An investigator-initiated study assessing the effect of intermittent pneumatic compression (IPC) on symptoms and quality of life in women with lipo-lymphedema (lipedema with swelling)

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TABLE OF CONTENTS

1.0 Contact Information

1.1 Sponsor and Principal Investigator Contact Information

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2.0 Introduction

2.1 Background and Rationale

Lipedema is a connective tissue disorder that affects up to 10% of women. It is characterized by painful, swollen subcutaneous tissue and disproportionate fat accumulation (primarily in the lower limbs, however it can spread to the abdomen and arms). Patients are often not aware they are affected by this disease; rather, they think they are just overweight or obese.

Patients with lipedema often feel frustrated and uncomfortable as symptoms such as heaviness, pain, and easy bruising impact quality of life. Affected limbs can become so large and heavy that daily tasks such as walking, cleaning, or shopping become impossible.

Lipedema is a progressive disease. There are currently 3 primary stages that describe disease severity: stage 1 involves thickening of subcutaneous tissue and disproportion accumulation of subcutaneous tissue in the extremities (tissue remains smooth and is generally not heavy or swollen), stage 2 is characterized by increased fibrous tissue, leading to a nodular feel in the subcutaneous tissue which results in increased swelling and tenderness of the affected areas, stage 3 involves progression to the formation of lobules of skin and subcutaneous tissue. Symptomatic lipedema patients at stage 2 and higher almost always have secondary swelling on physical exam. This swelling results from the fat on the legs, thighs, and ankles blocking transport of lymphatic fluid; which ultimately may lead to infection. This lipo-lymphedema (or lipedema with swelling) is a secondary lymphedema, much like veno-lymphedema, and can be easily distinguished from primary lymphedema as it spares the hands and feet.

There is currently no cure for lipedema, thus treatment focuses on symptom management and improved patient-reported outcomes. At present, the two main courses of treatment include non-surgical conservative treatment (e.g., Comprehensive Decongestive Therapy (CDT), diet, exercise, emotional/psychological/social support) and lymph-sparing liposuction performed by a surgeon trained in lipedema treatment. The primary goals for treatment include: reduction/elimination of inflammation, swelling, and pain; increase in lymphatic flow, which reduces/eliminates excessive fluid and swelling; overall management of the physical impact of lipedema; and quality of life improvements

which can include emotional, psychological/mental, spiritual, and social enhancement in addition to physical management.

Intermittent Pneumatic Compression (IPC) devices are often used as home-therapy to treat secondary lymphedema or lipo-lymphedema (lipedema with swelling) and may be helpful in preventing the progression of lipedema. IPC use moves lymphatic fluid and supports the elimination of proteinaceous fluids, thus leading to improved patient-reported symptoms, decreased limb girth and volume, increased elasticity of tissues, and fewer episodes of infection (1-3). Szolnoky reported daily treatment with CDT, IPC, and multilayered short-stretch bandaging performed for 5 days led to significant improvements in leg volume, capillary fragility, and pain in women with lipedema (4).

The purpose of this study is to assess whether 3-4 weeks of IPC usage is associated with alleviation of symptoms and improvement in quality of life in women with lipo-lymphedema (lipedema with swelling).

2.2 Ethics

This study will be submitted to a central IRB for approval to begin research and study oversight.

Informed consent will be conducted by a member of the research team. When possible, a copy of the consent will be provided to the study candidate prior to the clinic visit. At the first clinic visit, a private room will be used to review the consent with the candidate and to answer any questions or concerns they may have regarding participation in the research study.

2.3 Device Description

2.3.1 Flexitouch Plus

The Flexitouch Plus (Tactile Medical™, Minneapolis, MN, USA) is a segmental, programmable, gradient advanced pneumatic compression device cleared for market in the USA (K170216, HCPCS code E0652). The device stimulates the lymphatic system by directing and moving excess fluid from an impaired lymphatic region to healthy regions where fluid can be absorbed and processed naturally by the body.

The system consists of two primary components: a controller unit and garments. The controller unit has connector outlets for garment hoses to plug into such that air can pass through the hoses and deliver treatment through sequential inflation and deflation of air chambers within the garments. The garments are constructed of nylon and have 27-32 chambers, depending upon garment size. The pressure setting is variable between “decreased,” “normal,” and “increased.”

The device is intended to provide in-home Manual Lymphatic Drainage (MLD) therapy for approximately 1 hour treatment duration. Indications for use include lymphedema, primary lymphedema, post-mastectomy edema, edema following trauma and sports injuries, post immobilization edema,

venous insufficiency, reducing wound healing time, and treatment and assistance in healing stasis dermatitis, venous stasis ulcers, or arterial and diabetic leg ulcers.

2.3.2 Conservative Care

Standard care for patients under the Principal Investigator's care includes 30-40 mmHg graduated compression up to waist, dietary counseling, exercise, and a referral for Complete Decongestive Therapy (CDT). Based on each patient's situation (e.g., insurance coverage, willingness/ability to independently comply with care, time constraints, etc.), some or all of these recommendations are typically followed. In this "real-world" study, no attempt is being made to control what will or won't be used in terms of conservative care since it varies in clinic practice for each patient.

3.0 Study Objective

The primary objective of the study is to assess the effectiveness of bilateral Flexitouch Plus use with conservative care based upon:

- Circumferential measurements at ankle, mid-calf, lower thigh, upper thigh, hip, and waist,
- Quality of life (RAND 36-Item Health Survey 1.0), and
- Patient-reported symptoms and pain intensity (PROMIS Pain Interference – Short Form 6b, Wong-Baker Faces Scale, and the NIH Toolbox numerical rating scale (NRS)).

Exploratory endpoints include:

- Mobility (PROMIS Mobility v2.0), and
- Bioimpedance measurements (Whole Body and Segmental Extracellular Water/Total Body Water (ECW/TBW) ratios using InBody 770).
- Comparing all objectives and endpoints between treatment groups.

4.0 Study Design

This is a prospective, randomized, two-arm study comparing Flexitouch Plus with conservative care to conservative care alone (Figure 1). This post-market study involves on label use of the Flexitouch Plus device given eligible patients must have concurrent diagnosis with lymphedema (as noted by Stage 2/3 lipedema with presence of secondary swelling upon physical exam) and obtain the device through normal commercial means (self-pay, patient assistance, or insurance programs).

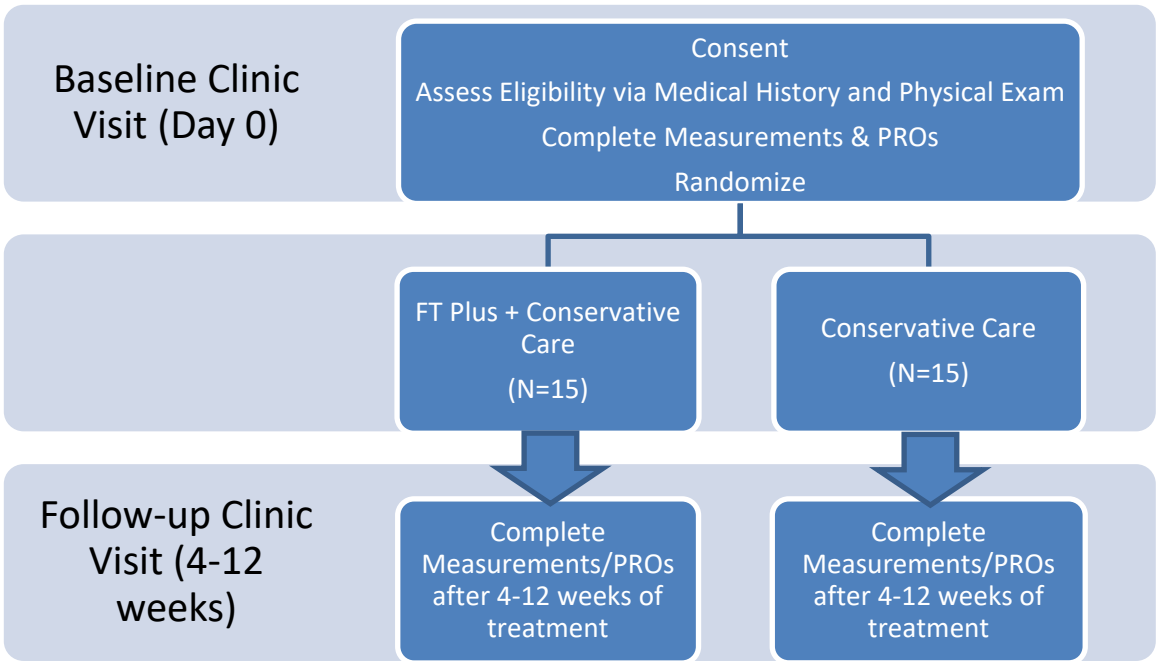

Figure 1. Study Design

4.1 Endpoint Mapping

Endpoint	Outcome Measure	Analysis
Primary	• Circumferential Measurements	• Calculate percent reduction at Follow-up compared to Baseline for 6 sites on each leg as well as a composite total.
Primary	• Quality of Life	• Compare Follow-up RAND SF36 score to Baseline.[1]
Primary	• Symptoms & Pain Intensity	• Compare Follow-up PROMIS Pain Interference[2], Wong-Baker Faces Scale, and the NIH Toolbox numerical rating scale (NRS) scores to Baseline.
Exploratory	• Mobility	• Compare Follow-up PROMIS Mobility score to Baseline.[2]

[1] https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html

[2] http://www.healthmeasures.net/index.php?option=com_instruments&task=Search.pagination&Itemid=992

Endpoint	Outcome Measure	Analysis
Exploratory	• Bioimpedance Measurements	• Calculate mean reduction at Follow-up compared to Baseline for the Segmental (Right/Left Arm/Leg, Trunk) and Whole Body Extracellular Water (ECW)/Total Body Water (TBW) ratios.

4.2 Subject Selection

The target population includes patients who have bilateral lipedema, meet the criteria listed below, and have provided informed consent.

4.2.1 Inclusion Criteria:

1. Female age 18-70 years.
2. Stage 2-3 (Schmeller Type 2-3) lipedema with secondary lymphedema.
3. Willing and able to follow prescribed care for study period.
4. Able to access (via self-pay, patient assistance, or insurance programs) prescribed care within 60 days of Baseline visit.

4.2.2 Exclusion Criteria:

1. BMI > 50.
2. Heart failure (acute pulmonary edema, decompensated acute heart failure).
3. Pacemaker or implantable cardioverter defibrillator (ICD).
4. Acute venous disease (acute thrombophlebitis, acute deep venous thrombosis, acute pulmonary embolism).
5. Severe peripheral artery disease (critical limb ischemia including ischemic rest pain, arterial wounds, or gangrene).
6. Active skin or limb infection/inflammatory disease (acute cellulitis, other uncontrolled skin or untreated inflammatory skin disease) on the arms or trunk.
7. Active cancer (cancer that is currently under treatment, but not yet in remission).
8. Poorly controlled kidney disease (glomerular filtration rate < 30 mls per minute), hypoproteinemia, pulmonary hypertension, hypothyroidism, cyclic edema, or Munchausen Syndrome.
9. Any circumstance where increased lymphatic or venous return is undesirable.

10. Currently pregnant or trying to become pregnant.

4.3 Point of Enrollment

Subjects will be considered enrolled in the study once the Informed Consent Form is signed and eligibility criteria are met. The investigator will keep a record, or subject screening log, of subjects who enter screening. Any subjects who do not meet inclusion/exclusion criteria will be considered screen failures.

4.4 Treatment Assignment and Duration

Eligible patients will be randomized (1:1) using sealed envelopes to one of the following treatment cohorts:

- Conservative care alone (may include 30-40 mmHg graduated compression up to waist, dietary counseling, exercise, and/or referral for CDT); or
- Flexitouch Plus with conservative care.

Following randomization, a product demo may take place to confirm the subject is able to tolerate prescribed care.

4.5 Study Timeline

The expected study duration is approximately 24 months with 1 month spent in activation, 21 months enrolling and following subjects, and 2 months completing the data analysis.

5.0 Study Assessment

Case Report Forms (CRFs) and Data Clarification Forms (DCFs) will be used for data collection and query handling. The Investigator will ensure the accuracy, completeness, and timeliness of the data recorded.

All data will be entered into an Excel spreadsheet and validated to confirm integrity of data entry. Data may be transferred to an electronic data capture system at some point. When all data have been coded, validated, and signed, the database will be locked (password protected with copy saved as PDF), and available for analysis.

The study schedule of activities is shown in Table 1.

Table 1. Schedule of Activities

Procedures	**Baseline (Day 0)**	**Follow-up (4-12 weeks)**
Informed Consent	X	
Demographics & Medical History	X	
Inclusion/Exclusion Assessment	X	
Pregnancy Test (if applicable)	X	
Vitals	X	X
Physical Exam	X	X
Circumferential Measurements	X	X^
Bioimpedance Measurements	X	X^
QOL Assessment (RAND SF-36)	X	X
Mobility Assessment (PROMIS Mobility)	X	X
Symptom & Pain Intensity Assessment (PROMIS Pain Intensity, NRS Pain & Symptom Scale, Wong-Baker Faces Scale)	X	X
Randomization	X	
Training on Flexitouch Plus and/or Conservative Care*	X	
Adverse Event, Complication, & Device Observation Assessment	X	X

* If subject is unable to obtain prescribed care and complete training on use within 60 days of the Baseline visit (e.g., due to insurance coverage/scheduling delays, etc.), the subject will be considered a screen failure.

^ Optional: Circumferential and bioimpedance measurements may be taken again after an in-clinic treatment with Flexitouch Plus.

6.0 Study Procedures

6.1 Informed Consent

Subjects will need to sign an informed consent form that has been approved by both the Sponsor and reviewing IRB to be considered for participation in this study. Subjects must meet all of the inclusion and none of the exclusion criteria.

Each subject (or a legally authorized representative) must give written consent, in accordance with local requirements, after the nature of the study has been fully explained and questions answered. The consent form must be signed prior to any study-related procedures, and the process of informed consent must be documented in the medical record.

6.2 Demographics & Medical History

Demographics will be collected including age, ethnicity, race, and sex. Significant medical history, including lipedema and lymphedema history, will be collected.

6.3 Laboratory Testing

Any women who are not surgically sterile or ≥1 year post-menopause will be tested for pregnancy according to the site specific procedures at the Baseline visit. If the pregnancy test is positive, the subject will not be enrolled in the study.

Subjects must agree to use one of the following forms of birth control prior to starting and during treatment with the Flexitouch:

- Abstinence (not having sexual relations with a person of the opposite sex)
- Implantable hormone (e.g. Norplant)
- Intrauterine Device
- Male partner must have a vasectomy
- Female sterilization
- Hormonal injection
- Oral contraceptives

6.4 Vital Signs

Height and weight (without shoes or coat) will be collected at Baseline and Follow-up. Results will be recorded on the respective data collection forms. If the BMI is > 50 at the Baseline visit, the subject will not be enrolled in the study.

6.5 Randomization

If the subject meets all of the inclusion criteria and none of the exclusion criteria, they will be randomly assigned to Flexitouch Plus with conservative care or conservative care alone. Randomization codes will be generated in a permuted block design. The block size will be balanced within each block, and will maintain a 1:1 ratio between the treatment groups.

The randomization code will be distributed by sealed envelope and assigned sequentially as soon as an eligible subject completes the Baseline measurements. The appropriate staff member will obtain the next sequentially sealed randomization envelope and open it while the subject is present.

The randomization assignment cannot be changed or chosen by the subject or the investigator. The randomization envelope, as well as evidence of treatment group assignment, should be placed in the subject's binder.

6.6 InBody 770 Bioimpedance Measurements

The InBody is a medical-grade bioimpedance device that measures body water and composition, providing objective measures of fluid and muscle-fat balance. The unit is non-invasive and generates a comprehensive results sheet that provides accurate, objective, and easily understandable measurements in less than 60 seconds to evaluate a patient's current health status and track efficacy of treatments and interventions. Clinicians can use the InBody to: monitor body water and composition for early detection and treatment of lymphedema, identify fluid imbalances through tracking segmental body water values and edema index variables, and evaluate additional health risks related to muscle-fat balance.

For the purposes of this study, bioimpedance measurements will be collected at the beginning of the Baseline and Follow-up visit (immediately before and after removal of graduated compression). Subjects will be asked to:

- Stand on the InBody 770 with graduation compression on (covering the foot and heel pads while holding the hand pieces). The arms will then be raised up and away from the trunk for 20 seconds while the testing begins.
- Remove shoes and socks, clean hands and feet with a wipe, and stand on the InBody 770 (covering the foot and heel pads while holding the hand pieces). The arms will then be raised up and away from the trunk for 20 seconds while the testing begins.

Data from the Body Water and Composition Analysis will be recorded on the respective data collection forms and a copy of each comprehensive results sheet will be retained in the subject's medical record (Figure 2 and 3).

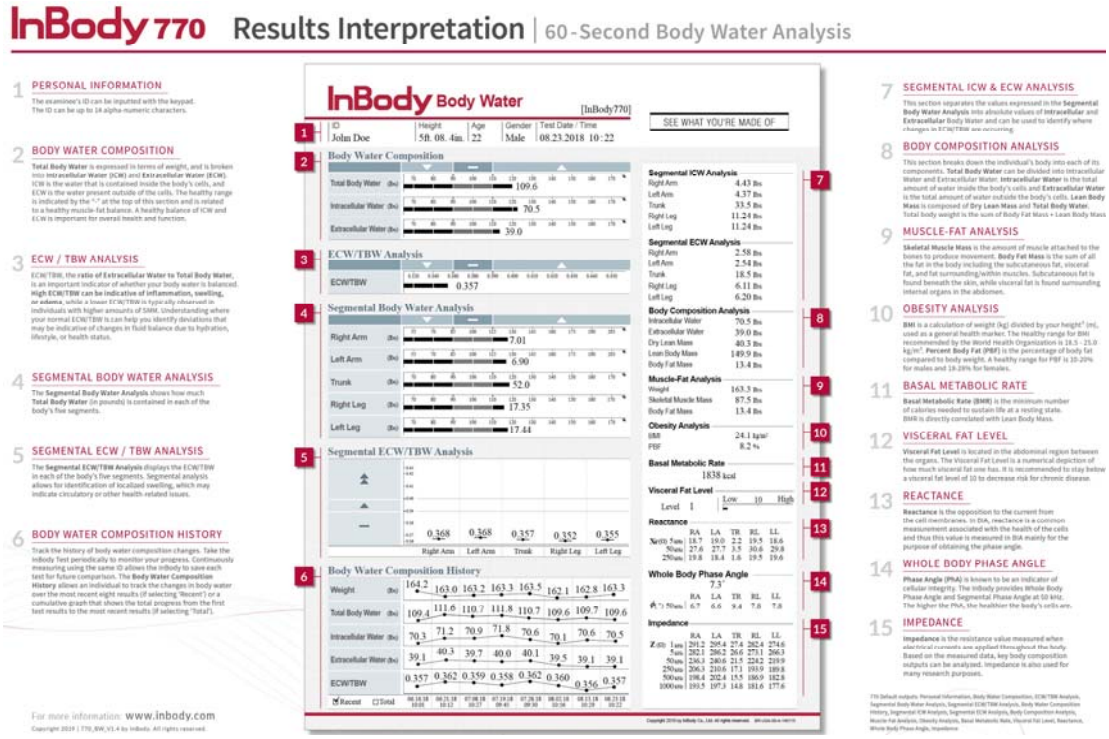

Figure 2. Body Water Analysis

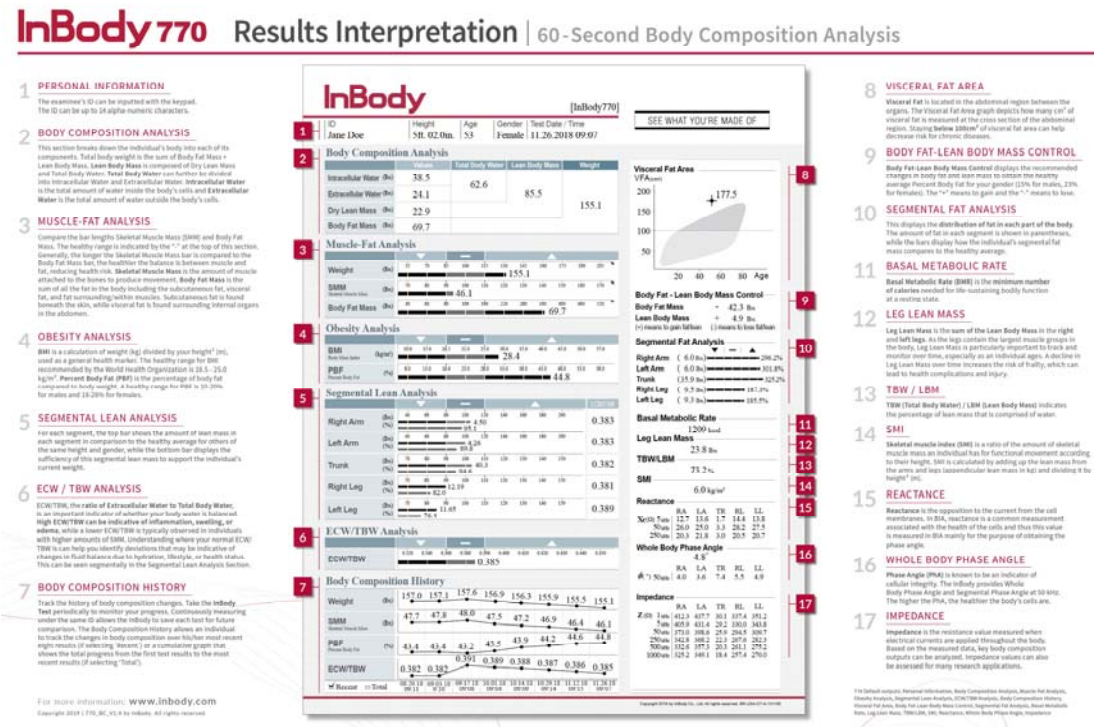

Figure 3. Body Composition Analysis

At the Follow-up visit, additional bioimpedance measurements (including whole body ECW/TBW ratio, as well as segmental ratios for the Right/Left Arm, Right/Left Leg, and Trunk) may be collected immediately after an approximately 60-minute in-clinic treatment with FT Plus. The measurements will be collected and recorded in the same fashion outlined above.

Generally speaking, if there is any type of inflammation or water retention occurring in the body, body water will accumulate in the extracellular space. Thus, injuries, disease, aging, high sodium diets, as well as low muscle mass, will cause the ECW/TBW to increase. The unit renders a whole body ECW/TBW ratio, as well as segmental ratios for the Right/Left Arm, Right/Left Leg, and Trunk. A whole body or segmental ECW/TBW ratio of >0.39 is considered abnormal. The segmental ratios are used to identify problem areas for fluid retention and inflammation. A 0.005 difference in ECW/TBW between right and left limbs may be indicative of inflammation or water retention. Larger discrepancies are required between upper and lower body given the legs have a slightly higher ECW/TBW ratio due to gravity and increased blood volume.

6.7 Circumferential Measurements

Circumferential measurements will be taken at Baseline and Follow-up per standard care at the beginning of the visit at 4 sites on each leg (immediately after biocompression measurements and the removal of graduated compression), 1 site at the hips, and 1 site at the waist (for a total of 10 measurements) using a Gulick II tape measure. Sites include:

- Site 1=narrowest part of the ankle (right and left leg),
- Site 2=largest part of the calf (right and left leg),
- Site 3=top of knee cap for lower thigh (right and left leg),
- Site 4=thickest part of the upper thigh (right and left leg),
- Site 5=widest part of the hips, and
- Site 6=narrowest part of the waist.

Results will be recorded in centimeters on the respective data collection form.

At the Follow-up visit, additional circumferential measurements (including 4 sites on each leg, 1 site at the hips, and 1 site at the waist using a Gulick II tape measure) may be collected immediately after an approximately 60-minute in-clinic treatment with FT Plus. The measurements will be collected and recorded in the same fashion outlined above. .

6.8 Physical Exam

The investigator (or designee) will perform a physical exam at Baseline and Follow-up to assess stage of lipedema and lymphedema, presence of edema at Sites 1-6 (where circumferential measurements were taken), and presence/absence of clinical symptoms. It is important to note that progression to lipo-lymphedema (lipedema with swelling), a requirement of this study, typically develops during Stage 2/3 of lipedema.

- Lipedema Stage:
  - Stage 1 = Smooth/normal skin surface with enlarged hypodermis/homogenous thickening of the subcutis.
  - Stage 2 = Bumpy, wave-like skin surface with indentations/nodular structures (masses, lipomas, angiolipomas) in the thickened subcutis.
  - Stage 3 = An increase in nodular changes/deformations and overhanging masses of tissue (especially on the thighs and around the knees).
- Lymphedema Stage:
  - Stage 0 = Latent or subclinical condition where swelling is not yet evident despite impaired lymph transport, subtle alterations in tissue fluid/composition, and changes in subjective symptoms.
  - Stage 1 = Early accumulation of fluid relatively high in protein content which subsides with limb elevation. Pitting may occur.
  - Stage 2 = Limb elevation alone rarely reduces the tissue swelling and pitting is manifest. Later in state 2, the limb may not pit as excess subcutaneous fat and fibrosis develop.

- Stage 3 = Symptoms of lymphostatic elephantiasis where pitting can be absent and trophic skin changes such as acanthosis, alterations in skin character and thickness, further deposition of fat and fibrosis, and warty overgrowths have developed.

- Edema at Sites 1-6:
  - None = No pitting
  - 1+ = Trace: Tissue returns to normal almost immediately
  - 2+ = Mild: Tissue returns after 15-59 seconds
  - 3+ = Moderate: Tissue returns after 1-2 minutes
  - 4+ = Severe: Tissue returns after > 2 minutes
  - NA = Tissue no longer pits due to induration

6.9 QOL, Symptoms, Mobility & Pain Assessments

The following assessments will be completed by the subject at the Baseline and Follow-up visits. Subjects will be instructed to answer all of the items (i.e., questions or statements) presented. Prior to departure, study personnel will review each assessment for missing data to ensure the subject addressed each item.

6.9.1 QOL

The RAND 36-Item Health Survey (Version 1.0) taps eight health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. (*Appendix A*)

6.9.2 Mobility

The PROMIS Mobility v2.0 (29 November 2016) is a 15-item questionnaire completed by subjects that focuses on activities of physical mobility such as getting out of bed/chairs to activities such as running. The adult Mobility measures include selected items from the full Physical Function item bank. *(Appendix B)*

6.9.3 Pain Interference & Symptoms

To assess pain and symptoms related to lipo-lymphedema (lipedema with swelling), subjects will complete:

- The PROMIS Pain Interference - Short Form 6b v1.0 (2 May 2016) measures self-reported consequences of pain on relevant aspects of a person's life and may include the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. *(Appendix C)*
- The Wong-Baker Faces Pain Rating Scale is a pain scale that shows a series of faces ranging from a happy face at 0, or "no hurt," to a crying face at 10, which represents "hurts like the worst pain imaginable." Based on the faces and written descriptions, the patient chooses the face that best describes

their level of pain associated with lipo-lymphedema (lipedema with swelling). *(Appendix D)*

- Subjects will be asked to rate their perceptions of swelling, heaviness, pain, fatigue, tenderness, and tightness independently for each leg using a 10-point numerical rating scale where 0 represents none/not present and 10 is worst imaginable.[3] *(Appendix E)*

6.10 Treatment

Following randomization, collection of measurements, and the completion of questionnaires, patients will be trained on the conservative care prescribed by the investigator (or designee).

Patients randomized to the Flexitouch Plus will obtain a device through standard commercial means (via self-pay, patient assistance, or insurance programs). The standard prescription of 'Full Leg and Core (L1)' with daily simultaneous bilateral lower extremity treatment (~60 minutes) at normal pressure levels will be used unless alternate programming is selected by the investigator. Alternate programming (e.g., twice daily, high pressure, additional supplemental lower leg program, etc.) may be used at the investigators discretion if a subject reports inadequate control of lymphedema symptoms prior to the next study visit. While alternate programming is not expected to be necessary, it is important subjects have access to the best care possible at all times in a "real world" study.

Once the prescription is submitted/processed at the Baseline visit, device shipment and training on device use must take place within 60 days or the subject will not be enrolled in the study.

At the Follow-up visit, some or all subjects may receive an in-clinic treatment with Flexitouch Plus after the Follow-up data collection is complete. Additional circumferential (including 4 sites on each leg, 1 site at the hips, and 1 site at the waist using a Gulick II tape measure) and bioimpedance (including whole body ECW/TBW ratio, as well as segmental ratios for the Right/Left Arm, Right/Left Leg, and Trunk) measurements may be collected and recorded immediately after completion of the in-clinic Flexitouch Plus treatment.

6.11 Adverse Events, Device Observations, & Complications

Reportable events and device observations, as defined below, will be recorded in the subject's medical record and on the appropriate forms.

6.11.1 Serious Adverse Event (SAE)

A serious adverse event is an untoward medical occurrence where the outcome is:

- Death;

[3] Cook et al. Neurology. 2013 Mar 12; 80(11 Suppl 3): S49–S53.

- Life-threatening event (places the subject at immediate risk of death from the experience as it occurred);
- Hospitalization (initial or prolonged) if admission to hospital was warranted as a result of an adverse event;
- Disability or permanent damage (substantial disruption of one's ability to carry out normal life functions);
- Congenital anomaly or birth defect;
- Required intervention to prevent permanent impairment or damage; or
- Important medical event that required medical or interventional treatment to prevent one of the previous outcomes.

Investigators will record SAEs on the AE log and report to Tactile Medical and IRB (as required) within 10 working days of becoming aware of the event.

6.11.2 Device-Related Adverse Event (AE)

A device-related AE is defined as any untoward medical occurrence in a subject that is associated with the use of the Flexitouch Plus device.

All device-related AEs will be recorded on the AE log. Complaint reporting will be reported through standard commercial means.

6.11.3 Adverse Event Severity

Severity will be assess by the investigator using the following definitions:

- Mild: Subject awareness of sign or symptom, but easily tolerated.
- Moderate: Interferes with normal activities.
- Severe: Incapacitating, with inability to perform normal activities.

6.11.4 Venous-, Lymphedema-, and Lipedema-Related Complications

Information about venous-, lymphedema-, and lipedema-related complications, including cellulitis, lymphangitis, deep vein thrombosis, skin breakdown, lymphorrhea, and lymphangiosarcoma, will be recorded on the Complication & Healthcare Utilization log.

6.11.5 Device Observations

Device observations regarding the Flexitouch Plus will be recorded on a Device Observation log and reported to Tactile Medical to assess the need for complaint reporting. Device observations include device failures, device malfunctions, use errors, and user preferences, as defined below:

- **Device Failure**
  A device failure has occurred when the device is used in accordance with the IFU but does not perform as described in the IFU and also negatively impacts treatment of the study subject.

- **Device Malfunction**
  A device malfunction occurs when an unexpected change to the device that is contradictory to the IFU is observed, which may or may not affect device performance.
- **Use Error**
  A device use error is an act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. Use error includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not itself constitute a use error.
- **Device Issue**
  Any other issue with the device that does not fall into one of the above categories.
- **User Preference**
  Information on user expectations, likes, dislikes, motivations, and inclinations that drive subject satisfaction with the device.

Any unexpected side effects, product quality problems, use errors, or therapeutic failures related to graduated compression will be reported through the standard commercial means, including: direct communication with manufacturer personnel or online filing by the investigator at MedWatch (https://www.accessdata.fda.gov/scripts/medwatch/index.cfm).

7.0 Subject Discontinuation or Exit

7.1 Early Discontinuation

Subject participation may be discontinued prior to study completion for any of the following reasons:

- **Withdrawal of Consent**
  Subjects may withdraw their consent to participate at any time. If a subject withdraws consent, previous information that has already been obtained will be available for analysis.
- **Adverse Event**
  Subject experiences an adverse event that in the investigator's clinical judgement necessitates discontinuation of their participation in this study.
- **Discretion of the Investigator**
  Subjects may be withdrawn at the investigator's discretion in the event of subject noncompliance, changes in the subject's health, or other reasons based on the investigator's clinical judgment.

Subjects withdrawn prior to completing the study will be asked to return to clinic to complete Study Exit procedures.

7.2 Study Exit

A Study Exit form will be completed for all subjects to document the reason for discontinuation or the date of study completion. In addition, subjects randomized to conservative care who express an interest in continuing in-home treatment with the Flexitouch Plus outside of the study will receive information from a Tactile Medical representative per standard procedure.

8.0 Risk Analysis and Adverse Events

Study subjects will be informed of any significant new findings that develop during the course of this study that may affect their willingness to continue participation. The investigator will oversee all safety aspects of the study, report all adverse events to the IRB, and ensure each subject is treated identically. Should a subject choose to terminate his or her participation in the study, he or she will be treated according to the standard of care that applies at the point of withdrawal.

8.1 Treatment Risks

Participants enrolled in this study are not expected to be at any higher or additional risk than those who use conservative care (compression garments), since IPC pressures do not exceed the pressures of static compression garments. IPC and static compression are minimal risk therapies with nominal complications or adverse events.

Likely:

- Local skin irritation
- Pain or discomfort
- Increased swelling

Less Likely:

- Cellulitis
- New or increased edema in the trunk and/or genital region

Highly Unlikely:

- Electric shock (if Flexitouch Plus device is not maintained or used properly)

8.2 Procedure Risks

All procedures and instruments used in this study are part of standard care. The Inbody 770 sends a minute current identical to current technology used on gym equipment, home scales, non-invasive heart monitors, watches, Fibit monitors, and the like. This technology is considered extremely safe with no known risks to patient health.

8.3 Risk Mitigation

Subjects will be made aware of known complications and adverse events at the time of consent and monitored closely throughout the study. Subjects will be informed of any significant new findings that develop during the course of the study that may affect their willingness to continue participation. Should a subject choose to

terminate his or her participation in the study, he or she will be treated according to the standard of care that applies at the point of withdrawal.

The Investigator and study team will oversee all safety aspects and report adverse events to the IRB, as required. Should a subject choose to terminate his or her participation, he or she will be treated according to the standard of care that applies at the point of withdrawal.

8.4 Potential Benefits

While there is no guarantee of a direct benefit to participants, there is a possible benefit of improved quality of life and relief of symptoms with use of the Flexitouch Plus.

9.0 Provisions to Protect the Privacy of Study Participants/Information Security Plan

The most likely risk posed to participants would be a breach of confidentiality if someone other than the research team obtained access to the data.

There are security measures in place to prevent a breach of confidentiality from happening including password protected electronic database and the use of subject codes to de-identify data).

Precautions will be taken to make sure that only authorized individuals will be accessing subject research records. The collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected.

10.0 Deviation from Study Plan

All deviations will be documented on the Deviation Log and reported to the IRB as required by IRB policies.

11.0 Quality Assurance Procedures

This study will be conducted in accordance with Good Clinical Practice (GCP), Code of Federal Regulations (CFR), institutional research policies and procedures, and other appropriate regulatory requirements to ensure subject safety and quality of clinical procedures related to the conduct of the clinical trial. As required by United States Food and Drug Administration (FDA) 21 CFR 56 and the Declaration of Helsinki, the protocol, amendments, and Informed Consent form will be reviewed and approved, according to 21 CFR §50 and §56, by each center's IRB.

11.1 Data Safety Monitoring

The Investigator will be responsible for the monitoring of study data and subject safety. Due to the small number of research subjects, the most comprehensive and effective method of monitoring will be an individual case review by the Investigator (or designee). The Investigator will be made aware of all serious and device-related adverse events; therefore, the responsibility for reporting adverse events is shared with the Investigator and research team.

11.2 Reports and Records

Records to be maintained by the Investigator in a designated study file include:

- Investigational plan and all amendments;
- IRB approval letter, including a copy of the approved consent forms, progress reports, and adverse event reports;
- IRB roster or Assurance number, if applicable;
- All correspondence relating to the conduct of this study between the site, IRB, Tactile Medical, and study monitor;
- Curriculum Vitae and professional license for key study personnel, if applicable;
- Site personnel signature and documentation regarding the Investigator's delegation of responsibility;
- Protocol/device related training records for all applicable study personnel;
- Screening log; and
- Reports (shown below).

The Investigator is required to prepare and complete reports on this investigation as required by regulations (Table 2).

Table 2. Required Reports

Reports	Submit To	Timeframe
SAE	Tactile Medical Reviewing IRB	10 business days of becoming aware. In accordance with IRB procedure.
Progress Report	Tactile Medical Reviewing IRB	Annually, at a minimum.

The following records must be maintained for each subject enrolled:

- Original, signed and dated informed consent form, as well as documentation of the process of consent;
- Completed CRFs, source document worksheets, and data clarification forms, as applicable; and
- Complete medical records including procedure reports, lab reports, etc., as applicable

Subject study records, correspondence files, all supporting study documentation, and reports will remain on file for a minimum of six years after the conclusion of this study.

12.1 Change to Investigational Plan

Should changes in the study plan or protocol become necessary during the course of the clinical research study, proposed changes will be appropriately reviewed and approved by the IRB before any changes are implemented. All changes must be documented.

13.0 Statistical Methods

13.1 Sample Size Determination

The study is not formally powered for a specific primary hypothesis, thus no formal power/sample size estimation was performed. The study sample size was determined based upon a desire to be able to estimate the means of the primary within group endpoints, using 95% confidence intervals, with the estimation of the endpoint means to have a precision (half width of the confidence intervals) of approximately 40% of the observed standard deviation. To achieve these parameters, we have determined a target analyzable sample size of 15 subjects (30 total legs as the observational units) per group. To accommodate an expected attrition rate of up to 20%, a total of 3 subjects per arm will be replaced, if they fail to fully complete the study.

13.2 Statistical Analysis

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, inter-quartile range, minimum, and maximum, based upon subjects with reported data for the variable being analyzed. Frequencies (numerator and denominator), percentages, and 95% confidence intervals will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing (unreported) data for the specific variable being analyzed and the count of the patients for each individual level of the categorical variable (the level specific numerators). Percentages will add up to 100%, unless otherwise indicated.

There are no plans to impute missing data and there are no plans to explicitly report missing data (counts and/or percentages) in the tables for all variables as part of the planned study report content. Variations in the reported sample sizes within and/or between relevant tables can be used to ascertain insights into unreported data. In some cases, unreported data may be due to it not being clinically relevant to a particular patient or may represent expected data that was not collected. Selected analyses pertaining to unreported and/or missing data may be discussed and considered as future findings warrant.

The exploratory nature of the study suggests that the statistical focus will be on estimation and hypothesis generation and not hypothesis testing. Though p-values will be reported as apropos, point estimates, and 95% confidence intervals will be used to guide exploratory analyses for potentially clinically meaningful differences or changes to be discussed and evaluated.

Primary within treatment group analyses of change from baseline will utilize paired tests (e.g. paired t-tests, McNemar chi-square) or similar non-parametric tests as appropriate, to compare the 30-day measurement to baseline.

Secondary between treatment group comparative analyses of change from baseline will utilize ANCOVA or similar methods as appropriate. These methods will include the 30-day measurement as the dependent (response) variable, while the baseline measurement and treatment group will be the independent variables. Assessments of any interactions between the baseline measurement and treatment group will be performed.

Other exploratory comparisons, when performed, will utilize chi-square, ANOVA, t-test, and appropriate non-parametric tests, unless otherwise specified.

In the case of multiple comparisons, when performed, the Hochberg adjustment method (1988) will be used to control the family-wise error rate.

Multivariable models (e.g., linear regression or logistic regression) may be used to assess the predictive relationships and control for possible confounding imbalances of selected multiple variables to specific outcome measures of interest.

Any formal null hypothesis-based statistical comparisons will be made using two sided tests at the α=0.05 significance level unless specifically stated otherwise. All null hypotheses will be of no inter-group difference, all alternative hypotheses will be two-sided, unless specifically stated otherwise.

All data processing, summarization, and analyses will be performed using R Version 3.6.0 or higher.

14.0 Publication Plan

All information obtained in this study may be used for publications, presentations, and conferences of a medical or scientific nature. All patient identifiers will be removed before data is disseminated in presentations and publications and any image will be de-identified to the greatest extent possible.

15.0 References

1 Zaleska M, Olszewski WL, Durlik M, Kaczmarek M. A Novel Clinical Test for Setting Intermittent Pneumatic Compression Parameters Based on Edema Fluid Hydromechanics in the Lymphedematous Calf. Lymphat Res Biol. 2015 Sep;13(3):208-14.

2 Blumberg SN, Berland T, Rockman C, Mussa F, Brooks A, Cayne N, Maldonado T. Pneumatic Compression Improves Quality of Life in Patients with Lower-Extremity Lymphedema. Ann Vasc Surg. 2016 Jan;30:40-4.

3 Muluk SC, Hirsch AT, Taffe EC. Pneumatic compression device treatment of lower extremity lymphedema elicits improved limb volume and patient-reported outcomes. Eur J Vasc Endovasc Surg. 2013 Oct;46(4):480-7.

4 Szolnoky G, Varga E, Varga M, Tuczai M, Dósa-Rácz E, Kemény L. Lymphedema treatment decreases pain intensity in lipedema. Lymphology. 2011 Dec;44(4):178-82.

Appendix A. RAND SF-36

Patient Name: _____ Date: _____

HEALTH CARE ☐ Before Lymph Sparing Liposuction Procedure
☐ After Lymph Sparing Liposuction Procedure

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
5. Lifting or carrying groceries	1	2	3
6. Climbing **several** flights of stairs	1	2	3
7. Climbing **one** flight of stairs	1	2	3
8. Bending, kneeling, or stooping	1	2	3
9. Walking **more than a mile**	1	2	3
10. Walking **several blocks**	1	2	3
11. Walking **one block**	1	2	3
12. Bathing or dressing yourself	1	2	3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?**

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	1	2
14. **Accomplished less** than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

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

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2
18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- 1 - Not at all
- 2 - Slightly
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- 1 - None
- 2 - Very mild
- 3 - Mild
- 4 - Moderate
- 5 - Severe
- 6 - Very severe

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

1 - Not at all

2 - A little bit

3 - Moderately

4 - Quite a bit

5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- 1 - All of the time
- 2 - Most of the time
- 3 - Some of the time
- 4 - A little of the time
- 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

ABOUT

The RAND Corporation is a research organization that develops solutions to public policy challenges to help make communities throughout the world safer and more secure, healthier and more prosperous. RAND is nonprofit, nonpartisan, and committed to the public interest.

Appendix B. PROMIS Mobility

Patient Name: _____

Date: _____

PROMIS® Item Bank v2.0 – Mobility

☐ Before Lymph Sparing Liposuction Procedure

☐ After Lymph Sparing Liposuction Procedure

Mobility

Please respond to each item by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFC39	Are you able to walk at a normal speed?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA15	Are you able to stand up from an armless straight chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA31r1	Are you able to get up from the floor from lying on your back without help?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB9	Are you able to jump up and down?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB10	Are you able to climb up five steps?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB24	Are you able to run a short distance, such as to catch a bus?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB32	Are you able to stand unsupported for 10 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA10	Are you able to stand for one hour?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB40	Are you able to stand up on tiptoes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

29 November 2016

 Page 1 of 2

Patient Name: _____ PROMIS® Item Bank v2.0 – Mobility

Date:_____

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFB42	Are you able to stand unsupported for 30 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFC37	Does your health now limit you in climbing one flight of stairs?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB49	Does your health now limit you in going for a short walk (less than 15 minutes)?....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC10	Does your health now limit you in climbing several flights of stairs?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

29 November 2016

 Page 2 of 2

Appendix C. PROMIS Pain Interference

SUBJECT ID:_____

DATE:_____

PROMIS Item Bank v1.0 – Pain Interference - Short Form 6b

Pain Interference – Short Form 6b

Please respond to each item by marking one box per row.

In the past 7 days…

		Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ3	How much did pain interfere with your enjoyment of life?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ8	How much did pain interfere with your ability to concentrate?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ9	How much did pain interfere with your day to day activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ10	How much did pain interfere with your enjoyment of recreational activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ14	How much did pain interfere with doing your tasks away from home (e.g., getting groceries, running errands)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
PAININ26	How often did pain keep you from socializing with others?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2 May 2016

Appendix D. Wong Baker Faces Pain Scale

Subject ID:_____ Date: _____

Wong-Baker FACES® Pain Rating Scale

0	2	4	6	8	10
No Hurt	Hurts Little Bit	Hurts Little More	Hurts Even More	Hurts Whole Lot	Hurts Worst

Instructions for Usage

Each face represents a person who has no pain (hurt), or some, or a lot of pain.

Face 0 doesn't hurt at all. Face 2 hurts just a little bit. Face 4 hurts a little bit more. Face 6 hurts even more. Face 8 hurt a whole lot. Face 10 hurts as much as you can imagine, although you don't have to be crying to have this worst pain.

Choose the face that best depicts the pain you are experiencing associated with your lipo-lymphedema.

Appendix E. NRS Symptom & Pain Scale

VISUAL ANALOG SCALE TO EVALUATE SYMPTOM SEVERITY

ID: _____ **DATE:** _____

We are trying to find out about your lipo-lipedema symptoms. There are 12 items we would like you to respond to. This should take less than 1 minute of your time.

DIRECTIONS: You are asked to circle a number on each of the following lines to indicate how you are feeling RIGHT NOW about symptoms in your left and right leg (these questions are not asking about other parts of your body).

PLEASE COMPLETE THE FOLLOWING ITEMS WHILE THINKING ABOUT WHILE YOUR LEFT LEG:

1.	No swelling	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable swelling
2.	No heaviness	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable heaviness
3.	No pain	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable pain
4.	No fatigue	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable fatigue
5.	No tenderness	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable tenderness
6.	No tightness	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable tightness

PLEASE COMPLETE THE FOLLOWING ITEMS WHILE THINKING ABOUT YOUR RIGHT LEG:

1.	No swelling	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable swelling

SYMPTOM ASSESSMENT v1

VISUAL ANALOG SCALE TO EVALUATE SYMPTOM SEVERITY

ID: _____ **DATE:** _____

2.	No heaviness	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable heaviness
3.	No pain	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable pain
4.	No fatigue	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable fatigue
5.	No tenderness	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable tenderness
6.	No tightness	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable tightness

THANK YOU!