Decongestive progressive resistance exercise with an adjustable compression wrap for breast cancer-related lymphoedema (DREAM): protocol for a randomised controlled trial

Mona M Al Onazi,1 Kristin L Campbell,2 Richard B Thompson,3 Sunita Ghosh,4,5 John R Mackey,5 Anne Muir,6 Margaret L McNeely1,5

INTRODUCTION

Breast cancer-related lymphoedema (BCRL), swelling in the arm on the side of the breast cancer surgery, affecting one in five women. To date, survivors with BCRL have been found to have a poorer health-related quality of life without worsening lymphoedema. 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 lymphoedema volume. The aim of this three-arm, provincial randomised controlled trial is to determine the efficacy of a 12-week decongestive progressive resistance exercise (DRE) programme in combination with the one of two types of compression garments compared with standard care.

Methods and analysis

Sixty women with BCRL will be recruited and randomly assigned to one of the following three groups: (1) Standard care, (2) DRE with use of a daytime compression garment during exercise and (3) DRE with use of an adjustable compression wrap during exercise. The primary outcome is the percentage reduction in arm lymphoedema 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 MRI 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 randomised 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 programme protocol will be shared with healthcare professionals and patient groups through clinical workshops and webinars.

Trial registration number NCT05022823.


Issue date 26 April 2021.

Strengths and limitations of this study

- Evaluation of the benefit of a combined programme involving a specialised decongestive resistance exercise programme and use of compression on arm lymphoedema 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 programme on arm tissue composition through MRI.
- 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.

© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to Dr Margaret L McNeely; mmcneely@ualberta.ca
condition involves conservative interventions aiming to reduce the swelling, prevent cellulitis and optimise the survivor’s function and QOL. The initial phase of treatment is a course of 2–4 weeks of intensive decongestive therapy, comprising skin care, bandaging using multilayered bandages, decongestive exercises and self-care, with or without manual lymphatic drainage. The aim of this phase is to reduce the swelling. The second phase of treatment, called the maintenance phase, involves daily use of a compression garment and decongestive exercise to enhance lymph drainage from the oedematous area through the use of the skeletal-muscle contraction to promote venous and lymphatic return, and the programme involves active exercises without external resistance. Recent evidence supports the safety of other types of general exercise such as aerobic and resistance exercise for BCRL. Progressive resistance exercise programmes twice a week at a mild to moderate intensity, using free weights and weight machines, have been found to improve symptoms and reduce the frequency of relapses (ie, flares) in lymphoedema. High adherence to use of a compression garment and decongestive exercises during the maintenance phase is positively associated with long-term lymphoedema control.

To date, no studies have been performed combining all potential therapeutic approaches to address lymphoedema: (1) use of the decongestive exercise sequence to enhance venous and lymphatic return, (2) progressive resistance exercise training to improve symptoms and prevent relapses in arm volume and (3) use of a compression garment during both exercise and daytime hours to improve long-term control of the lymphoedema. (11) We hypothesise that combining DRE with either a compression garment or adjustable compression wrap will result in a larger lymphedema relative volume (LRV) reduction when compared with 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 hypothesise that the difference between groups will fall inside the equivalence interval of ±10% in LRV 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 with standard care on the percentage change in arm lymphoedema volume.
2. To examine the efficacy of DRE with use of a daytime compression sleeve compared with standard care on the percentage change in arm lymphoedema volume.

Secondary objectives include examining the effect on arm tissue composition, bioimpedance analysis, shoulder ROM, upper and lower extremity muscle strength, physical activity, body image, QOL and adherence.

METHODS AND ANALYSIS
Study design
The DREAM study is a randomised controlled fast-track trial. Participants will be recruited from the Cross Cancer Institute (CCI) in Edmonton, and the Holy Cross Centre-Tom Baker Cancer Centre in Calgary, Canada. The study 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 programme. The proposed RCT will follow the same study methods and intervention as per the vanguard phase, with inclusion of patient data from this phase (online supplemental appendix 1).

Figure 1 Schematic of the theoretical concept—combined decongestive progressive resistance exercise (DRE) and compression therapy.
is a female with a history of breast cancer.

Outcome measures will be assessed at baseline, 12 and 24 weeks. See figure 2. The primary time point for the trial is 12 weeks.

Participants will be stratified by lymphoedema severity (mild: <20% vs moderate to severe: ≥20% inter-limb difference in limb), and then randomised using a computer-generated randomisation module within the Trial’s Research Electronic Data Capture (REDCap) database. Randomisation will occur following baseline testing, and participants will be assigned on a 1:1:1 basis to one of the three groups.

Eligibility criteria

A survivor will be included based on the following criteria:
- Has underwent 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), or regional lymphoedema, defined as a minimal volume difference of 100 mL or 5% in a segment of the arm (eg, hand and forearm region, elbow and upper arm).
- Has chronic lymphoedema, defined as lymphoedema that has been present for at least 3 months.
- Has completed intensive reduction treatment, and is in the lymphoedema maintenance phase of conservative treatment.
- Uses a well-fitted daytime compression garment (not older than 1 month and providing a minimum of 30 mmHg of pressure) and is agreeable to wear the garment for a minimum of 12 hours per day.
- Is agreeable to discontinuing other lymphoedema 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.

Randomisation procedure

Participants will be stratified by lymphoedema severity (mild: <20% vs moderate to severe: ≥20% inter-limb difference in limb), and then randomised using a computer-generated randomisation module within the Trial’s Research Electronic Data Capture (REDCap) database. Randomisation 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, 7 days a week.
Group A: standard care group
Participants in this group will receive standard care for lymphoedema maintenance that includes a home exercise programme involving the lymphoedema decongestive exercise regimen. Participants will be instructed to perform the exercise sequence once daily for 10–15 min. From weeks 13 to 24 of the study, participants in this group will be fast-tracked 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 programme 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 min of warm-up exercises.

The intervention programme 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 2 min rest period will be observed between exercises. The resistance exercise programme will use weight machines, free weights and/or resistance bands (RBs). Participants will be familiarised with the exercises, weight machines and RBs prior to the start of the training. We will determine the starting weight and the progression using a standardised protocol (online supplemental table S2). The exercise programme will be individualised to the respective participant and the resistance intensity will be tailored based on their baseline assessment and response to exercise in terms of lymphoedema 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 lymphoedema symptom (online supplemental 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 lymphoedema 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 programme 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 programme.

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

Primary outcome

Lymphoedema arm volume
The primary outcome will be the percentage change in arm LRV (online supplemental table S4: calculation formula). Lymphoedema will be objectively measured using the optoelectronic limb volumeter (perimeter). The perimeter 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 strength31 32 Participants will be tested using standardised 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 ROM
Shoulder active and passive ROM will be measured following standardised procedures33 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 QOL
The Lymphoedema Functioning, Disability and Health is a lymphoedema-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 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.\textsuperscript{11,37} The BIRS has been shown to have a satisfactory test–retest reliability and internal consistency in addition to convergent and divergent validity.\textsuperscript{37}

Physical activity
The Godin Leisure-Time Exercise Questionnaire will be used to assess the physical activity level. It is a valid, reliable and sensitive tool among different populations, including breast cancer survivors.\textsuperscript{38,39}

Body mass index
Body height and weight will be measured, and body mass index will be calculated.

Adherence
Participants will be asked to record their adherence to their assigned exercise and compression intervention programme 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 (ie, 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 programme and the compression use.

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

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
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 characterised 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 $\sim1400$ ms. Increased $T_1$ values reflect oedema and fibrosis within the muscle tissue with values reaching $\sim3000$ ms 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 characterise the water environment in all tissues.\textsuperscript{40} Multiple axial slices ($4\text{mm}$ slice thickness, $0.5\text{mm}$ 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 lymphoedema for diagnosis and treatment evaluation.\textsuperscript{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:

\begin{itemize}
  \item Self-Circumference Measurements\textsuperscript{43} will replace arm volume measurements.
\end{itemize}

\section*{STATISTICAL CONSIDERATIONS}

\subsection*{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 lymphoedema (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

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{MRI—one sample slice.}
\end{figure}
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 nine 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 lymphoedematous arm, and adverse events of the three groups will be compared using one-way Analysis of Variance (ANOVA) for continuous data and Pearson’s χ² 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 lymphoedema volume, arm tissue composition, bioimpedance analysis, muscle strength, shoulder range of motion, physical activity, QOL, body image and adherence-related outcomes. The comparisons over time (baseline, 12 weeks and 24 weeks follow-ups) will be conducted using repeated measures ANOVA and between groups comparisons will be conducted using one-way ANOVA on change scores. Generalised linear models will be used to evaluate the treatment effect in subgroups defined by the strata adjusting for lymphoedema 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) V.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 anonymised 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 disseminated through stakeholder groups including the Canadian Lymphoedema Framework, Canadian Physiotherapy Association and the International Lymphoedema Framework to the broader lymphoedema 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 lymphoedema 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 programme protocol will be presented to healthcare professionals and shared with patient groups through clinical workshops and webinars.

**Author affiliations**

1Department of Physical Therapy, University of Alberta, Edmonton, Alberta, Canada
2Department of Physical Therapy, University of British Columbia, Vancouver, British Columbia, Canada
3Department of Biomedical Engineering, University of Alberta, Edmonton, Alberta, Canada
4Department of Mathematics and Statistical Sciences, University of Alberta, Edmonton, Alberta, Canada
5Department of Oncology, University of Alberta, Edmonton, Alberta, Canada
6Cancer Rehabilitation Clinic, University of Alberta, Edmonton, Alberta, Canada

**Twitter** Margaret L McNeely @MargieMcNeely

**Contributors** MMO, AM and MLM created the concept of the study. MMO, KLC, RBT, JRM, AM and MLM developed the study concept, the exercise program and protocol. SS 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.

**Funding** This work was supported by the Alberta Cancer Foundation Investigator Initiated Trials. Grant number CCI IT: Fall 2019. Grant Oversight: Clinical Trials Unit, Cross Cancer Institute. Sponsor’s Reference: CCI IT: Fall 2019. Contact name: CCI IT Project Manager & Quality and Regulatory Advisor, Address: Clinical Research Unit, Cross Cancer Institute, 11 560 University Avenue Edmonton, Alberta Canada T6G 1Z2; Telephone: 780-577-8149; Email: ACB.CCITrial.ITITProjectManager@albertarehab.healthservices.ca.

**Disclaimer** This study received no funding. This funding body had no role in the design of this study and will have any role in its execution, analyses, interpretation of the data, or decision to submit results.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.
Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Kristin L Campbell http://orcid.org/0000-0002-2266-1382
Margaret L McNeely http://orcid.org/0000-0003-4376-4847

REFERENCES