UCSF Helen Diller Family Comprehensive Cancer Center

NCT# 03252145

Treatment of breast cancer-related LE with a negative pressure device: a pilot randomized controlled study

Protocol Number: CC #16802
Study Drug: N/A

Version Number: 3.3
Version Date: 3/13/2018

IND Number: N/A

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Revision History

Version 2.0	7/12/2016
Version 3.0	12/4/2016
Version 3.1	12/22/2016
Version 3.2	12/14/2017
Version 3.3	3/13/2018

Protocol Signature Page

Protocol No.: 16802 **Version Date:** 3/13/2018

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Committee on Human Research (CHR), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with CHR policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

Betty Smoot

Printed Name

Signature

3/13/2018

Date

Participating Site(s)

Telephone:	Telephone:	Telephone:
E-mail:	E-mail:	E-mail:

Principal Investigator	**Site**
Printed Name	
Signature	Date

Abstract

Title	Treatment of breast cancer-related lymphedema (LE) with a negative pressure device: a pilot randomized controlled study
Patient population	Women with upper extremity LE following breast cancer treatment
Rationale for Study	Approximately 1 in 5 women will develop upper extremity LE after breast cancer treatment and experience reduced function and quality of life as a result. Chronic LE is difficult to treat and responses to treatment are variable. Better understanding of effectiveness and responses to LE treatment will improve our ability to offer targeted interventions, improve outcomes, and reduce the devastating negative sequelae associated with the condition. Moreover, an improved understanding of the mechanisms underlying responses to LE treatment will provide the foundation for development and testing of new LE interventions.
Primary Objective	Aim 1. To determine the recruitment and retention rates for both arms of this 4-week pilot study of a novel LE treatment using a negative pressure device. Feasibility of recruitment, randomization, retention, assessment procedures, and implementation of the intervention will be evaluated. These assessments will be used to determine whether or not a larger, hypothesis-testing study is feasible and warranted. Aim 2. Evaluate for treatment-emergent adverse events
Secondary Objectives	Aim 3. To determine effect sizes for treatment outcomes, comparing changes in the intervention group to changes in the control group, following the 4-week study. Effect sizes will be determined for: • Total limb volume calculated from arm circumference • Bioimpedance resistance ratios as a measure of change in limb extracellular fluid volume • Tissue indentation as a measure of change in tissue induration • Shoulder range of motion and grip strength as objective measures of upper extremity function; and • Patient reported outcomes of arm function, quality of life, body image, and treatment satisfaction. Aim 4. To evaluate for changes in circulating biomarkers of inflammation and fibrosis (IL-4, IL-6, IL-10, and TGF-beta 1) from enrollment to 4-weeks.
Study Design	This study will be a 4-week pilot randomized, controlled, assessor blinded, trial of a novel LE treatment using a negative pressure massage device (intervention group), compared to standard manual lymph drainage massage (control group), in breast cancer patients with chronic upper extremity LE.
Number of patients	A sample size of 80 achieves 80% power to detect a Cohen's d effect size of 0.35, with a 2-sided alpha of 0.05, beta of 0.20, and correlation of 0.60 between the pre- and post-test bioimpedance measures.
Duration of Therapy	Patients will receive treatment for 4 to 6 weeks from the time of study entry.

Duration of Follow up	Final assessment will be done within one week of last treatment administration. Online follow up, using the NQ, will be conducted 4 months after the final visit to evaluate LE symptoms and any LE treatment sought after delivery of the intervention or control treatment.
Duration of study	The study will reach completion 2 years from the time the study opens to accrual.
Study Intervention	The intervention is treatment with a negative pressure massage device compared to standard manual lymph drainage massage, delivered 2 to 3 times per week over 4 to 6 weeks for a total of 12 treatments.
Safety Assessments	All patients will be carefully screened for any medical problems that would preclude participation in the assessment procedures or the intervention. Screening for adverse responses will include assessment of pain, erythema, and skin integrity at each visit, and weekly circumference monitoring. An increase in affected limb volume of 5% from enrollment levels will trigger referral to a LE therapist for further assessment.
Efficacy Assessments	To evaluate responses to treatment, comparison of changes in the intervention group (negative pressure device) to changes in the control group (MLD), following the 4-week study will be done by calculation of effect sizes for: • Total limb volume calculated from limb circumference measurements • Bioimpedance resistance ratios as a measure of change in limb fluid volume • Tissue indentation as a measure of induration • Shoulder range of motion and grip strength as objective measures of upper extremity function; and • Patient reported outcomes (arm function, quality of life, body image, treatment satisfaction) The effect size for the difference between groups in changes in limb volume, resistance ratios, tissue indentation, shoulder range of motion and grip strength, and in patient reported outcomes will be estimated as the standardized difference in means of each measure at the last assessment, and as the difference between the groups in the percent change from enrollment to the last assessment.

Unique Aspects of this Study	This study is the first to evaluate a novel negative pressure device that mobilizes the skin and subcutaneous tissue through vertical and horizontal stretching, which may decrease fibrosis, while increasing the subcutaneous space for lymphatic circulation and reducing limb volume. Another novel feature of this proposal is the use of a portable indentation instrument that yields a quantitative measure of skin and subcutaneous tissue changes associated with chronic LE. Currently, these changes are evaluated through examination of tissue texture and pitting to digital pressure. Tissue indentation can be more precisely and objectively measured, which will assist in more accurate objective assessment and staging of LE and evaluation of responses to LE treatment. Additionally, we will evaluate for changes in circulating biomarkers for inflammation and fibrosis following treatment. Limited data are available on the mechanisms by which current treatments reduce LE in breast cancer survivors. Findings from this pilot study may provide information on the mechanisms by which the proposed intervention works

List of Abbreviations

AE	Adverse event
BC	Breast cancer
CDT	Complete decongestive therapy
CHR	Committee on Human Research (UCSF IRB)
CRC	Clinical Research Coordinator
CRF	Case report form
CTCEA	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DASH	Disability of Arm, Shoulder, and Hand Questionnaire
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FDA	Food and Drug Administration
HDFCCC	Helen Diller Family Comprehensive Cancer Center
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LE	Lymphedema
MedDRA	Medical Dictionary for Regulatory Activities
MLD	Manual lymph drainage
NCI	National Cancer Institute
NPWT	Negative Pressure Wound Therapy
PD	Disease progression
PRC	Protocol Review Committee (UCSF)
PROMIS	Patient Reported Outcome Measurement System
QOL	Quality of Life
RCT	Randomized controlled trial
SD	Standard deviation

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1 Introduction

1.1 Background on Indication

Improved detection and treatment of breast cancer (BC) has led to increased survival rates.[1] Despite improvements in care, BC treatments are not without complications. Lymphedema (LE) is one of the most common and feared complications. Untreated, LE worsens and leads to significant disability. LE is the accumulation of interstitial fluid as a result of impaired lymphatic function.[2] Cancer-related LE is the accumulation of interstitial fluid as the result of damage to lymph nodes and lymphatic pathways through surgical removal, fibrosis, or direct endothelial trauma from irradiation.[3] As lymph transport is impeded, increased pressure in lymphatic vessels leads to lymphatic vessel valvular insufficiency and further impairment in lymph drainage. Lymph stasis and excess interstitial protein creates a condition of chronic inflammation that contributes to fibrosis and fatty deposition in the subcutis, which further impairs lymphatic function.[3]

Estimates of LE prevalence vary widely, from 3% to 42%,[4-9] due to differences in measurement methods, diagnostic criteria, sample characteristics, and follow-up time. However, recent evidence suggests that of the nearly 3 million BC survivors in the United States,[1] 1 in 5 will develop LE as a result of their BC treatment.[10] This statistic means that over 600,000 women have LE and many more will develop this chronic and potentially disabling condition. Women who develop LE have greater limitations in shoulder function, greater restrictions in activity, and report poorer quality of life (QOL) than women without lymphedema.[11-14] These women are at greater risk for lymphangitis, cellulitis, and secondary infections, and incur higher medical costs.[15] Better understanding of effectiveness and responses to LE treatment will improve our ability to offer targeted interventions, improve outcomes, and reduce these devastating negative sequelae.

1.2 Rationale for the Proposed Study

The current treatment standard for LE is complete decongestive physiotherapy (CDT).[16] The primary goal of CDT is to reduce limb volume. The intense phase of CDT consists of daily manual lymph drainage (MLD), multi-layer bandaging, remedial exercises, and meticulous skin care. Responses to CDT are variable and multi-factorial. For example, LE duration of >2 years and higher BMI are associated with poorer outcomes in response to CDT.[17,18] Chronic LE is associated with persistent inflammation resulting in progressive fibrosis and adipose tissue deposition.[19,20] In the presence of fibro-adipose deposition in the limb, treatments directed primarily at volume reduction may be less effective. Treatments are needed that address the changes in the skin and subcutaneous tissues associated with chronic LE, as well as increases in limb volume. Negative pressure therapy, using a suction treatment device, has been proposed and marketed as stimulating lymphatic fluid flow by providing stretch to skin and subcutaneous fascial structures.[21] If shown to reduce volume and reduce skin and subcutaneous induration, negative pressure may be an important part of LE management. While there is evidence to support the use of complete decongestive therapy (CDT) in the management of lymphedema, the effectiveness of manual lymph drainage (MLD), in the context of CDT or alone, is disputed.[22-25] MLD is a practitioner-applied manual massage technique designed to decrease limb volume in LE by enhancing movement of lymph fluid, resulting in reductions in interstitial fluid and soft tissue induration.[26] Systematic reviews that evaluated the effectiveness of MLD have found conflicting results and reported primarily on limb volume outcomes. Huang et al.[25] reported variable results across randomized controlled trials, and when data were pooled in this meta-analysis, no statistically significant benefit in volume reduction from MLD was found. While Moseley, et al.[26] found significant reductions in limb volume from MLD, findings from Ezzo et al.[22] were not consistent. Additional research is needed that compares the effects of alternative treatments, such as negative pressure treatments, with MLD. Negative pressure therapy is a novel treatment that is being marketed to and is gaining popularity in clinics that treat LE. However, no RCTs have evaluated its efficacy. Moreover, few

studies have reported changes in skin and subcutaneous induration in response to treatment for chronic LE.

PhysioTouch (HLD Healthy Life Devices Ltd., Espoo, Finland) is a U.S. Food and Drug Administration approved therapeutic massage device (Figure 1). This hand-held device uses negative pressure (suction) administered under the treatment head. With the application of negative pressure, the underlying tissue is gently pulled into the suction cup, producing a stretch in the subcutaneous tissue space,[21] which pulls on the lymphatic anchoring filaments attached to lymphatic capillary endothelial cells (Figure 2). The anchoring filaments are stretched both horizontally and vertically. This filament tension results in opening of the gaps between the lymphatic capillary endothelial cells, which allows interstitial fluid to move from higher to lower pressure areas, into the lymphatic capillary. This process is thought to facilitate lymphatic flow from the interstitium into the lymphatic vessels. In a 2013 TEKES (the Finnish Funding Agency for Technology and Innovation) report, the authors described outcomes for a sample of 13 patients with post-mastectomy arm LE who were randomized to two treatment groups: negative pressure or MLD. Somewhat larger improvements were seen in the negative pressure treatment group in limb volume, skin stiffness, and QOL. No adverse events were reported in this very small, unpublished, study.[27]

Figure 1. The PhysioTouch negative pressure device

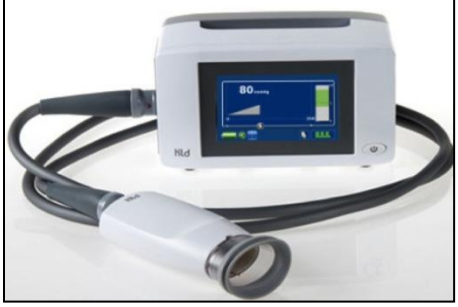
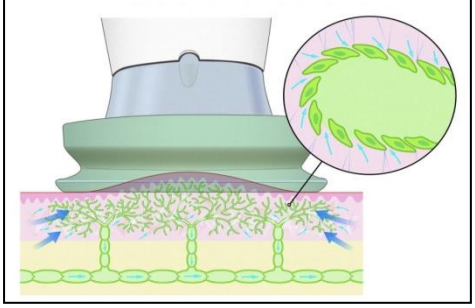


Figure 2. Effect of negative pressure on underlying soft tissue



Negative pressure wound therapy (NPWT) has been used to treat open wounds for over 2 decades. The use of NPWT results in the removal of protease-rich wound fluid and reduces interstitial edema and inflammatory mediators.[28,29] Mechanical strain created by the vacuum results in deformation and stretch at the tissue and cellular levels. This strain promotes chemotaxis, angiogenesis, and new tissue formation through recruitment of growth factors.[29] Additionally, NPWT promotes a hypoxic gradient, with increased vascular endothelial growth factor (VEGF) expression that results in neovascularization.[28] Additional support for the use of NPWT for treatment of LE comes from a porcine study in which its use was evaluated as a preventive strategy for hematoma/seroma formation under a closed wound, following wound induction.[30] Application of NPWT decreased hematoma/seroma levels without fluid collection in the NPWT canister, which the authors suggested might be related to increased lymph clearance. In a systematic review of 14 RCTs, adverse events associated with use of NPWT were mild or were not reported.[31] Evidence for the use of negative pressure in the treatment of LE is limited to conference abstracts, modeling, and simulation studies,[21] and non peer-reviewed manufacturer-initiated studies. The pilot study proposed in this application will be the first to evaluate the feasibility and efficacy of this novel treatment for LE, using negative pressure to improve limb volume and tissue fibrosis and will provide pilot data for a larger scale hypothesis-driven RCT.

In a mouse study of LE, lymph stasis resulted in CD4+ T-cell inflammation and T-helper 2 (Th2) differentiation.[32] In mice, the CD4+ inflammatory response was required for the pathological changes associated with LE, including fibrosis, adipose deposition, and lymphatic dysfunction.[32] Activated Th1 and Th2 cells release a number of cytokines: Th1 cells produce interferon-γ, interleukin (IL)-2 and tumor necrosis factor (TNF)-β. Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13.[33] Cytokines play a key role in modulating inflammatory responses, and may be involved in the development of LE and the associated fibro-adipose changes seen in chronic LE. CD4+ Th2 cells promote the production of pro-fibrotic cytokines and growth factors,

including transforming growth factor beta 1 (TGF-b1), IL-4 and IL-13.[34] TGF-b1, a cytokine released by many types of immune cells, is known to regulate the response of fibroblasts to injury, as well as the pathological production of fibrosis. TGF-b1 plays a key role in connective tissue remodeling, scar formation, and fibrosis.[35,36] In addition, elevated levels of IL-6 were found in patients with LE and elevated expression of IL-6 correlates with adipose deposition and inflammation.[37]

This study is innovative in three important ways. First, the proposed pilot intervention will evaluate the feasibility and efficacy of a novel treatment for LE, using negative pressure to improve limb volume and tissue induration (hardness). Currently, no published studies were found on the efficacy of this treatment, despite its growing popularity in clinical practice.

Second, tissue induration as a marker of fibrosis will be evaluated using a fibrometer to record skin responses to a short-term load. This device provides an objective measure of tissue deformation. The most widely used clinical assessment of skin induration associated with peripheral edema is the application of digital pressure. The pit depth and time needed for the skin to return to its original appearance is scored from 0 to 4. This method lacks objectivity and sensitivity to change.[38] The use of the fibrometer will provide an objective measure of changes in skin induration during the pilot study.

Third, we will evaluate for changes in circulating biomarkers for inflammation and fibrosis following treatment. Limited data are available on the mechanisms by which current treatments reduce LE in breast cancer survivors. Findings from this pilot study may provide information on the mechanisms by which the proposed intervention works.

1.3 Correlative Studies

No correlative studies will be conducted in this study.

2 Objectives of the Study

2.1 Primary

- Aim 1: To determine the recruitment and retention rates for both arms of this 4-week pilot study of a novel LE treatment using a negative pressure device.
- Aim 2: To evaluate for treatment-emergent adverse events

2.2 Secondary

- Aim 3: To determine effect sizes for treatment outcomes, comparing changes in the intervention group to changes in the control group, following the 4-week study. Effect sizes will be determined for:
    - Total limb volume calculated from circumference
    - Bioimpedance resistance ratios as a measure of change in limb fluid volume
    - Tissue indentation as a measure of change in skin and subcutaneous fibrosis
    - Shoulder range of motion and grip strength as objective measures of upper extremity function; and
    - Patient reported outcomes (PROs) of arm function, QOL, body image, and treatment satisfaction.
- Aim 4. To evaluate for changes in circulating biomarkers of inflammation and fibrosis (IL-4, IL-6, IL-10, and TGF-beta 1) from enrollment to 4 weeks.

2.3 Endpoints

Primary Endpoints

Aim 1: To determine the recruitment and retention rates for both arms of this 4-week, pilot study, the numbers of women screened and enrolled as well as completion rates for each arm of the study, will be recorded. Feasibility of recruitment, randomization, retention, assessment procedures, and implementation of the novel intervention will be evaluated. Information regarding treatment satisfaction will be collected. These assessments will be used to determine whether or not a larger, hypothesis-testing RCT to assess the efficacy of this intervention is feasible and warranted and if modifications are needed.

Aim 2: To evaluate for treatment-emergent adverse events. Safety analyses will involve examination of and comparison between groups for the incidence, severity, and type of treatment- emergent adverse events. The numbers of patients whose BIS resistance ratio increases by 5% or more will be compared between groups.

2.3.2 Secondary Endpoints

Aim 3: To determine effect sizes for limb volume, bioimpedance resistance, tissue induration, and patient reported outcomes, comparing changes in the intervention group (negative pressure device)

1. Limb volume: Arm Circumference will be used to assess total limb volume. Circumferential measurements of both limbs will be done twice using a spring-loaded tape measure at 10 cm intervals from the pisiform prominence of the wrist up to a total distance of 40 cm. Circumferences will be measured using the procedures outlined by Cornish et al.[39] Limb volume will be calculated using the formula for volume of a truncated cone ($V= 1/12\Pi \Sigma h (C_1^2 + C_1C_2 + C_2^2)$).[40] Inter-rater reliability for volume measured via circumference was 0.94 to 0.99.[41]

2. Bioelectrical Impedance Spectroscopy (BIS): BIS measurements of both arms will be done using established procedures (ImpediMed, San Diego, CA).[39,42,43] Two 'measurement' electrodes will be placed at either end of the 40 cm length over which the circumference measurements were made and the 'drive' electrodes will be placed 8 to 10 cm distal to these measurement electrodes. Two readings of resistance will be averaged for each arm. BIS inter-rater reliability is 0.987 and intra-rater reliability is 0.993.[44] The bioimpedance ratio is the ratio of resistance in the unaffected arm to the resistance in the affected arm and will be used to measure change in limb fluid volume.

3. Tissue induration: The SkinFibroMeter (Delfin Technologies, Finland) will be used to measure change in skin and subcutaneous induration/fibrosis. The SkinFibroMeter consists of a 1 mm long indenter and a force sensor. The device is gently pressed against the skin. The indenter imposes a constant deformation when the reference plate is in full contact with the skin. The skin and the underlying superficial subcutis resist the deformation. The induration value in Newtons (N) is recorded. Measurements will be taken bilaterally at 7 locations: the dorsal hand; the ventral, lateral, and medial forearm - midway between the elbow crease and the distal wrist crease, and the ventral, medial and lateral arm midway between the elbow crease and acromion. Five recordings will be taken at each location and a mean score will be calculated.

4. UE function: Objective assessments of change in UE function will be evaluated through assessments of shoulder range of motion (ROM) and grip strength.
    a. Shoulder range of motion: In a prospective study of 115 women with Stage 0-III breast cancer,[45] reductions in shoulder flexion and abduction ROM were found in 60% of the women 1 month after breast cancer surgery. We previously found that women with LE have greater limitations in shoulder abduction ROM than women without LE.[11] Active shoulder flexion and abduction ROM will be assessed with

patients in supine using a goniometer and standardized procedures reported by Norkin and White.[46] Bilateral ROM will be assessed. Two measurements will be taken for each motion and a mean obtained.

b. Grip strength: Upper extremity strength is commonly measured by assessment of grip strength.[47] Sagen et al.[48] found an 11% bilateral reduction in grip strength from preoperative levels to 2.5 years following breast cancer surgery in women who had an axillary lymph node dissection. Grip strength will be assessed using a Jamar hydraulic hand dynamometer (Patterson Medical, Bolingbrook, IL). Patients will be tested in sitting with the feet flat on the floor, the arm at the side with the elbow flexed to 90 degrees. The patient will be instructed to maximally squeeze the handle and hold for a count of 3. The peak-hold needle will automatically record the highest force exerted. Two trials for each extremity will be done and a mean grip score calculated.

5. Arm function will be assessed using the Disability of Arm, Hand, and Shoulder (DASH) questionnaire[49] and the PROMIS Physical Function Computer Adaptive Test (PF CAT) for the Upper Extremity. The DASH is a valid and reliable 30-item self-report questionnaire that measures upper limb symptoms and ability to perform common functional activities in people with musculoskeletal disorders of the upper limb and is frequently used in LE research. DASH scores range from 0 to 100. Higher scores indicate greater limitation. The PROMIS PF CAT for the Upper Extremity is reliable[50] and addresses disability with physical activities that involve upper limb activities.[51] The PF CAT items include 5 response options, from 1 “not at all” to 5 “very much.” Total scores range from 0 to 100.
6. Quality of Life will be assessed with the the PROMIS 29 Version 2 - Participant Version and the Functional Assessment of Cancer Therapy-Breast (FACT-B),[52] The PROMIS 29 consists of 29 questions that address physical function, anxiety, depression, fatigue, sleep, social roles, and pain. Higher scores indicate higher levels of function. The FACT-B is a valid and reliable self-report instrument that measures multidimensional QOL in patients with BC.[52] The FACT-B includes 37 questions that address physical, social, emotional, and functional well-being, with specific questions relevant to women with BC.
7. Body image will be assessed using the Body Image Scale,[53] a 10-item questionnaire that gathers information about body image specifically in people with cancer. Items include 4 response options, from 1 “not at all” to 4 “very much.” The scale showed high reliability, good clinical validity, and sensitivity to change.[53]
8. Satisfaction with treatment will be evaluated at the 4-week assessment using the Functional Assessment of Chronic Illness Therapy - Treatment Satisfaction – General (FACIT-TSG- Version 4).[54]

Based on the Item Response Theory method, raw scores for the DASH and the Body Image Scale will be converted to logit scores (the natural log of the probability of obtaining a particular set of responses versus the probability of not obtaining that set of responses). This analysis will allow conversion of the raw scores to an authentic interval scale. The PROMIS instruments will be automatically scored through the PROMIS Assessment Center.

The effect size for the difference between groups in changes in total limb volume, resistance ratios, tissue indentation, shoulder range of motion and grip strength, and patient reported outcomes will be estimated as the standardized difference in means of each measure at the last assessment, and as the difference between the groups in the percent change from enrollment to the last assessment.

Aim 4: To evaluate for changes in circulating biomarkers of inflammation and fibrosis (IL-4, IL-6, IL-10, and TGF-beta 1) from enrollment to 4 weeks. Peripheral venous blood samples will be obtained before and at the completion of the intervention for assessment of circulating

biomarkers. Venous blood samples (20 ml) will be drawn from the non-LE limb at enrollment and at 4 weeks. Serum IL-4, IL-6, and IL-10, and TGF-b1 will be measured using multiplex bead assays (BioRad Luminex). Multiplex bead assays are molecular assays that permit the simultaneous measurement of an array of cytokines in a single, small volume sample to profile cytokine responses. We cannot obtain tissue biopsy samples for analysis due the inherent risk associated with skin puncture in these women at increased risk for cellulitis.

3 Study Design

3.1 Characteristics

This study is a 4-week pilot randomized, controlled, assessor blinded, trial of a novel LE treatment using a negative pressure massage device (intervention group), compared to standard manual lymph drainage massage (control group), in breast cancer patients with chronic upper extremity LE (n=80). The primary outcomes are recruitment and retention rates for both arms of the study. Secondary outcomes are total limb volume, bioimpedance resistance ratios as a measure of change in limb fluid volume, tissue indentation as a measure of change in skin and subcutaneous fibrosis, shoulder range of motion and grip strength as objective measures of upper extremity function, and PROs for arm function, QoL, body image, and circulating biomarkers of inflammation and fibrosis.

3.2 Number of Subjects

A sample size estimate was conducted to evaluate the sample size needed to compare secondary outcomes. No randomized controlled studies were identified that reported the mean difference with the SD of the difference in bioimpedance measures between groups. Thus, the effect size between the pre- and post-intervention bioimpedance measures (standardized, within-group patient change in a secondary efficacy measure) was used in the calculation of sample size for one group, based on an estimated mean change of 4 and SD of 10 (bioimpedance L-Dex units),[55] with a 2-sided alpha of 0.05, beta of 0.20, and correlation of 0.60 between the pre- and post-test bioimpedance measures. This yielded a sample size of 39 in one group, which was doubled, then rounded up to 80.

Women will be recruited from an ongoing UCSF 5-year cross-sectional study (CA187160) of 815 patients (i.e., 612 with LE and 203 without LE) that began data collection in January 2016 (>150 enrolled to date). In addition, flyers will be made available to participants at lymphedema and breast cancer conferences and patient symposia. Community collaborators (breast surgeons, lymphedema specialists, support group leaders) will be sent informational materials related to the study. Study staff will follow-up with calls and personal visits to explain the study if needed.

3.3 Eligibility Criteria

Women will be included in the parent 5-year study if they: are adults >18 years of age; have completed active treatment for breast cancer six months previously but not longer than 20 years ago; their cancer treatment included a surgical procedure, radiation therapy (RT), and/or chemotherapy (CTX); and they are mentally and physically able to participate in the study. Pre and postmenopausal women will be included. Patients with LE who received treatment for LE will not be excluded. Patients will be excluded if they have a current infection or lymphangitis involving the affected arm; have neuromuscular conditions that would affect upper limb function; have experienced recurrence of their breast cancer (local or distant); had pre-existing LE prior to their breast cancer diagnosis; or have a condition that precludes measurement of LE using bioimpedance spectroscopy (BIS). Additional criteria for eligibility into this pilot RCT are listed below.

Women recruited through community collaborators will need to meet the eligibility requirements listed below.

Patients will have baseline evaluations performed prior to the first treatment and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent will be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

To be included women must:

1. Be over 18 years of age
2. Have had cancer treatment that included a surgical procedure, radiation therapy (RT), and/or
3. chemotherapy (CTX)
4. Have completed active cancer treatment at least 1 year prior to study enrollment
5. Have been diagnosed with lymphedema (LE) at least one year prior to study enrollment
6. Have arm lymphedema on one side only
7. Have confirmed LE based on one of the following: bioimpedance measurements with an LDex score of >7.1 (which corresponds to a bioimpedance resistance ratio of 2 SD above normative values); a 2 centimeter difference in arm circumference at any single measurement site; have a 150 milliliter volume difference between arms, based on volume calculated from circumference measures; or have a volume ratio of 1.04 (affected:unaffected limb).
8. Have stable arm LE. LE will be considered "stable" if during the 3 months prior to study enrollment there was no arm infection requiring antibiotics, no change in ability to perform activities of daily living related to LE, and no subjective report of significant persistent changes in limb volume.
9. Be mentally and physically able to participate in the study.
10. Be able to attend the sessions at the UCSF Parnassus campus
11. Be able to understand a written informed consent document and the willingness to sign it

3.3.2 Exclusion Criteria

Women cannot have:

1. Bilateral upper extremity LE
2. Current infection or lymphangitis involving the affected arm
3. Current recurrence of their BC (local or distant)
4. Pre-existing LE prior to their BC diagnosis
5. Have a condition that precludes measurement of LE using BIS, including pregnancy
6. Current venous thrombosis in either upper extremity or be on current anticoagulant therapy
7. Extremity edema due to heart failure

3.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment will continue for 4 to 6 weeks (2 to 3 times per week), for a total of 12 visits or until:

- LE progression (increase in limb volume > 5%)
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the investigator.

3.5 Duration of Follow Up

Online follow up, using the NQ, will be conducted 4 months after the final visit to evaluate LE symptoms and any LE treatment sought after delivery of the intervention or control treatment.

3.6 Randomization Procedures

The study statistician, Dr. Bruce Cooper, will use SPSS to randomly assign participant id numbers to the 2 groups. An independent researcher will make and conceal random allocation cards using the computer-generated sequence. The assignment will be revealed after baseline assessment has been conducted, and the appropriate treatment will be implemented.

An assessor, blinded to group allocation, will assess each patient at enrollment (prior to allocation) and at 4 weeks. Patients will be instructed not to reveal information about group assignment to the outcomes assessor.

3.7 Study Timeline

The anticipated rate of enrollment is 5 patients per month. At this rate, the goal of 80 patients will be achieved by 16 months. This number allows for completion of the intervention by 18 months, data analysis by 20 months, and manuscript completion/grant submission by 2 years.

3.7.1 Primary Completion

The study will reach primary completion 18 months from the time the study opens to accrual.

3.7.2 Study Completion

The study will reach study completion 2 years from the time the study opens to accrual.

4 Study Intervention

The treatment device to be used in this study is the PhysioTouch (HLD Healthy Life Devices Ltd., Espoo, Finland) and is a U.S. Food and Drug Administration approved therapeutic massage device.

5 Treatment Plan

<u>Study Procedures</u>

Women with LE from the parent R01 will be invited to participate in the pilot RCT. Prior to completing the enrollment measures, patients will provide written informed consent. Then, patients will complete the enrollment questionnaires and PROs and have the following measures done: height, weight, circumference, BIS, and fibrometer.

Peripheral venous samples will be obtained before and at the completion of the intervention for assessment of circulating biomarkers. Venous blood samples will be drawn from the non-LE limb at enrollment and at the final assessment visit by the study nurses. Pre and post intervention blood samples will be obtained at the same time of day for an individual study participant.

Study design: This study will be an assessor-blinded randomized controlled trial of 80 women with LE. Women will be randomized to the intervention (PhysioTouch) or control (MLD) groups. An assessor, blinded to group allocation, will assess each patient at enrollment and at 4 weeks. Primary outcomes are recruitment and retention rates. Secondary outcomes are total limb volume, bioimpedance resistance ratios, tissue induration, shoulder range of motion, grip strength, and PROs for arm function, QOL, body image, treatment satisfaction, and biomarkers.

Data collection: All instruments will be completed and outcomes assessed at enrollment and 4 weeks. If the patient's BIS resistance ratio increases by 5% or more, she will be referred for LE management from a certified LE therapist. Enrollment and 4 week assessments will be done at the School of Nursing at the UCSF Parnassus campus

Intervention Group: The experimental group will receive 60 minutes of PhysioTouch treatment 3 times a week for 4 weeks to the lymphedematous upper limb, using the LE treatment sequence for unilateral arm LE described by Vodder.[57] Following each treatment, the patient will don her compression sleeve. The negative pressure range is 20–250 mmHg. Higher pressures are used in the axillary regions and over indurated areas.

Control Group: The control group will receive 60 minutes of MLD treatments 3 times a week for 4 weeks to their lymphedematous upper limb, using the LE treatment sequence for unilateral arm LE described by Vodder.[57] Following each treatment, the patient will don her compression sleeve.

Patients will be advised to continue usual self-care as previously instructed by a clinician, which may include use of a night compression garment, skin protection, and activity. If the woman does not have a compression sleeve, she will be asked to obtain or will be provided with one. Women will be advised not to seek out additional practitioner-delivered MLD treatments during the study period. Patients will be asked to keep a daily diary of their self-care activities. All patients will receive a LE educational pamphlet and video and will be invited to attend the UCSF LE Education class. Patients will be paid $25 at each assessment visit (enrollment and 4 weeks) for a total of $50 to improve retention. Transportation and parking costs will be reimbursed as needed.

General data analysis methods: Descriptive statistics and frequency distributions will be generated on the sample characteristics. Comparisons will be made between treatment groups on important demographic, clinical, and treatment characteristics, using independent sample t-tests, Chi-square analyses, and Mann Whitney U tests as appropriate. Unless otherwise indicated, statistical analyses will be performed using IBM SPSS Statistics Version 23 (Armonk, NY: IBM Corp.).

5.1 Monitoring and Toxicity Management

Testing will be done at the School of Nursing at the UCSF Parnassus Campus. All testing personnel are BLS certified and familiar with emergency procedures. All testing personnel are trained in physical assessment and patient safety and will monitor patient comfort and safety throughout all study visits.

Bioelectric impedance has no known side effects. However, potential patients will be excluded if they have adhesive allergies or have a pacemaker. Patients will be advised to report immediately any discomfort during all testing procedures or interventions. Patients may refuse any or all tests or interventions. Testing will be performed in a private room with the door closed.

The treatments for each arm of the study will be implemented by physical therapists who are certified LE therapists with expertise in oncology rehabilitation and LE management. They will be trained in the treatment protocol prior to study initiation with quarterly reviews thereafter.

All patients will be carefully screened for any medical problems that would preclude participation in the assessment procedures or the intervention. Screening for adverse responses will include

assessment of pain, erythema, and skin integrity at each visit, and weekly circumference monitoring. In addition, if a patient reports an exacerbation, circumference assessment will be performed. An increase in affected limb volume of 5% from enrollment levels will trigger referral to a LE therapist for further assessment**.** To monitor treatment tolerance, patients will rate current upper extremity symptoms prior to each session and will be asked if there was any change in arm swelling or interference with activities since their previous session. An increase in affected limb volume of >5% from enrollment levels will trigger referral to a LE therapist for further assessment.

Each patient will be assessed at each visit for the development of any toxicity as outlined in Section 6 Study Procedures and Observations. Toxicity will be assessed according to the NCI CTCAE v4.0.

6 Study Procedures and Observations

6.1 Schedule of Procedures and Observations

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

6.1.1 Pre-treatment Period Screening Assessments

The Screening procedures and assessments will be completed within one week of the first treatment visit:

- Demographic questionnaire
- Clinical health history questionnaire including information regarding BC treatments, menopausal status, duration of lymphedema, prior LE treatment, and current LE management strategies
- Karnofsky Performance Scale[58,59]
- Self-Administered Comorbidity Questionnaire[60]
- Symptom questionnaires
- Patient Reported Outcomes: DASH, PROMIS Physical Function Computer Adaptive Test (PF CAT) for the Upper Extremity, the PROMIS 29 Version 2, FACT-B, and the Body Image Scale)
- Height and weight
- Upper extremity circumference measurement
- Bioimpedance assessment
- Tissue induration

Peripheral venous blood samples will be obtained before the intervention for assessment of circulating biomarkers. Venous blood samples will be drawn from the non-LE limb. Blood draws will be done at the School of Nursing at the UCSF Parnassus campus.

6.1.2 Treatment Period Study Procedures

- Intervention Group: The experimental group will receive 60 minutes of PhysioTouch treatment 2 to 3 times a week for 4 to 6 weeks, for a total of 12 treatments sessions, to the lymphedematous upper limb, using the LE treatment sequence for unilateral arm LE described by Vodder.[57] Following each treatment, the patient will don her compression sleeve. The negative pressure range is 20–250 mmHg. Higher pressures are used in the axillary regions and over indurated areas.
- Control Group: The control group will receive 60 minutes of MLD treatments 2 to 3 times a week for 4 to 6 weeks, for a total of 12 sessions, to their lymphedematous upper limb, using the LE treatment sequence for unilateral arm LE described by Vodder.[57] Following each treatment, the patient will don her compression sleeve.
- Both groups:
    - Patients will be advised to continue usual self-care as previously instructed by a clinician, which may include use of a night compression garment, skin protection, and activity. If the woman does not have a compression sleeve, she will be asked to obtain or will be provided with one. Women will be advised not to perform self-MLD or seek out additional practitioner-delivered MLD treatments during the study period. Patients will be asked to keep a daily diary of their self-care activities. All patients will receive a LE educational pamphlet and video and will be invited to attend the UCSF LE Education class.
    - Patients will be asked at each treatment session about new or changing upper extremity symptoms, changes in upper extremity function, or subjective changes in limb volume. Screening for pain, erythema, and skin integrity will be performed at each visit.
    - Circumference will be assessed at the end of each week.

6.1.3 Post-Treatment Study Procedures

To be completed within one week of the last treatment.

- Karnofsky Performance Scale[58,59]
- Self-Administered Comorbidity Questionnaire[60]
- Symptom questionnaires
- Patient Reported Outcomes: DASH, PROMIS Physical Function Computer Adaptive Test (PF CAT) for the Upper Extremity, the PROMIS 29 Version 2, FACT-B, and the Body Image Scale)
- Upper extremity circumference measurement
- Bioimpedance assessment
- Tissue induration
- Treatment satisfaction

Peripheral venous blood samples will be obtained after the intervention for assessment of circulating biomarkers. Venous blood samples will be drawn from the non-LE limb.

Online follow up, using the NQ, will be conducted 4 months after the final visit to evaluate LE symptoms and any LE treatment sought after delivery of the intervention or control treatment.

6.1.4 Discontinuation of Therapy

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or an concurrent illness, a patient's request to end participation, a patient's non-compliance or simply significant uncertainty on the

part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

Table 6.1 Schedule of Study Procedures and Assessments

Procedure	Pre-treatment screening	Week 1	Week 2	Week 3	Week 4	End of Treatment visit	*4 month online follow up*
Informed consent	X						
Venipuncture	X					X	
Demographic questionnaire	X						
Karnofsky Performance Scale	X					X	
Self-Administered Comorbidity Questionnaire	X					X	
Symptom Questionnaire	X					X	X (Norman)
Patient reported outcomes (DASH, PROMIS measures, FACT-B, Body Image)	X					X	
Height	X						
Weight	X						
Limb volume (circumference)	X	X	X	X	X	X	
Bioimpedance	X					X	
Tissue induration	X					X	
Shoulder mobility and grip strength	X					X	
Numbers of women screened and enrolled as well as completion rates for each arm of the study, will be recorded.						X	
Treatment satisfaction						X	
AE assessment		X	X	X	X	X	

6.2 Usage of Concurrent/Concomitant Medications

N/A

6.3 Dietary Restrictions

None

6.4 Prohibited Medications

None

7 Reporting and Documentation of Results

7.1 Evaluation of Efficacy (or Activity)

Patients who receive at least one treatment and have their status re-evaluated will be considered evaluable for response.

To evaluate responses to treatment, comparison of changes in the intervention group (negative pressure device) to changes in the control group (MLD), following the 4-week study will be done by calculation of effect sizes for:

- Total limb volume calculated from limb circumference measurements
- Bioimpedance resistance ratios as a measure of change in limb fluid volume
- Tissue indentation as a measure of induration
- Upper extremity function (Shoulder flexion and abduction range of motion; grip strength)
- Patient reported outcomes (DASH, QoL, Body Image, Treatment Satisfaction):

The effect size for the difference between groups in changes limb volume, resistance ratios, tissue indentation, shoulder range of motion, grip strength, and in patient reported outcomes will be estimated as the standardized difference in means of each measure at the last assessment, and as the difference between the groups in the percent change from enrollment to the last assessment.

Circulating cytokines and growth factors: Peripheral venous blood samples will be obtained before and at the completion of the intervention. Serum IL-4, IL-6, and IL-10, and TGF-b1 will be measured using multiplex bead assays (BioRad Luminex). Multiplex bead assays are molecular assays that permit the simultaneous measurement of an array of cytokines in a single, small volume sample to profile cytokine responses.

7.2 Evaluation of Safety

All patients will be carefully screened for any medical problems that would preclude participation. All testing personnel are BLS certified and familiar with emergency procedures. All testing personnel are trained in physical assessment and patient safety and will monitor patient comfort and safety throughout all study visits.

Bioelectric impedance has no known side effects. However, potential patients will be excluded if they have adhesive allergies or have a pacemaker. Patients will be advised to report

immediately any discomfort during all testing procedures or interventions. Patients may refuse any or all tests or interventions. Testing will be performed in a private room with the door closed.

The treatments for each arm of the study will be implemented by physical therapists who are certified LE therapists with expertise in oncology rehabilitation and LE management. They will be trained in the treatment protocol prior to study initiation with quarterly reviews thereafter.

Safety analyses will involve examination of the incidence, severity, and type of treatment-emergent adverse events and changes in subjective and objective measures from enrollment to 4 weeks. To monitor treatment tolerance, patients will rate current upper extremity symptoms prior to each session and will be asked if there was any change in arm swelling or interference with activities since their previous session. Screening for adverse responses will include assessment of pain, erythema, and skin integrity at each visit, and weekly circumference monitoring. An increase in affected limb volume of 5% from enrollment levels will trigger referral to a LE therapist for further assessment. Safety analyses will involve examination of and comparison between groups for the incidence, severity, and type of treatment-emergent adverse events. The numbers of patients whose circumference volume and/or BIS resistance ratio increases by 5% or more will be compared between groups. Telephone follow up, using the NQ, will be conducted 4 months after the final visit to evaluate LE symptoms and any LE treatment sought after delivery of the intervention or control treatment.

Each patient will be assessed at each visit for the development of any toxicity as outlined in Section 6 Study Procedures and Observations. Toxicity will be assessed according to the NCI CTCAE v4.0.

7.3 Definitions of Adverse Events

7.3.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the treatment in humans, whether or not considered treatment related. More specifically, an adverse event (can be any unfavorable and unintended sign, symptom, or disease temporally associated with the intervention, without any judgment about causality.

7.3.2 Adverse reaction

An adverse reaction is defined as any adverse event caused by the intervention. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the intervention caused the event.

7.3.2.1 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the intervention caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.3.2.2 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent

with the risk information described in the general investigational plan or elsewhere in the current application.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

7.3.2.3 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.3.2.4 Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.4 Recording of an Adverse Event

All grade 3 and above adverse events will be entered into OnCore®, whether or not the event is believed to be associated with the study intervention. Data about these events and their severity will be recorded using the NCI CTCAE v4.0.

The Investigator will assign attribution of the possible association of the event with use of the intervention, and this information will be entered into OnCore® using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0	No AE (or within normal limits)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4:	Life-threatening consequences; urgent intervention indicated
Grade 5:	Death related to AE

7.5 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.6 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the intervention, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board, the Committee on Human Research (CHR).

All adverse events entered into OnCore® will be reviewed by the Helen Diller Family Comprehensive Cancer Center Site Committee on a weekly basis. The Site Committee will review and discuss at each weekly meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study treatment(s).

In addition, all adverse events and suspected adverse reactions considered "serious," entered into OnCore® will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis, discussed at DSMC meetings which take place every six (6) weeks.

7.7 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study and it is determined to be related to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Committee on Human Research (Institutional Review Board)

The Principal Investigator must report events meeting the UCSF CHR definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

Statistical Considerations and Evaluation of Results

8.1 Study Endpoints

Study Design

This study proposed in this application is a 4-week pilot randomized, controlled, assessor blinded, trial of a novel LE treatment using a negative pressure massage device (intervention group), compared to standard manual lymph drainage massage (control group), in breast cancer patients with chronic upper extremity LE. Patients will receive treatment 2 to 3 times per week for 4 to 6 weeks, for a total of 12 treatment sessions. An assessor, blinded to group allocation, will assess each patient at enrollment and at 4 to 6 weeks. The study will be a single center study conducted at the University of California San Francisco.

8.1.2 Randomization

Study statistician, Dr. Bruce Cooper, using a computer-generated program, will randomize patients to the intervention (PhysioTouch) or control (MLD) groups. Patients will be instructed not to reveal information about group assignment to the outcomes assessor.

8.2 Determination of Sample Size and Accrual Rate

8.2.1 Sample Size and Power Estimate

A sample size estimate was conducted. No randomized controlled studies were identified that reported the mean difference and SD of the difference in bioimpedance measures between groups. Thus, the effect size between the pre- and post-intervention bioimpedance measures (standardized, within-group patient change in a secondary efficacy measure) was used in the calculation of sample size for one group, based on an estimated mean change of 4 and SD of 10 (continuous bioimpedance L-Dex units,), with a 2-sided alpha of 0.05, beta of 0.20, and correlation of 0.60 between the pre- and post-test bioimpedance measures. This yielded a sample size of 39 in one group, which was doubled, then rounded up to 80.

8.2.2 Replacement Policy

Withdrawals will be replaced.

8.2.3 Accrual estimates

Women will be recruited from the 5-year cross-sectional study (CA187160) of 815 patients (i.e., 612 with LE and 203 without lymphedema) that began data collection in January 2016 (>100 enrolled to date). Given that the parent study will recruit 612 patients with lymphedema, and the overwhelmingly positive responses from women to our previous studies, we do not anticipate problems recruiting the numbers of patients (n=80) needed for the pilot study.

The anticipated rate of enrollment is 5 patients per month. At this rate, the goal of 80 patients will be achieved by 16 months. This number allows for completion of the intervention by 18 months, data analysis by 20 months, and manuscript completion/grant submission by 2 years.

8.3 Interim Analyses and Stopping Rules

Recruitment and enrollment rates will be continuously monitored. Interim analyses of secondary outcomes will not be performed. The number of SAEs overall will be monitored. If the SAE is found to be related to the intervention, the study will be stopped. However, serious adverse events are not expected to occur during this study.

The risk to patients for injury or LE exacerbation due to the experimental or control treatments is anticipated to be minimal. MLD involves a very light massage technique that will be applied to the upper extremity. The suction pressure applied to the skin through the negative pressure device is low and will be provided within the limits of patient tolerance. However, if the negative pressure device results in an increase in >5% volume in 10% of anticipated enrollment, the study will be stopped.

8.4 Analyses Plans

Descriptive statistics and frequency distributions will be generated on the sample characteristics. Careful consideration will be given regarding evaluation of all demographic, clinical, and treatment characteristics as potential covariates. Comparisons will be made between treatment groups on important demographic, clinical, and treatment characteristics, using independent sample t-tests, Chi-square analyses, and Mann Whitney U tests as appropriate. Unless otherwise indicated, statistical analyses will be performed using IBM SPSS Statistics Version 23 (Armonk, NY: IBM Corp.)

The study biostatistician, Dr. Bruce Cooper (School of Nursing) will provide oversight of statistical analysis.

8.4.1 Analysis Population

All patients will be included in each analysis.

8.4.2 Primary Analysis

Aim 1: To determine the recruitment and retention rates for both arms of this 4-week, pilot study, the numbers of women screened and enrolled as well as completion rates for each arm of the study, will be recorded. Feasibility of recruitment, randomization, retention, assessment procedures, and implementation of the novel intervention will be evaluated. Information regarding treatment satisfaction will be collected. These assessments will be used to determine whether or not a larger, hypothesis-testing RCT to assess the efficacy of this intervention is feasible and warranted and if modifications are needed.

Aim 2: To evaluate safety of and tolerability to the intervention and control treatments, safety analyses will involve examination of the incidence, severity, and type of treatment-emergent adverse events and changes in subjective and objective measures from enrollment to 4 weeks. To monitor treatment tolerance, patients will rate current upper extremity symptoms prior to each session and will be asked if there was any change in arm swelling or interference with activities since their previous session. Screening for adverse responses will include assessment of pain, erythema, and skin integrity at each visit, and weekly circumference monitoring. An

increase in affected limb volume of 5% from enrollment levels will trigger referral to a LE therapist for further assessment. Safety analyses will involve examination of and comparison between groups for the incidence, severity, and type of treatment-emergent adverse events. The numbers of patients whose circumference volume and/or BIS resistance ratio increases by 5% or more will be compared between groups. Telephone follow up, using the NQ, will be conducted 4 months after the final visit to evaluate LE symptoms and any LE treatment sought after delivery of the intervention or control treatment.

We will compare the frequencies of adverse events between groups using Chi-square or Fisher's exact tests.

8.4.3 Secondary Analysis

To evaluate responses to treatment, comparison of changes in the intervention group (negative pressure device) to changes in the control group (MLD), following the 4-week study will be done by calculation of effect sizes for:

- Total limb volume calculated from limb circumference measurements
- Bioimpedance resistance ratios as a measure of change in limb fluid volume
- Tissue indentation as a measure of change in skin and subcutaneous induration/fibrosis: The mean induration value, in Newtons, will be calculated from 5 recordings, at each location.
- Shoulder range of motion and grip strength as objective measures of upper extremity function. Shoulder range of motion will be measured in degrees and grip strength in kilograms of force.
- Patient reported outcomes (DASH, QoL, Body Image, Treatment Satisfaction): Based on the Item Response Theory method, raw scores for the DASH and the Body Image Scale will be converted to logit scores (the natural log of the probability of obtaining a particular set of responses versus the probability of not obtaining that set of responses). This analysis will allow conversion of the raw scores to an authentic interval scale. The PROMIS instruments will be automatically scored through the PROMIS Assessment Center.

The effect size for the difference between groups in changes limb volume, resistance ratios, tissue indentation, shoulder range of motion, grip strength, and in patient reported outcomes will be estimated as the standardized difference in means of each measure at the last assessment, and as the difference between the groups in the percent change from enrollment to the last assessment.

Means and standard deviations for continuous data and frequencies and percents for categorical variables will be determined for baseline demographic and clinical characteristics and compared using independent t-tests, Mann-Whitney U, or chi square analysis as appropriate.

In addition to calculating between-groups effect sizes, we will compare differences in efficacy outcomes between groups using statistical tests of hypotheses. All outcomes will be treated as continuous data. Independent t-tests will be used to compare normally distributed outcomes; the Mann-Whitney U test will be used to compare data that violates the assumptions for parametric tests. Statistical significance will be set at $p > 0.05$.

We will evaluate for changes in circulating biomarkers of inflammation and fibrosis following treatment. For this exploratory aim, means and standard deviations will be calculated for enrollment and post-intervention levels of IL-4, IL-6, IL-10, and TGF-b1.

8.5 Evaluation of Safety

Analyses will be performed for all patients having received at least one treatment. The study will use the NCI CTCAE v4.0.

All patients will be carefully screened for any medical problems that would preclude participation in the assessment procedures and the intervention.

To evaluate safety of and tolerability to the intervention and control treatments, safety analyses will involve examination of the incidence, severity, and type of treatment-emergent adverse events and changes in subjective and objective measures from enrollment to 4 weeks. To monitor treatment tolerance, patients will rate current upper extremity symptoms prior to each session and will be asked if there was any change in arm swelling or interference with activities since their previous session. Screening for adverse responses will include assessment of pain, erythema, and skin integrity at each visit, and weekly circumference monitoring. An increase in affected limb volume of 5% from enrollment levels will trigger referral to a LE therapist for further assessment. Safety analyses will involve examination of and comparison between groups for the incidence, severity, and type of treatment-emergent adverse events. The numbers of patients whose circumference volume and/or BIS resistance ratio increases by 5% or more will be compared between groups. Online follow up, using the NQ, will be conducted 4 months after the final visit to evaluate LE symptoms and any LE treatment sought after delivery of the intervention or control treatment.

We will compare the frequencies of adverse events between groups using Chi-square or Fisher's exact tests.
The risk to patients for injury or LE exacerbation due to the experimental or control treatments is anticipated to be minimal. MLD involves a very light massage technique that will be applied to the upper quadrant of the affected arm.

8.6 Study Results

Recruitment and retention rates, the numbers of women screened and enrolled as well as completion rates for each arm of the study will be recorded.

Responses to treatment will be reported as effect sizes and 95% confidence intervals for total limb volume calculated from limb circumference measurements, bioimpedance resistance ratios as a measure of change in limb extracellular fluid volume, tissue indentation as a measure of change in skin and subcutaneous induration/fibrosis (in Newtons), shoulder range of motion (degrees), grip strength (kilograms of force) and patient reported outcomes (i.e., DASH, PROMIS measures, QoL, Body Image, and Treatment Satisfaction).

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment

materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects. .

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF CHR (UCSF Institutional Review Board). Prior to obtaining CHR approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the CHR-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF CHR, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the CHR prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to CHR approval. In this circumstance, however, the Investigator must then notify the CHR in writing within five (5) working days after implementation.

9.5 Case Report Forms (CRFs)

The Principal Investigator will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis.

All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit. The Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

9.6 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered “serious”. The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 1 Data and Safety Monitoring Plan.

9.7 Record Keeping and Record Retention

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational intervention or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, , monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

10 Protection of Human Subjects

Participant protection is accomplished through the CHR mechanism and the process of informed consent. The CHR reviews all proposed studies involving human experimentation and ensures that the subject’s rights and welfare are protected and that the potential benefits and/or

the importance of the knowledge to be gained outweigh the risks to the individual. The CHR also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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Appendix 1 Data and Safety Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study include:

- Review of subject data
- Review of suspected adverse reactions considered "serious"
- Biannual auditing (depending on study accrual)
- Minimum of a yearly regulatory audit

Monitoring and Reporting Guidelines

Investigators will conduct continuous review of data and subject safety and discuss each participant's treatment at twice monthly meetings. These discussions will be documented in the meeting minutes. The discussion will include the number of patients, significant toxicities in accordance with the protocol, and observed responses.

Adverse Event Review and Monitoring

All clinically significant adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study intervention, will be entered into OnCore®, UCSF's Clinical Trial Management System

In addition, all suspected adverse reactions considered "serious," entered into OnCore® will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six (6) weeks.

If a death occurs during the treatment phase of the study and it is determined to be related either to the study procedure, the Investigator or his/her designee must notify the DSMC Chair within **1 business day** of knowledge of the event. The contact may be by phone or e-mail.

If at any time the Investigator stops enrollment or stops the study due to safety issues the DSMC Chair and administrator must be notified within **1 business day** via e-mail. The DSMC must receive a formal letter within **10 business days** and the IRB must be notified.

Data and Safety Monitoring Committee Contacts:

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* DSMP approved by NCI 09/February2012