actively participated in the design of the study (AM). Findings will be disseminated to study participants and other survivors of breast cancer through workshops and presentations. Study findings will be dissemination through stakeholder groups including the Canadian Lymphedema Framework (CLF), Canadian Physiotherapy Association, and the International Lymphedema Framework (ILF) to the broader lymphedema stakeholder community.

ETHICS and DISSEMINATION

Ethical and safety Consideration:

Ethical approval was obtained from the Health Research Ethics Board of Alberta: Cancer Committee. All participants will be required to provide written informed consent and will be free to withdraw from the trial at any time, for any reason.

Dissemination Plan:

This trial will answer key questions on the effect of a combined exercise and compression intervention on arm lymphedema volume and tissue composition. The study results will be disseminated through scientific peer-reviewed publications, and presented at national and international conferences, and other media portals. The program protocol will be presented to healthcare professionals and shared with patient groups through clinical workshops and webinars.

Figure Legends:

Figure 1: Schematic of the Theoretical Concept - Combined Decongestive Progressive Resistance Exercise and Compression Therapy

Figure 2: Study Schema
Figure 3: Magnetic Resonance Imaging - one sample slice

Authors' contributions: MMA, AM, and MLM created the concept of the study. MMA, KLC, RBT, JRM, AM and MLM developed the study concept, the exercise program and protocol. SG assisted in the statistical analysis plan and sample size calculation. All authors will oversee the implementation of the protocol and contribute to the acquisition, analysis and interpretation of data. All authors were involved in drafting and revising the protocol manuscript. All authors read and approved the final manuscript.

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This funding body had no role in the design of this study and will not have any role in its execution, analyses, interpretation of the data, or decision to submit results.

Competing interest statement. None declared.

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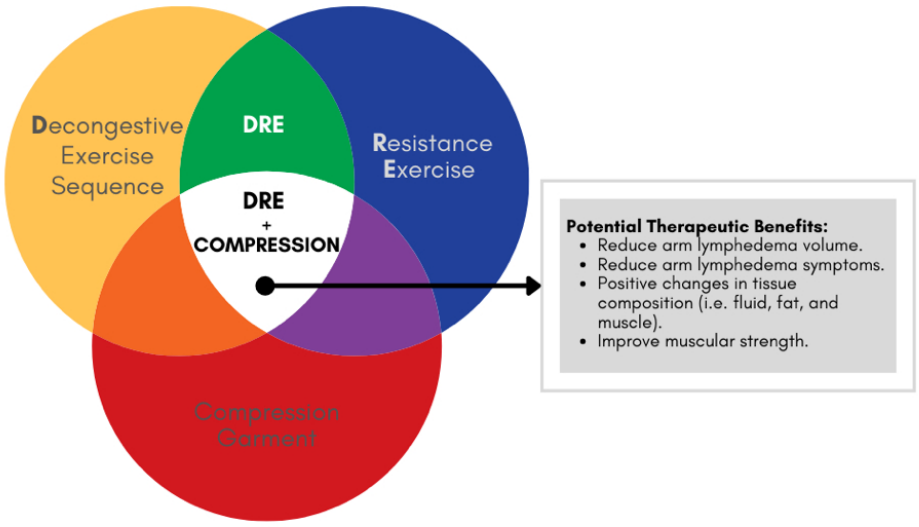


Figure 1: Schematic of DRE and Compression Theoretical Concept

164x123mm (150 x 150 DPI)

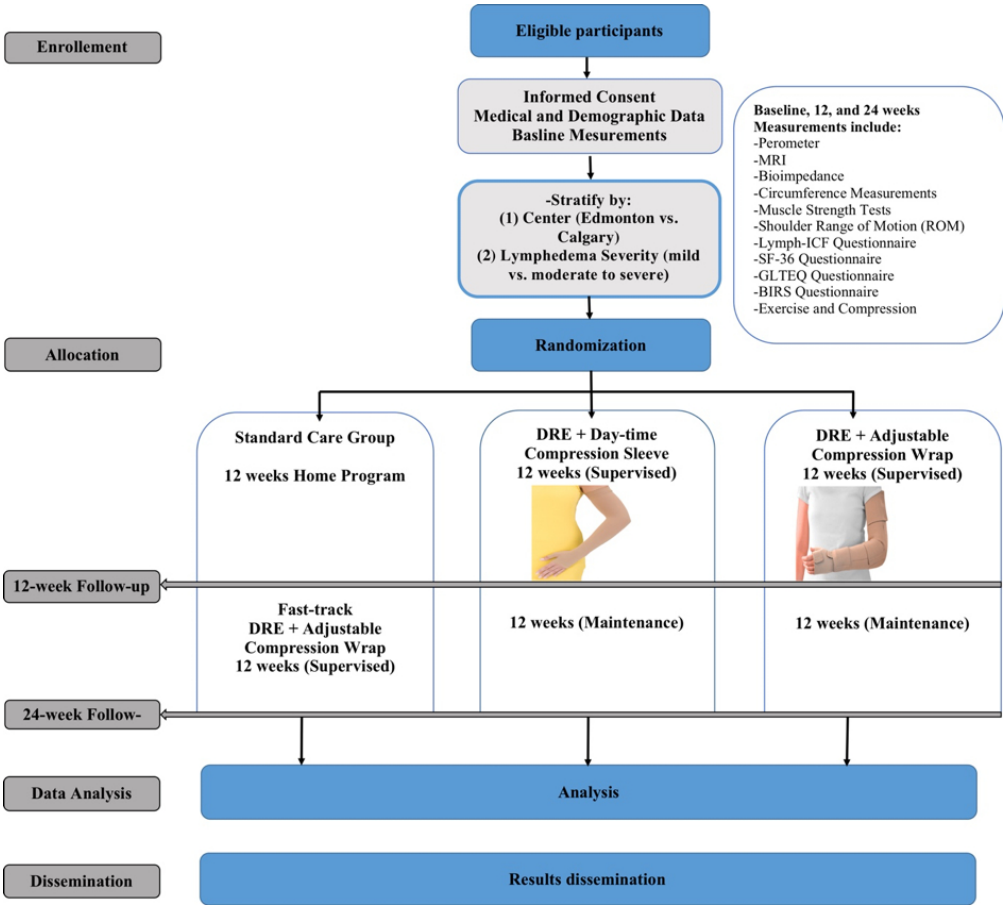


Figure 2: Study Schema

159x143mm (150 x 150 DPI)

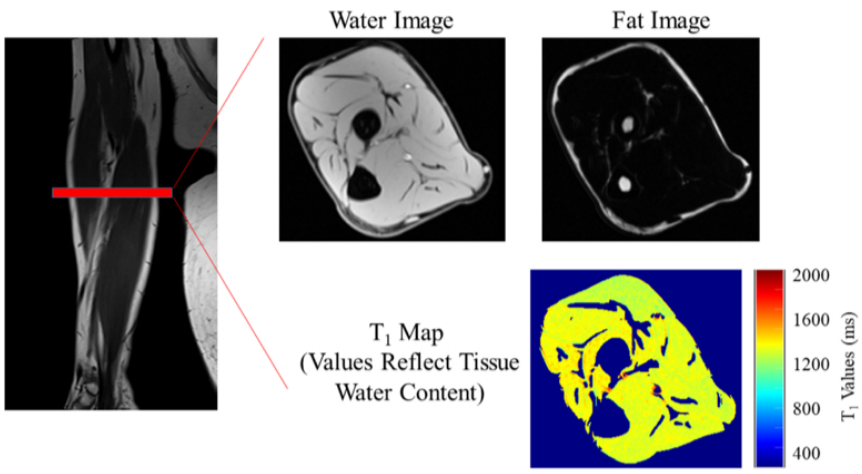


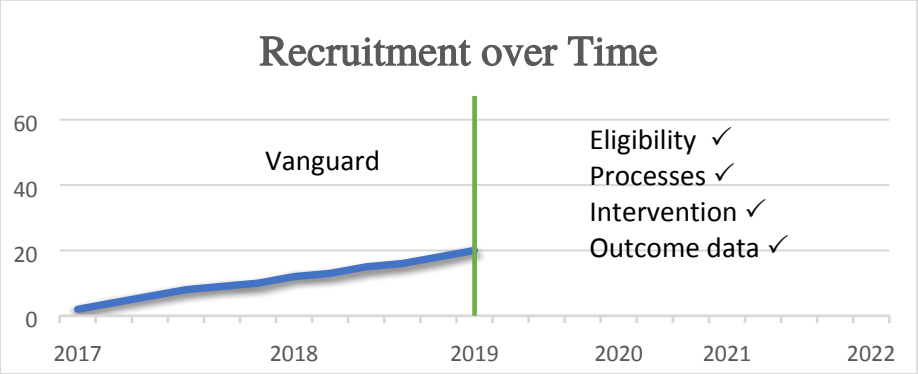
Figure 3: MRI one sample slice

152x78mm (150 x 150 DPI)

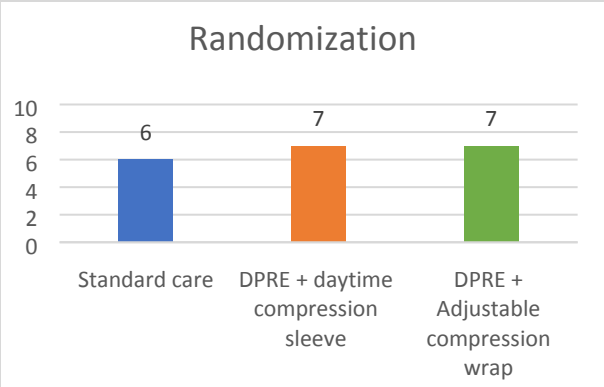
Supplementary Materials

Appendix 1: Vanguard Phase: Summary of Progress

A. Recruitment



B. Randomization



Interim analysis:
Standard care vs. Intervention Groups (combined)
Difference: 18% in favour of intervention groups
Standard deviation: 16

C. Progression Criteria for full RCT

Criterion	Metric	Outcome	Decision
Recruitment	Recruitment rate	37% (1 per month)	Amend: minor
Protocol Adherence	Completion of procedures *(the percentage of participants who are completing study including the exercise intervention, and all follow-up assessment)*	100%: no issues identified	Proceed
	Intervention delivery	100% - no modifications	
	Exercise adherence *(the percentage of sessions, sets, and repetitions completed by participants)*	Intervention: 91%; Standard care: 84%	
	Compression adherence *(adherence to compression use during exercise and nonexercise day-time use)*	100% all groups	
Outcome Data	Adverse events	No SAE	Proceed
	Study completion	96% (19/20 completed)	
	Missing data	Individual items on outcomes: range: 96-100% complete; All outcomes completed	

Supplementary Materials

Table S1: Exercise principles

Components	***Principles***	***Benefits***
Decongestive exercise sequence[1-3]	*Follow a sequence from proximal to distal*	- *Enhance lymph drainage from the edematous area through the use of the skeletal-muscle contraction to promote venous and lymphatic return w*
Resistance exercise[4, 5]	*Overload, progression, and specificity*	- *Improve lymphedema symptoms* - *Improve muscle strength, and quality of life*
Compression[6-8]	*Enhancement of muscle pump*	*Improve long-term control of the lymphedema*

Table S2: Exercise protocol

	Weight machines and free weights	***Resistance Band (RB)****
Exercise	• *Upper limb:* *Shoulder shrugs, chest press, seated row, lateral raise, biceps curls, triceps pulldown, wrist curl, reverse wrist curl, handgrip* • *Lower limb:* *Leg press, leg curl*	
Initial/starting weight	• *Upper limb:* *1RM: 30-35%* *RPE: 2-3 (mild)* • *Lower limb:* *1RM: 60%* *RPE: 4-5* *- The intensity will be adjusted by adding/removing weight.*	• *Upper limb:* *RPE: 2-3 (mild)* • *Lower limb:* *RPE: 4-5* *-The intensity will be adjusted by tension first and then by RB strength (color).*
Progression**		
• ***Intensity***	• Upper limb: *-Weight will be increased by 5% of the 1 RM (weekly)* *-RPE: 3-5 (mild to moderate)* • Lower limb*:* *-Weight will be increased by 5-10% of the 1 RM (weekly)* *-RPE: 5-6 (moderate)*	• Upper limb: *-RB intensity will be increased by band tension, or band strength (color, or combining two RB.* *-RPE: 3-5 (mild to moderate)* • Lower limb*:* *-RB intensity will be increased by band tension first and then by RB strength (color, or combining two RB.* *-RPE: 5-6 (moderate)*
• ***Volume***	*2 X 10, 2X12, 2X15* *(then increase resistance and drop number of repetitions)*	
• ***Rest intervals***	*2 min*	
• ***Velocity***	*Slow to moderate with breathing (two seconds concentric, four seconds eccentric)*	
• ***Frequency***	*2Xwk*	

** Adopted training protocols from (Colado and Triplett, 2008)[9]. Each participant will be provided with 1.5-2 meter of 3- levels RB. Each band will be marked with reference points (10cm) to control the intensity. The band reference values provided by (Uchida et. al 2016)[10] will be used to estimate the starting RB color.*

***The exercise will be progressed in the second week, first by increasing the number of repetitions, and then by increasing the intensity. The RPE will be used to quantify the exercise intensity and to inform the progression of exercise resistance. The exercises will be tailored based on the lymphedema symptoms for each participant.*

Supplementary Materials

Table S3: Exercise monitoring

Symptoms	***Response***
Exacerbation of lymphedema symptoms (tension, tightness, heaviness, pain, or increased swelling)	• *Participant will be monitored and examined by lymphedema therapist* • *Exercise intensity will be reduced by decreasing the number of repetitions and/or resistance*
Worsening of fatigue	• *Exercise intensity will be reduced by decreasing the number of repetitions*

Table 4: The percentage change in arm lymphedema calculation formula

Lymphedema absolute volume (LAV)	*LAV=affected volume – unaffected volume (mls)*
Absolute change in excess volume (mls)	*LAV (baseline) – LAV (12-weeks)*
Lymphedema relative volume (LRV) change	*(1) LAV baseline – LAV 12-weeks* *(2) LAV at baseline* $\frac{(1)}{(2)} \times 100$

References:

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____2_____
	2b	All items from the World Health Organization Trial Registration Data Set	supplementary document_
Protocol version	3	Date and version identifier	_____2_____
Funding	4	Sources and types of financial, material, and other support	_____15_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____14,15_____
	5b	Name and contact information for the trial sponsor	_____15_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____15_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____15_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5,6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6,7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8,9,10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10,11,12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6,7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12,13

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8,9,10,11,12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13,14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12,13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12,13

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13,14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Clinical Trials Unit oversight
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13,14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**Supplementary material**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Decongestive Progressive Resistance Exercise with an Adjustable Compression Wrap for Breast Cancer Related Lymphedema [DREAM]: Protocol for a Randomized Controlled Trial

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Oncology
Keywords:	Rehabilitation medicine < INTERNAL MEDICINE, Breast tumours < ONCOLOGY, COMPLEMENTARY MEDICINE, Adult oncology < ONCOLOGY

Decongestive Progressive Resistance Exercise with an Adjustable Compression Wrap for Breast Cancer Related Lymphedema [DREAM]: Protocol for a Randomized Controlled Trial

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ABSTRACT

Introduction: Breast cancer-related lymphedema (BCRL) is a chronic swelling in the arm on the side of the breast cancer surgery, affecting one in five women. Recent studies in BCRL have demonstrated that resistance exercise can improve symptoms and quality of life without worsening lymphedema. No studies have explored whether combining the principles of progressive resistance exercise training with therapeutic strategies of compression therapy and the decongestive lymphatic exercise sequence are beneficial in reducing arm lymphedema volume. The aim of this 3-arm, provincial randomized controlled trial is to determine the efficacy of a 12-week decongestive resistance exercise (DRE) program in combination with the one of two types of compression garments compared to standard care.

Methods and analysis: Sixty women with BCRL will be recruited and randomly assigned to one of the following three groups: (i) Standard care, (ii) DRE with use of a daytime compression garment during exercise, and (iii) DRE with use of an adjustable compression wrap during exercise. The primary outcome is the percentage reduction in arm lymphedema volume. Secondary outcomes include bioimpedance analysis, muscular strength, shoulder range of motion, physical activity level, and health-related quality of life. Exploratory outcomes include evaluating changes in arm tissue composition using Magnetic Resonance Imaging and examining outcomes between the two DRE experimental groups. The primary analysis will compare changes between the groups from baseline to week 12 reflecting the end of the randomized control trial period.

Ethics and dissemination: The trial has received ethics approval from the Health Research Ethics Board of Alberta: Cancer Committee. The study results will be disseminated through scientific peer-reviewed publications, and presented at national and international conferences, and other media portals. The program protocol will be shared with healthcare professionals and patient groups through clinical workshops and webinars.

Trial registration number: NCT05022823
Protocol version: November 12, 2021
Issue Date: 26 April 2021

Strengths and limitations of this study

- Evaluation of the benefit of a combined program involving a specialized decongestive resistance exercise program and use of compression on arm lymphedema volume.
- Prospective collection of data on compression garment type and wear-time during exercise and throughout the day.
- Exploratory analyses on the benefit of the program on arm tissue composition through Magnetic Resonance Imaging.
- Use of a fast-track design was chosen to enhance the recruitment and retention; however, this design limits comparison of the originally assigned groups at 24-week follow-up.
- Data collection may be impacted by restrictions related to COVID-19.

INTRODUCTION

Background and rationale

Breast cancer-related lymphedema (BCRL), swelling in the arm, breast and chest wall on the side of the breast cancer, results from damage to the lymphatic system due to cancer or cancer treatment.[1] It occurs in an estimated 21% of cases of breast cancer.[2] To date, it is an incurable, progressive, distressing, and debilitating condition requiring lifelong management.[3] Impairments associated with lymphedema include pain, fatigue, and heaviness and tightness in the extremity; and lymphedema may negatively impact shoulder range of motion, strength and function of the upper extremity.[1, 3] Not surprisingly, survivors with BCRL have been found to have a poorer health-related quality of life compared with those without the condition.[4]

There is currently no cure for lymphedema; therefore, management of the condition involves conservative interventions aiming to reduce the swelling, prevent cellulitis and optimize the survivor's function and quality of life (QOL). The initial phase of treatment is a 2-4-week course of intensive decongestive therapy, comprising skin care, bandaging using multilayered bandaging, decongestive exercises, and self-care, with or without manual lymphatic drainage. The aim of this phase is to reduce the swelling.[5] The second phase of treatment, called the maintenance phase, involves daily use of a compression garment[6, 7] and a home program involving a specialized decongestive exercise program.[5-7]

Using a compression garment is essential to maintain the volume reduction during the maintenance phase.[5] There are two main types of compression garments; standard daytime compression garments and adjustable compression wraps. The standard daytime compression garments are available as ready-to-wear (off-shelf) or can be custom-made. Survivors with BCRL are told to wear their daytime compression garments during waking hours each day for 10-12 hours. Adjustable Compression Wraps, available on the market, are made of soft, non-elastic material, with an additional Velcro wrapping system allowing adjustment of compression for exercise and activity.

The principle of the decongestive exercise program is to enhance lymph drainage from the edematous area through the use of the skeletal-muscle contraction to promote venous and lymphatic return, and the program involves active exercises without external

resistance.[7,8] Recent evidence supports the safety of other types of general exercise such as aerobic and resistance exercise for BCRL. Progressive resistance exercise programs twice a week at a mild to moderate intensity, using free weights and weight machines[8], have been found to improve symptoms and reduce the frequency of relapses (i.e. flares) in lymphedema.[9-11] High adherence to use of a compression garment and decongestive exercises during the maintenance phase is positively associated with long-term lymphedema control.[12, 13]

To date, no studies have been performed combining all potential therapeutic approaches to address lymphedema: i) use of the decongestive exercise sequence to enhance venous and lymphatic return, ii) progressive resistance exercise training to improve symptoms and prevent relapses in arm volume, and iii) use of daytime compression both during exercise and during the day to improve long-term control of the lymphedema.[11, 14-17] Figure 1 and (Supplementary Material: Table S1) illustrate the theoretical concept and provide the rationale for a combined program titled Decongestive Resistance Exercise (DRE) respectively.

We recently completed the vanguard phase of the randomized control trial (RCT) that aimed to examine the feasibility the DRE program. Twenty participants were enrolled, and 19 completed the study (95%). Feasibility data also demonstrate high exercise attendance (94%) and excellent adherence to the prescribed protocol of DRE program (97%). All participants reported 100% adherence to wearing their assigned compression garment during exercise (either using a daytime sleeve or adjustable compression wrap), and a daily average of 12 hours of wear-time. There were no minor or severe adverse events during the program. The proposed RCT will follow the same study methods and intervention as per the vanguard phase, with inclusion of patient data from this phase (Supplementary material: Appendix 1).

We hypothesize that combining DRE with either a compression garment or adjustable compression wrap will result in a larger lymphedema relative volume reduction when compared to standard care. We will explore the mean difference between the two experimental groups performing DRE to see if there is a difference between use of a daytime sleeve or adjustable compression wrap; however, we hypothesize that the difference between groups will fall inside the equivalence interval of +/- 10% in

lymphedema relative volume change. We will also explore the benefits of using Magnetic Resonance Imaging (MRI) in informing the effect of the intervention on arm tissue composition.

Objectives

The primary objectives are the following:

1. To examine the efficacy of DRE with use of adjustable compression wrap compared to standard care on percentage change in arm lymphedema volume.
2. To examine the efficacy of DRE with use of a daytime compression sleeve compared to standard care on the percentage change in arm lymphedema volume.

Secondary objectives include examining the effect on arm tissue composition, shoulder range of motion (ROM), upper and lower muscle strength, physical activity, body image, QOL, and adherence.

METHODS AND ANALYSIS

Study Design

The DREAM study is a randomized controlled fast-track trial. Participants will be recruited from the Cross Cancer Institute (CCI) in Edmonton, and the Holy Cross Centre-Tom Baker Cancer Center in Calgary, Canada. The study will compare the results of three groups: A) Standard care (control), B) DRE + daytime compression garment, and C) DRE + adjustable compression wrap. The study will be conducted over 24 weeks comprising a 12-week supervised intervention and a 12-week follow-up period. Outcome measures will be assessed at baseline, 12 and 24 weeks. See Figure 2. The primary time point for the trial is 12-week. From week 13 to 24, the standard care group participants will be fast-tracked to Group C (DRE + adjustable compression wrap experimental intervention). The randomized fast-track trial design (with a delayed assignment of the standard care group to the experimental intervention) was chosen given the strong preference identified by our patient representatives for assignment to the DRE + adjustable compression group. Moreover, this design, used in the vanguard phase, will serve to optimize recruitment as well as retention of participants in the standard care group."

Setting and Participants

Between January 2022 and December 2023, potential participants will be identified through outpatient physical therapy clinics at the CCI and Holy Cross Centre, as well as local and provincial lymphedema patient support groups and organizations. Patients will be provided with an information pamphlet, and if interested in taking part they will be required to initiate contact with the investigators.

Eligibility Criteria

A survivor will be included based on the following criteria:

- Is a female with a history of breast cancer;
- Has undergone surgery, including sentinel lymph node biopsy or axillary lymph node dissection;
- Has unilateral BCRL of at least 200 ml or 10% inter-limb volume difference (as per the criteria of the International Society of Lymphology),[18] or regional lymphedema: defined as a minimal volume difference of 100 ml or 5% in a segment of the arm (e.g. hand and forearm region, elbow and upper arm);[18-20]
- Has chronic lymphedema, defined as lymphedema that has been present for at least three months;[21]
- Has completed intensive reduction treatment, and is in the lymphedema maintenance phase of conservative treatment;
- Uses a well-fitted daytime compression garment (not older than one month) and is agreeable to wear the garment for a minimum of 12 hours per day (providing a minimum of 30 mm Hg of pressure);
- Is agreeable to discontinuing other lymphedema treatments beyond standard care, including manual lymphatic drainage and intermittent pneumatic compression during the 12-week RCT period of the study;
- Is able to read and understand English.

A survivor will be excluded if she:

- Is undergoing or scheduled to receive chemotherapy, radiotherapy or biological therapy;
- Presents with limb infection/ cellulitis, deep vein thrombosis, or has active metastatic disease;
- Has any neurological or cognitive deficit, is pregnant, uses a pacemaker, or has any other uncontrolled health condition that may interfere with assessment and/or the exercise training intervention;
- Has any contraindications related to use of compression on the limb, such as arterial insufficiency or congestive heart failure.

Randomization Procedure

Participants will be stratified by lymphedema severity (mild: < 20% versus moderate to severe: ≥ 20% inter-limb difference in limb), and then randomized using a computer-generated randomization module within the Trial's REDCap database. Randomization will occur following baseline testing, and participants will be assigned on a 1:1:1 basis to one of the three groups.

Blinding

A single independent assessor, who will be blinded to the group assignment, will carry out all objective measurements. Independent assessor training will be conducted and intra-rater reliability will be established for the primary outcome measure prior to trial continuation.

Intervention

As per standard of care, participants in all groups will be required to wear their daytime compression garments (during non-exercise times) for at least 12 hours per day, seven days a week.

Group A: Standard care group

Participants in this group will receive standard care for lymphedema maintenance that involves a home exercise program involving the lymphedema decongestive exercise regimen. Participants will be instructed to perform the exercise sequence once daily for 10-15 minutes. From weeks 13 to 24 of the study, participants in this group will be fast-track to the experimental protocol as per Group C below.

Group B: DRE and daytime compression garment group

Participants will take part in the supervised DRE program either in-person or virtually twice a week for 12 weeks and will be required to wear their daytime compression garment during each DRE session. Sessions will be offered in a group-based format with a ratio of one therapist to two-three participants. Exercise sessions will start with 5 minutes of warm-up exercises.

The intervention program involves upper and lower limb exercise and will commence with deep breathing and follow the principles of the decongestive lymphatic sequence from proximal to distal, and then will be performed in reverse order. A two-minute rest period will be observed between exercises. The resistance exercise program will use weight machines, free weights and resistance bands (RB). Participants will be familiarized with the exercises, weight machines and resistance bands prior to the start of the training. We will determine the starting weight and the progression using a standardized protocol (Supplementary material: Table S2). The exercise program will be individualized to the respective participant and the resistance intensity will be tailored based on their baseline assessment and response to exercise in terms of lymphedema symptoms.

The exercise intensity will be monitored and adjusted, as needed, based on the participant's reported rate of perceived exertion (RPE) ranging on a scale from 1 (very light) to 10 (maximal exertion/ hard). Responses to exercise sessions will also be monitored for each lymphedema symptom (Supplementary material: Table S3). Participants will be asked prior to exercise and after each session to rate their perceived exertion and to report if they experienced any increase in fatigue, or negative changes in lymphedema symptoms. If the symptoms are stable, and the participant's exercise perceived exertion falls within the recommended mild to moderate intensity range (2-5 on RPE), the exercise program will be progressed. This will be done by first increasing the number of repetitions (10, 12, 15 reps) and then the resistance weight.

Group C: DRE and adjustable compression garment group

Participants in this group will follow the same supervised DRE protocol as per Group B; however, they will be assigned to wear an adjustable compression wrap when performing the DRE program.

After the 12- week intervention, women in Group B and C will continue the same program (maintenance exercise period) twice weekly for an additional 12 weeks with the option of continuing in-person or virtually.

Primary Outcome

Lymphedema Arm Volume. The primary outcome will be the percentage change in arm lymphedema relative volume (LRV) (Supplementary material: Table S4: calculation formula). Lymphedema will be objectively measured using the optoelectronic limb volumeter (perometer). The perometer is a valid, reliable and sensitive method for quantifying limb volume.[22-24]

Secondary outcomes

Extracellular Fluid Status. Bioimpedance analysis (BIA) is specially designed to estimate extracellular fluid status within the arm. BIA measures the affected and unaffected limb's impedance ratio, and the resulting calculated index provides an estimate of extracellular fluid volume.[25] The BIA is a sensitive, valid, and reliable measurement method.[26-29]

Muscle Strength. Muscle strength will be assessed with the one-repetition maximum (1-RM) method for bench press, leg press, and seated row. The 1-RM is the maximal weight that can be lifted once using proper form, a smooth motion and without pain or other symptoms.[30]

Grip Strength. The Jamar hydraulic hand dynamometer, a valid and reliable tool, will be used to measure grip strength [31, 32] Participants will be tested using standardized procedures. Participants will be standing with their arm slightly abducted and elbow extended, and will be asked to squeeze the handle of the dynamometer as hard as possible for five seconds. Two measurements will be taken for each hand and the highest value will be recorded.

Shoulder Range of Motion (ROM). Shoulder active and passive ROM will be measured following standardized procedures[33,34] using a traditional goniometer. Each arm will be measured separately for the following movements: flexion, abduction, internal, external rotation, and horizontal abduction. Active ROM will be assessed with the participant in a sitting position with their back in an upright position to prevent compensation by trunk muscles. Passive shoulder ROM and horizontal abduction will be performed in the supine position.

Health-related Quality of Life. The Lymphedema Functioning, Disability, and Health (Lymph-ICF) is a lymphedema-specific outcome questionnaire that will be used to assess HRQOL. It is a valid tool with high reliability (ICC > 0.90) in women with BCRL.[35] The Rand Short Form-36 Version 2 (SF-36) will be used to assess general HRQOL. It is a validated self-report measure with excellent test-retest reliability.[36]

Body Image. The Body Image and Relationships Scale (BIRS) is a self-report measure of body image and relationships.[11, 37] The BIRS has been shown to have a satisfactory test-retest reliability and internal consistency in addition to convergent and divergent validity.[37]

Physical Activity. The Godin leisure-time exercise questionnaire (GLTEQ) will be used to assess the physical activity level. It is a valid, reliable, and sensitive tool among different populations, including breast cancer survivors.[38, 39]

Body Mass Index (BMI). Body height and weight will be measured, and BMI will be calculated.

Adherence. Participants will be asked to record their adherence to their assigned exercise and compression intervention program using a daily diary. The adherence diary will collect details on exercise sessions performed each day, including sets, repetitions, and resistance weight, as well as use of the assigned compression sleeve (i.e. use of the garment during exercises and number of hours per day and days per week the compression sleeve is worn). Adherence is considered to be high if participants report 80% or greater adherence to the exercise program and the compression use.

Adverse Events. We will monitor adverse events as well as any additional treatments required to manage any exacerbations of lymphedema.

Exploratory Outcomes

The Difference in Mean Outcomes Between DRE Groups. We will explore differences between groups B and C to inform future research.

Arm Tissue Composition Volume. Magnetic resonance imaging (MRI) will be used to determine differences in arm muscle mass, fat and extracellular fluid between limbs over time. An approach called chemical shift encoded (CSE) MRI will be used to separate the signal sources from water and fat. Additionally, the water environments will be further characterized using a method called T_1-mapping. The T_1 time (longitudinal relaxation

time constant) is an MRI property of the water that reflects the local environment, where water within healthy skeletal muscle has T_1 values of ~1400ms. Increased T_1 values reflect edema and fibrosis within the muscle tissue with values reaching ~3000ms for free water pools, such as those contained within subcutaneous fat. A combined CSE and T_1-mapping approach will be used to quantify volumes of muscle and fat and to characterize the water environment in all tissues.[40] Multiple axial slices (4 mm slice thickness, 0.5 mm in-plane resolution) will provide full three-dimensional coverage of the arm. See Figure 3. MRI is a reliable method that has been used in lymphedema for diagnosis and treatment evaluation. [14, 41, 42]

COVID-19 accommodations: in the event of limitations related to, or suspension of in-person testing, objective testing will be conducted virtually and will include the following minimal dataset:

- Self-Circumference Measurements[43] will replace arm volume measurements

STATISTICAL CONSIDERATIONS

Sample Size

The sample size for the study was based on the findings of the pilot vanguard trial phase. Using the point estimates and measures of variability derived for LRV of the 12-week post intervention, we estimated a mean reduction of 18% in lymphedema (SD: 16%) in favour of the combined data from the intervention groups. As a result of the interim analyses, an alpha adjustment was required to preserve the overall Type I error rate. Thus, the value for the level of significance for this study was revised from 0.05 to 0.01. The estimated sample size of 51 participants or 17 per group achieves about 86% power (significance level: $p = 0.01$). Considering a 10% loss to follow-up/ withdrawal, and one level of stratification, an additional 9 participants will be added for a total sample size of 60 including the 20 participants from the pilot study. Thus, 40 more participants will be recruited to the trial

Statistical Analysis Plan

Baseline medical and demographic characteristics, arm dominance relative to the lymphedematous arm, and adverse events of the three groups will be compared using

one-way ANOVA for continuous data and Pearson's Chi-square tests for categorical data. The primary analysis will compare changes between the groups from baseline to week 12 with regard to percent change in arm lymphedema volume, arm tissue composition, arm function, physical activity, QoL, body image, and adherence-related outcomes. The comparisons over time (baseline, 12-week and 24-week follow-ups) will be conducted using repeated measures ANOVA and between groups comparisons will be conducted using one-way ANOVA on change scores. Generalized linear models (GLM) will be used to evaluate the treatment effect in subgroups defined by the strata adjusting for lymphedema severity (mild or moderate-severe).

Analyses of primary outcomes will be performed at the end of the RCT portion of the trial using an intention to treat analysis. Within-group analyses will also be conducted for primary and secondary outcomes from weeks 13 to 24 following completion of all follow-up measures. If missing data is greater than 30%, multiple imputation techniques will be used. Appropriate sensitivity analysis will be performed to determine the type of missing data, and statistical methods accounting for the type of missing data will be used. All statistical analysis will be conducted using SAS (SAS Institute Inc., Cary, NC) version 9.3 software.

Data management and quality control

The Clinical Trials Unit of the Cross Cancer Institute will be responsible for trial oversight. Storing and processing of all patient data will occur in compliance with institutional guidelines. A REDCap database will be used for data collection and monitoring. For quality control, the objective data of participants will be entered by the independent assessor and will be checked by a second independent research assistant. Any hard copy data involving the trial participants will be stored in a secure location in a locked cabinet at the respective centre that can only be accessed by study personnel. Data will be anonymized and stored according to participant number. A linking log is stored separately from the data. On trial completion, data will be accessible through the University of Alberta Libraries Dataserve Network.

Patient and public involvement

The idea for this study was born from patients' input. Women with BCRL often report a worsening of the swelling with exercise, and a need for better support for exercise. A

patient representative actively participated in the design of the study (AM). Findings will be disseminated to study participants and other survivors of breast cancer through workshops and presentations. Study findings will be dissemination through stakeholder groups including the Canadian Lymphedema Framework (CLF), Canadian Physiotherapy Association, and the International Lymphedema Framework (ILF) to the broader lymphedema stakeholder community.

ETHICS and DISSEMINATION

Ethical and safety Consideration:

Ethical approval was obtained from the Health Research Ethics Board of Alberta: Cancer Committee. All participants will be required to provide written informed consent and will be free to withdraw from the trial at any time, for any reason.

Dissemination Plan:

This trial will answer key questions on the effect of a combined exercise and compression intervention on arm lymphedema volume and tissue composition. The study results will be disseminated through scientific peer-reviewed publications, and presented at national and international conferences, and other media portals. The program protocol will be presented to healthcare professionals and shared with patient groups through clinical workshops and webinars.

Figure Legends:

Figure 1: Schematic of the Theoretical Concept - Combined Decongestive Progressive Resistance Exercise and Compression Therapy
Figure 2: Study Schema
Figure 3: Magnetic Resonance Imaging - one sample slice

Authors' contributions: MMA, AM, and MLM created the concept of the study. MMA, KLC, RBT, JRM, AM and MLM developed the study concept, the exercise program and protocol. SG assisted in the statistical analysis plan and sample size calculation. All authors will oversee the implementation of the protocol and contribute to the acquisition, analysis and interpretation of data. All authors were involved in drafting and revising the protocol manuscript. All authors read and approved the final manuscript.

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This funding body had no role in the design of this study and will not have any role in its execution, analyses, interpretation of the data, or decision to submit results.

Competing interest statement. None declared.

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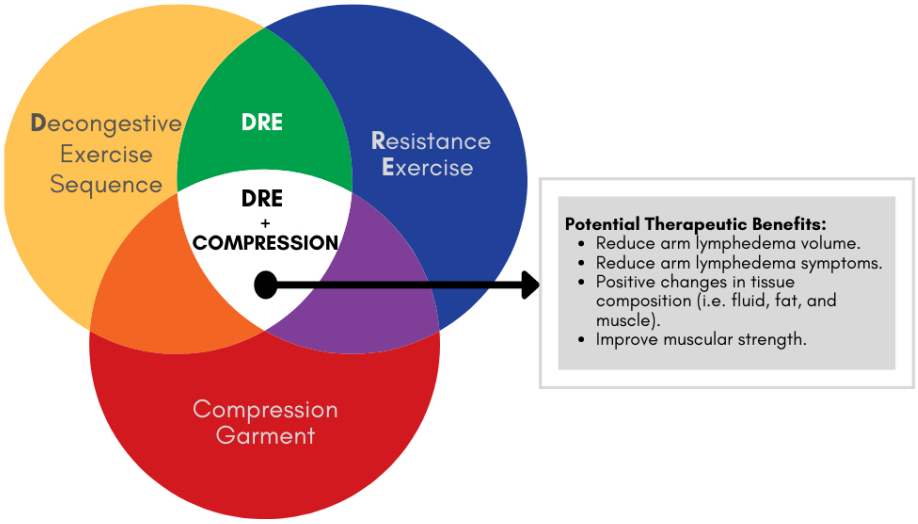

Figure 1. Schematic of Theoretical Concept

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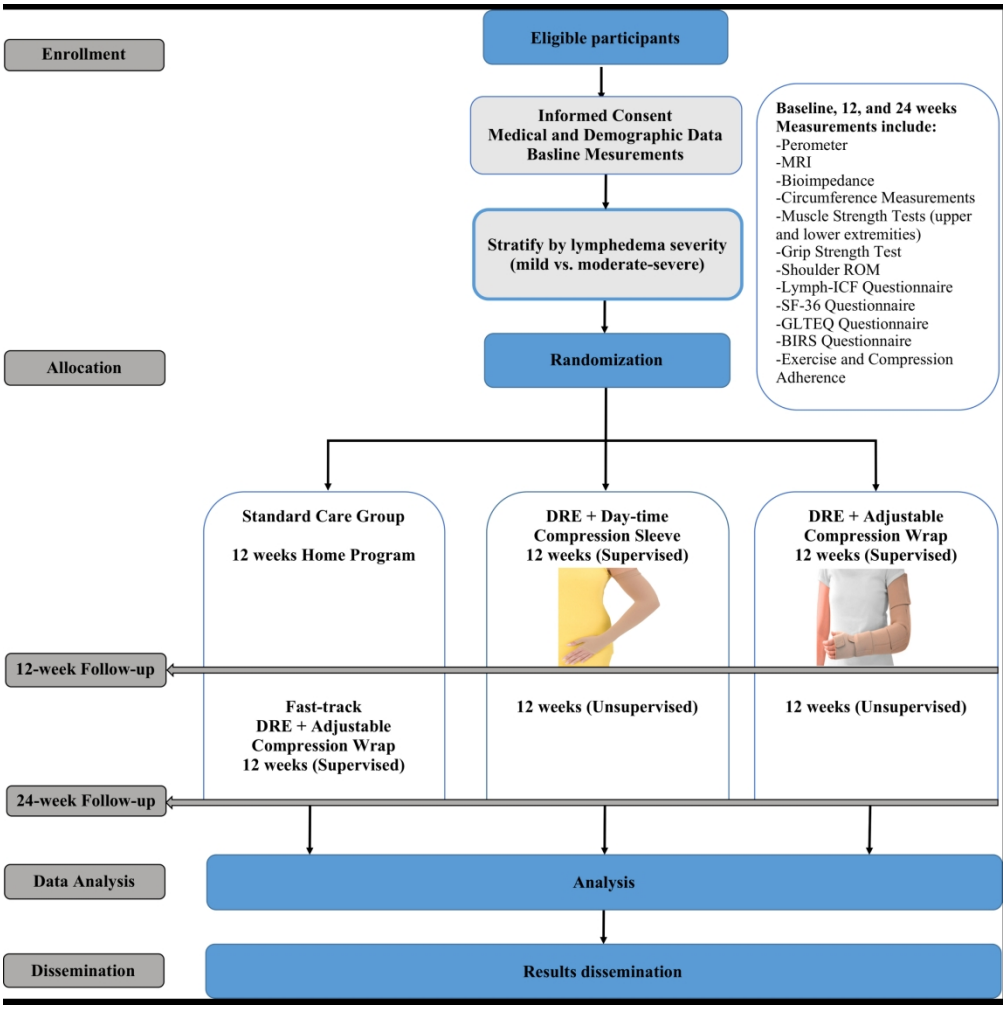
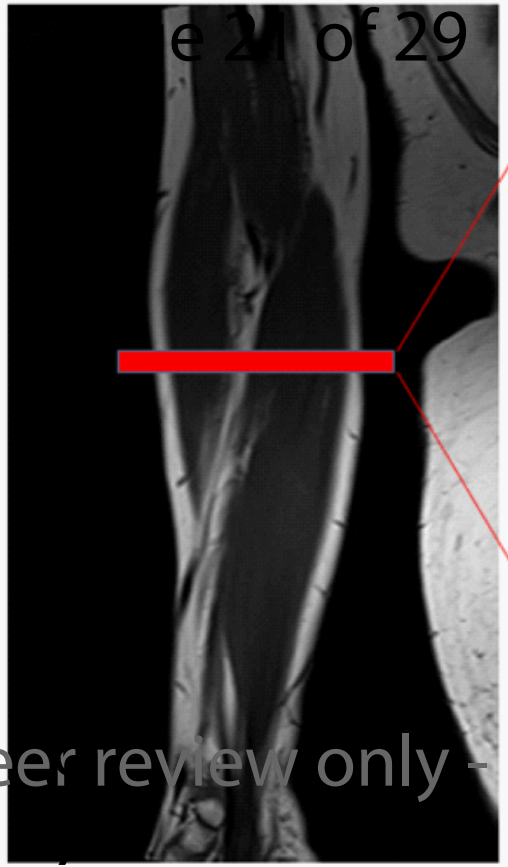
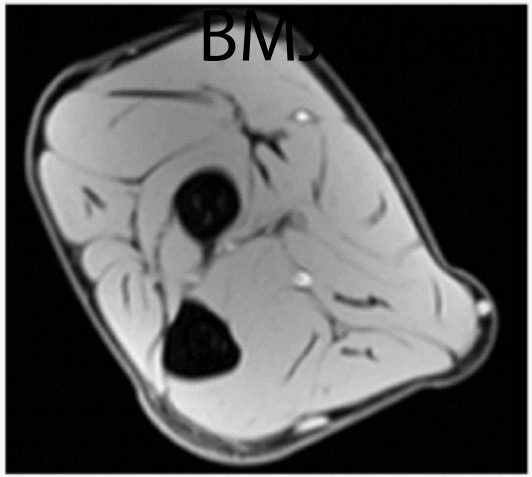


Figure 2. Study Schema

228x228mm (300 x 300 DPI)



Water Image



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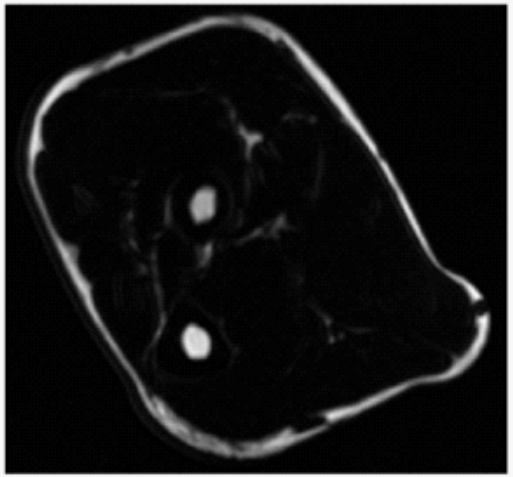
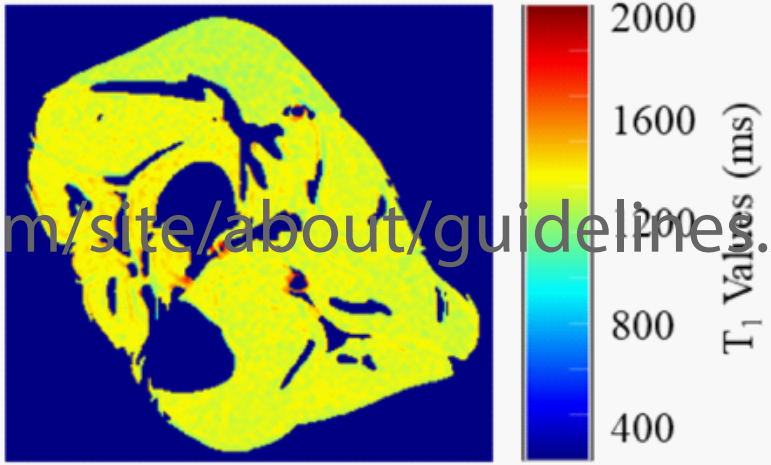


T_1 Map
(Values Reflect Tissue Water Content)



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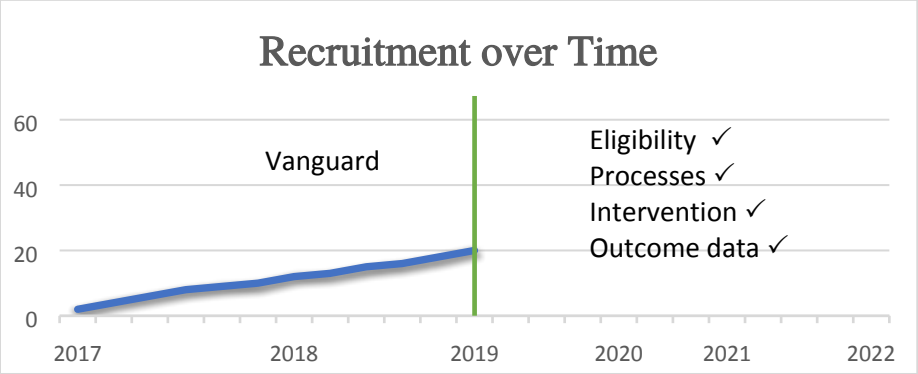
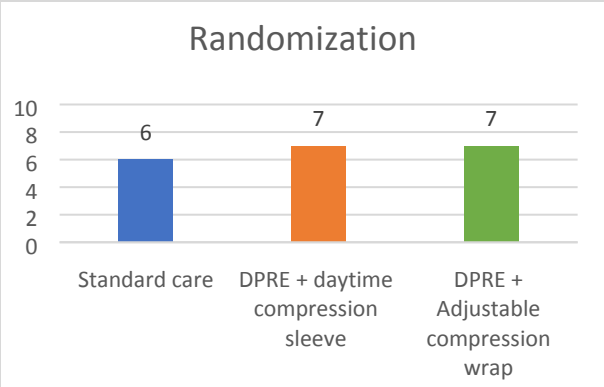
Supplementary Materials

Appendix 1: Vanguard Phase: Summary of Progress

A. Recruitment



B. Randomization



Interim analysis:
Standard care vs. Intervention Groups (combined)
Difference: 18% reduction in lymphedema volume in favour of intervention groups

C. Progression Criteria for full RCT

Criterion	Metric	Outcome	Decision
Recruitment	Recruitment rate	37% (1 per month)	Amend: minor
Protocol Adherence	Completion of procedures *(the percentage of participants who are completing study including the exercise intervention, and all follow-up assessment)*	100%: no issues identified	Proceed
	Intervention delivery	100% - no modifications	
	Exercise adherence *(the percentage of sessions, sets, and repetitions completed by participants)*	Intervention: 91%; Standard care: 84%	
	Compression adherence *(adherence to compression use during exercise and nonexercise day-time use)*	100% all groups	
Outcome Data	Adverse events	No SAE	Proceed
	Study completion	96% (19/20 completed)	
	Missing data	Individual items on outcomes: range: 96-100% complete; All outcomes completed	

Supplementary Materials

Table S1: Exercise principles

Components	***Principles***	***Benefits***
Decongestive exercise sequence[1-3]	*Follow a sequence from proximal to distal*	- *Enhance lymph drainage from the edematous area through the use of the skeletal-muscle contraction to promote venous and lymphatic return w*
Resistance exercise[4, 5]	*Overload, progression, and specificity*	- *Improve lymphedema symptoms* - *Improve muscle strength, and quality of life*
Compression[6-8]	*Enhancement of muscle pump*	*Improve long-term control of the lymphedema*

Table S2: Exercise protocol

	Weight machines and free weights	***Resistance Band (RB)****
Exercise	• *Upper limb:* *Shoulder shrugs, chest press, seated row, lateral raise, biceps curls, triceps pulldown, wrist curl, reverse wrist curl, handgrip* • *Lower limb:* *Leg press, leg curl*	
Initial/starting weight	• *Upper limb:* *1RM: 30-35%* *RPE: 2-3 (mild)* • *Lower limb:* *1RM: 60%* *RPE: 4-5* *- The intensity will be adjusted by adding/removing weight.*	• *Upper limb:* *RPE: 2-3 (mild)* • *Lower limb:* *RPE: 4-5* *-The intensity will be adjusted by tension first and then by RB strength (color).*
Progression**		
• ***Intensity***	• Upper limb: *-Weight will be increased by 5% of the 1 RM (weekly)* *-RPE: 3-5 (mild to moderate)* • Lower limb*:* *-Weight will be increased by 5-10% of the 1 RM (weekly)* *-RPE: 5-6 (moderate)*	• Upper limb: *-RB intensity will be increased by band tension, or band strength (color, or combining two RB.* *-RPE: 3-5 (mild to moderate)* • Lower limb*:* *-RB intensity will be increased by band tension first and then by RB strength (color, or combining two RB.* *-RPE: 5-6 (moderate)*
• ***Volume***	*2 X 10, 2X12, 2X15* *(then increase resistance and drop number of repetitions)*	
• ***Rest intervals***	*2 min*	
• ***Velocity***	*Slow to moderate with breathing (two seconds concentric, four seconds eccentric)*	
• ***Frequency***	*2Xwk*	

** Adopted training protocols from (Colado and Triplett, 2008)[9]. Each participant will be provided with 1.5-2 meter of 3- levels RB. Each band will be marked with reference points (10cm) to control the intensity. The band reference values provided by (Uchida et. al 2016)[10] will be used to estimate the starting RB color.*

***The exercise will be progressed in the second week, first by increasing the number of repetitions, and then by increasing the intensity. The RPE will be used to quantify the exercise intensity and to inform the progression of exercise resistance. The exercises will be tailored based on the lymphedema symptoms for each participant.*

Supplementary Materials

Table S3: Exercise monitoring

Symptoms	***Response***
Exacerbation of lymphedema symptoms (tension, tightness, heaviness, pain, or increased swelling)	• *Participant will be monitored and examined by lymphedema therapist* • *Exercise intensity will be reduced by decreasing the number of repetitions and/or resistance*
Worsening of fatigue	• *Exercise intensity will be reduced by decreasing the number of repetitions*

Table 4: The percentage change in arm lymphedema calculation formula

Lymphedema absolute volume (LAV)	*LAV=affected volume – unaffected volume (mls)*
Absolute change in excess volume (mls)	*LAV (baseline) – LAV (12-weeks)*
Lymphedema relative volume (LRV) change	*(1) LAV baseline – LAV 12-weeks* *(2) LAV at baseline* $\frac{(1)}{(2)} \times 100$

References:

1. National Lymphedema Network. Position Statement of the National Lymphedema Network: Topic: Exercise for Lymphedema Patients. 2011. https://lymphnet.org/position-papers.
2. Fu MR, Deng J, Armer JM. Putting evidence into practice: cancer-related lymphedema. Clinical journal of oncology nursing. 2014;18.
3. Ridner SH, Fu MR, Wanchai A, Stewart BR, Armer JM, Cormier JN. Self-management of lymphedema: a systematic review of the literature from 2004 to 2011. Nursing research. 2012;61(4):291-9.
4. Kraemer WJ, Ratamess NA. Fundamentals of resistance training: progression and exercise prescription. Medicine & science in sports & exercise. 2004;36(4):674-88.
5. Paramanandam VS, Roberts D. Weight training is not harmful for women with breast cancer-related lymphoedema: a systematic review. Journal of physiotherapy. 2014;60(3):136-43.
6. Hirai M, Niimi K, Iwata H, Sugimoto I, Ishibashi H, Ota T, et al. Comparison of stiffness and interface pressure during rest and exercise among various arm sleeves. Phlebology. 2010;25(4):196-200.
7. Boris M, Weindorf S. Persistence of lymphedema reduction after noninvasive complex lymphedema therapy. Cancer. 1997;11(1).
8. Ko DS, Lerner R, Klose G, Cosimi AB. Effective treatment of lymphedema of the extremities. Archives of Surgery. 1998;133(4):452-8.
9. Colado JC, Triplett NT. Effects of a short-term resistance program using elastic bands versus weight machines for sedentary middle-aged women. The Journal of Strength & Conditioning Research. 2008;22(5):1441-8.
10. Uchida MC, Nishida MM, Sampaio RAC, Moritani T, Arai H. Thera-band® elastic band tension: reference values for physical activity. Journal of Physical Therapy Science. 2016;28(4):1266-71.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	supplementary document_
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14,15
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5,6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6,7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8,9,10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10,11,12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6,7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12,13

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8,9,10,11,12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13,14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12,13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12,13

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13,14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Clinical Trials Unit oversight
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13,14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**Supplementary material**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.