Assessment of Quality of Life Changes on Lower Extremity Lymphedema Patients using an Advanced Pneumatic Compression Device at Home.

Protocol# 5010

03 July 2019
Protocol Version 3.1

Investigator Signature

Protocol Title: Assessment of Quality of Life Changes on Lower Extremity Lymphedema Patients using a Pneumatic Compression Device at Home.

Protocol Number: 5010
Date: 03 July 2019, Version 3.1

I confirm that I have read this protocol. I will comply with the protocol and the principles of Good Clinical Practices (GCP), institutional research policies and procedures and other appropriate regulatory requirements.

_____
Site Principal Investigator Name (Print)

_____ _____
Site Principal Investigator Signature Date

SYNOPSIS

Title of Study	Assessment of Quality of Life Changes on Lower Extremity Lymphedema Patients using an Advanced Pneumatic Compression Device at Home.
Protocol Date	3 July 2019
Protocol Version	3.1
Name of Sponsor	Tactile Medical™
Device	Flexitouch® system or Flexitouch® Plus
Primary Endpoint	Quality of life (QoL), lymphedema symptoms, lymphedema and venous related complication rate, lymphedema and venous related unscheduled visits
Secondary Endpoint	Limb circumference changes, Flexitouch compliance, skin changes, QoL
METHODOLOGY	
Study Design	Multi-center, single arm, observational clinical trial
Treatments	Subjects will be instructed to use the Flexitouch system or Flexitouch Plus as prescribed and will be followed for 52 weeks. The subjects will be seen in clinic 4, 8, 12, 24 and 52 weeks after completion of device training. The subject will also have phone call follow-ups at 1, 18, 32 and 40 weeks after device training.
Treatment Duration	As prescribed
SUBJECT POPULATION	
Number Planned	300
Inclusion Criteria	1) Age 18 or older 2) Diagnosis of primary or secondary, unilateral or bilateral, LE lymphedema 3) Ability and willingness to participate in all aspects of the study including following prescribed care 4) Ability to provide informed consent 5) Must have a prescription for the Flexitouch (Flexitouch system or Flexitouch Plus)
Exclusion Criteria	1) Diagnosis of active or recurrent cancer, or less than 3 months at the time of initial evaluation from the completion of chemotherapy, radiation therapy or primary surgery for the treatment of cancer. 2) Active skin or limb infection/inflammatory disease (acute cellulitis, or other uncontrolled skin or untreated inflammatory skin disease) 3) Acute thrombophlebitis (in last 2 months) 4) Pulmonary embolism within the previous 6 months 5) Deep Vein Thrombosis (DVT) within the previous 3 months 6) Severe peripheral artery disease (critical limb ischemia including ischemic rest pain, arterial wounds, or gangrene) 7) Pulmonary edema 8) Heart failure (acute pulmonary edema, decompensated acute heart failure) 9) Patients with poorly controlled asthma 10) Previous use of the study pneumatic compression device (PCD) 11) Currently using multi-layer bandaging (MLB) unless bandages can be removed for limb circumference measurements 12) Pregnant women or women of childbearing potential not on contraception 13) Any condition where increased venous and lymphatic return is undesirable 14) Currently participating in another medical device or drug clinical trial 15) Signs of noncompliance at the week 4 visit, including: using the device less than 3 times per week and/or not attending the scheduled visit

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1.0 Contact Information

1.1 Sponsor Contact Information

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2.0 Abbreviations

CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
DVT	Deep Vein Thrombosis
ER	Emergency Room
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCU	Health Care Utilization
IC	Informed Consent
IRB	Institutional Review Board
LE	Lower Extremity
MLB	Multi-Layer Bandaging
PCD	Pneumatic Compression Device
QoL	Quality of Life
SAE	Serious Adverse Event
SF-36	Short Form-36

3.0 Introduction

3.1 Background and Rationale

The purpose of this study is to evaluate the effect of an advanced pneumatic compression device in improving symptoms and quality of life in patients with lower extremity lymphedema.

Lymphedema is a chronic and disfiguring disease usually secondary to excessive fluid and protein accumulation in the interstitium as result of lymphatic system obstruction.[1] It can occur either primarily (as a result of congenital malformations)

or secondarily (as a result of trauma to the lymphatic system, surgery, radiation therapy, obesity and chronic venous insufficiency).[2,3] This leads to limb swelling in early stages with progression to thickening skin and fibrosis leaving the affected extremity susceptible to skin breakdown and repeated infections. There is no cure for lymphedema, and the available treatment modalities consist of manual lymphatic drainage, compression therapy, and in very severe cases lymphatic exchange, a costly and invasive procedure.[4]

Pneumatic Compression Devices (PCDs) offer a novel modality for treatment of lymphatic obstruction. The Flexitouch®System and Flexitouch® Plus are PCDs that target all major lymphatic beds and release pressure in a systematic manner, mimicking a functional drainage system.[5] Prior studies demonstrated improvement in control of edema and ease of use; however improvement in quality of life (QoL) and decrease in symptoms has not been thoroughly evaluated.[6,7,8] Therefore we propose to demonstrate improved QoL and symptoms in patients with lower extremity (LE) lymphedema.

3.2 Device Description

The Flexitouch system and Flexitouch Plus (Tactile Medical™, Minneapolis, MN, USA) are segmental, programmable, gradient PCDs which have been cleared by the Food and Drug Administration (FDA) for market in the US (K013061), (US HCPCS code E0652). The devices consist of a controller and garment set. The garments are constructed of nylon and have 27-32 chambers, depending upon garment size. The pressure setting is variable between "normal" and "increased." The Flexitouch system and Flexitouch Plus are intended for the treatment of lymphedema, primary lymphedema, post mastectomy edema, edema following trauma and sports injuries, post immobilization edema, venous insufficiencies, reducing wound healing time and assistance in healing stasis dermatitis, venous stasis ulcers, or arterial and diabetic leg ulcers.

The Flexitouch Plus is functionally equivalent to the Flexitouch system, however it permits bilateral treatment of the lower extremities, incorporates a color display with larger buttons on the controller, and provides more comfortable garments that are easier to put on and take off.

4.0 Study Objectives

The study will assess QoL, lymphedema symptoms, lymphedema and venous related complication rate, lymphedema and venous related unscheduled visits, Flexitouch compliance, and skin and limb circumference changes in primary or secondary, unilateral or bilateral, lower extremity lymphedema patients using the Flexitouch system or Flexitouch Plus during the 52 week study period.

5.0 Study Design

This investigation is a post-market, on label, multi-center, single arm, observational clinical trial of a prospective cohort of 300 subjects with primary or secondary, unilateral or bilateral, lower extremity lymphedema in the United States. All subjects will receive PCD treatment for 52 weeks (*Figure 1*).

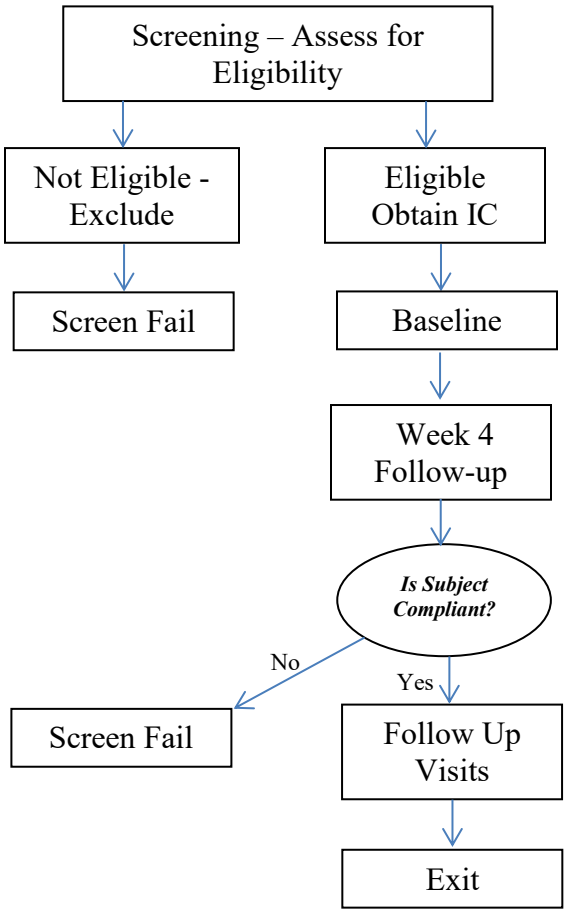

Figure 1. Study Design

5.1 Study Endpoints

5.1.1 Primary Endpoints

The following primary endpoints for this study will compare changes after 12 weeks of treatment to baseline for the following parameters:

- QoL
- Lymphedema symptoms

In addition, the number of occurrences after 52 weeks of treatment will be compared to the number of occurrences in the year preceding treatment for the following variable:

- Lymphedema and venous related health care utilization

5.1.2 Secondary Endpoints

The secondary endpoints for this study will compare changes after 12 and 52 weeks of treatment to baseline for the following:

- Limb circumference
- Skin evaluation

In addition, changes after 24 and 52 weeks of treatment to baseline for the following parameter:

- QoL

To assess Flexitouch compliance, subjects will be categorized as noncompliant, partially compliant, or compliant (Table 1). Primary and secondary outcomes will then be compared across the defined compliance categories.

Table 1. Compliance Category Definitions

Compliance Category	Definition
Noncompliant	Prescribed care followed an average of 0-2 days per week.
Partially Compliance	Prescribed care followed an average of 3-4 days per week.
Compliant	Prescribed care followed an average of 5-7 days per week.

5.2 Subject Selection

5.2.1 Inclusion Criteria

1. Age 18 or older
2. Diagnosis of primary or secondary, unilateral or bilateral, LE lymphedema
3. Ability and willingness to participate in all aspects of the study including following prescribed care
4. Ability to provide informed consent
5. Must have a prescription for the Flexitouch (Flexitouch system or Flexitouch Plus)

5.2.2 Exclusion Criteria

1. Diagnosis of active or recurrent cancer, or less than 3 months at the time of initial evaluation from the completion of chemotherapy, radiation therapy or primary surgery for the treatment of cancer.
2. Active skin or limb infection/inflammatory disease (acute cellulitis, or other uncontrolled skin or untreated inflammatory skin disease)
3. Acute thrombophlebitis (in last 2 months)
4. Pulmonary embolism within the previous 6 months
5. Deep Vein Thrombosis (DVT) within the previous 3 months
6. Severe peripheral artery disease (critical limb ischemia including ischemic rest pain, arterial wounds, or gangrene)
7. Pulmonary edema
8. Heart failure (acute pulmonary edema, decompensated acute heart failure)
9. Patients with poorly controlled asthma
10. Previous use of the study PCD

11. Currently using multi-layer bandaging (MLB) unless bandages can be removed for limb circumference measurements
12. Pregnant women or women of childbearing potential not on contraception
13. Any condition where increased venous and lymphatic return is undesirable
14. Currently participating in another medical device or drug clinical trial
15. Signs of noncompliance at the week 4 visit, including: using the device less than 3 times per week and/or not attending the scheduled visit

5.2.3 Subject Withdrawal or Early Termination

Subjects will exit the study if they meet any of the following criteria:

- Subject death
- Subject voluntarily withdraws
- Subject acquires one or more of the exclusion criteria whereby the investigator deems study discontinuation a necessity
  - If subject acquires an infection, they may be treated for the infection and continue in the trial at the investigator's discretion. Detailed information regarding the infection, nature, treatment, and duration will be recorded.
- Subject diary shows an unwillingness to remain partially compliant or compliant with prescribed care (subject will be considered a screen failure if he or she uses the device <3 times per week on average at the Week 4 visit).

5.3 Dosage and Rationale

Study subjects will be instructed to conduct LE treatment as prescribed by their physician. They will also be instructed to wear clinically appropriate compression garments and participate in proper skin care as part of their routine care.

5.4 Study Timetable

Table 2. Study Timetable

	1-6 months	7-12 months	12-24 months	24-36 months
IRB Review	X			
Enrollment	X	X	X	X
Treatment	X	X	X	X
Data Entry	X	X	X	X
Data Analysis				X
Manuscript Draft				X
Publication				2021

6.0 Study Visit Summaries

The sections below provide a summary of procedures at each study visit. For further detail for each procedure, please refer to section 7 (Study Procedures) of the protocol.

In the event a patient is unwilling or unable to attend a scheduled Follow-Up Visit, the site will have the discretion to offer a home visit to the patient.

6.1 Screening/Baseline Visit

- Informed Consent Discussion

- Inclusion/Exclusion criteria assessment
- Collection of demographics, significant medical history, and lymphedema history
- Urine pregnancy test (as applicable)
- Weight (kg) and height (cm)
- Skin assessment
- Limb circumference
- Photographs (Leg)
- Prescribed care and treatment protocol
- Medication review
- Qol Questionnaires
    - SF-36
    - LYMQOL
- Subject Diary (dispense)

6.2 Week 0/Training

- The subject will receive the Flexitouch system or Flexitouch Plus and be instructed on use from a Tactile Medical trainer. Device treatment will commence following the visit from the trainer.

6.3 Weeks 1 (+7 days), 18, 32, & 40 (± 14 days) Follow-up Phone Calls

- Prescribed care and treatment protocol
- Medication review
- Flexitouch compliance assessment
- Complication, adverse event, and device observation assessment

6.4 Weeks 4, 8, 12 (± 7 days), 24, and 52 (± 14 days) In-Clinic Follow-Up Visit(s)

- Weight (kg)
- Skin assessment
- Limb circumference
- Photographs (Leg)
- Prescribed care and treatment protocol
- Medication review
- QoL Questionnaires (Weeks 12, 24, and 52 only)
    - LYMQOL
    - SF-36
- Subject diary collection
- Flexitouch compliance assessment
- Complication, adverse event, and device observation assessment

7.0 Study Procedures

7.1 Informed Consent

Signed consent for participation in this study will be obtained prior to any research procedures. All study participants are required to sign an Intuitional Review Board

(IRB) approved informed consent document that outlines the purpose of the study, requirements for participation, risks and benefits to participation, and subject's rights. Adequate time will be given for patients to read the consent form, to confirm their comprehension, and to decide on consent. Comprehension and capacity for consent will be assessed by the research staff.

The study staff will ensure that a valid consent is documented and placed in the patient's medical chart. A signed copy will be given to the subject/authorized representative and a copy will be maintained in the study file.

7.2 Demographics & Medical History

Demographics will be collected at baseline including the date of birth, ethnicity, race, gender, and employment status.

If the subject is female and of childbearing potential, a urine pregnancy test will be performed to ensure the subject is not pregnant. Per exclusion criterion 11, if a subject is pregnant or a women of childbearing potential not on contraception, they will be excluded from the study.

Significant medical history and lymphedema history will be collected at baseline including number of lymphedema and venous related visits that required health care utilization (HCU) (includes clinic visits, hospitalization, walk-in clinic/urgent care, and ER visits).

7.3 Vital Signs

At the screening/baseline visit, height (cm) and weight (kg) will be collected. Weight will be collected at all other clinic visit follow-ups.

7.4 Skin Assessment

Skin will be assessed at each clinic visit by fibrosis grading, assessment of skin changes, and staging of lymphedema using ISL guidelines.

7.4.1 Fibrosis Grading

Fibrosis grading will use the following guidelines:

- Grade 0: Latent with no evident fibrosis
- Grade 1: Soft tissues responds only minimally or moderately to elevation (raising the limb) or compression; texture is moderately firm or spongy
- Grade 2: Marked increase in density and firmness; "tethering" of skin (changes in texture that makes skin look as it is being pulled from within)
- Grade 3: Very marked density and firmness with evident tethering

7.4.2 Assessment of Skin Changes

The assessment of skin changes will be done by recording the presence or absence of:

- Hyperpigmentation, Discoloration
- Hyperkeratosis

- Dermatitis, Eczema
- Ulceration, Blisters
- Positive Stemmer Sign
- Squaring of Toes
- Deep Creasing at Flexion Points
- Papillomas
- Puffy Forefoot/Swelling on Dorsum
- Increase of Fat or Muscle Bulk
- Lymphorrhea, Weeping Edema

7.4.3 Lymphedema Staging

The staging of lymphedema will follow ISL guidelines as shown in Table 3.

Table 3. ISL Staging Guidelines

Stage	Description
Stage 0	Latent with no clinical signs (no evident swelling).
Stage 1	Soft swelling (pitting) that resolves with elevation.
Stage 2	Spongy swelling (pitting and non-pitting) that does not resolve with elevation; fibrosis may or may not be present.
Stage 3	Symptoms of lymphostatic elephantitis where pitting is absent and tropic skin changes develop; extensive fibrotic swelling, blistering, ulceration, lymphorrea, papilloma, and/or recurrent infections may be present.

7.5 Limb Circumference Measurements

Limb circumference measures will be taken at each in-clinic visit for both legs. The circumference measurements will be completed by research personnel with documented training showing the individual was able to independently and accurately conduct the measurements. Measurements will be collected using a Gulick II tape measure provided by Tactile Medical. In addition, if possible, the same clinician will be asked to take the measurements for each subject serially.

Standard limb measurement will involve taking two circumference measurements at 18 cm from the floor and 10 cm above the popliteal.

7.5.1 Mark Anatomical Sites

Using a pen or skin marker, with the subject standing upright and bearing weight on the limb being measured, mark the subject at the lateral aspect of the leg 18 cm from the floor (see Figure 2), at the popliteal, and 10 cm from the popliteal (Figure 3).

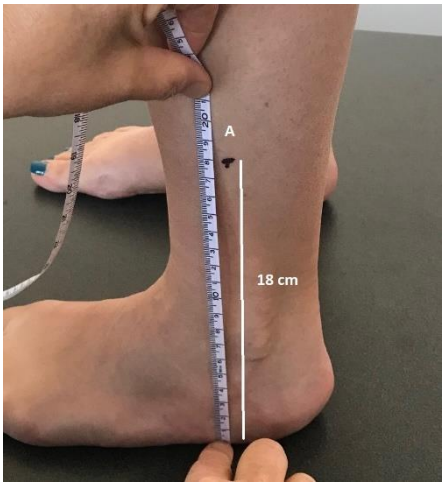

Figure 2. Site A is 18 cm from the floor on lateral aspect of the leg.

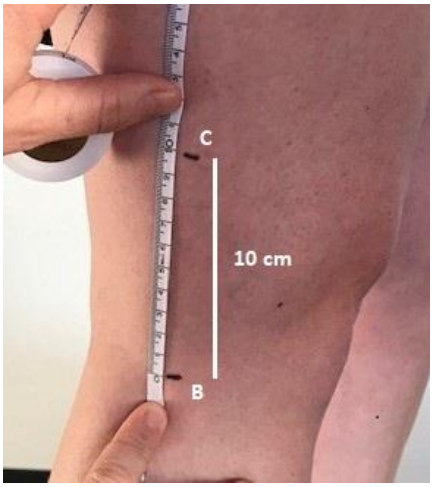

Figure 3. Site B is the popliteal and Site C is 10 cm above the popliteal.

7.5.2 Circumference Measurements

After marking the anatomical sites, measure and record the circumference, in cm, at sites A (see Figure 4) and C (see Figure 5). The tape measure must be placed precisely over (covering) the skin marking. Adjust the tension of the tape measure so that one red ball is visible in the tension indicator and record the circumference measurement.

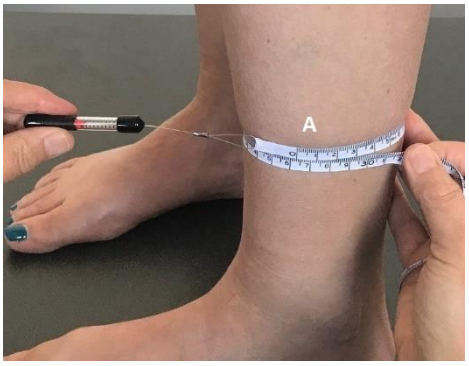

Figure 4. Site A circumference measurement.

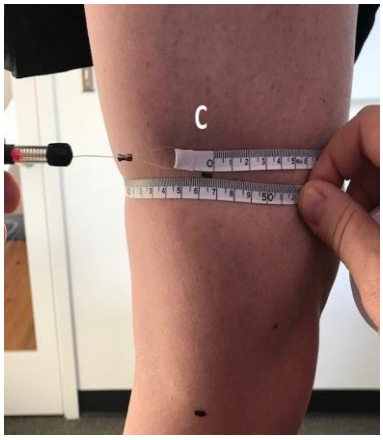

Figure 5. Site C circumference measurement.

7.6 Photograph (Legs)

A digital photograph of the subject's legs will be taken at each study visit. The subject's legs should be exposed, at minimum, from the bottom of the ankle to the mid-thigh. Subjects should sit and straighten their legs as much as possible (see Figure 6).

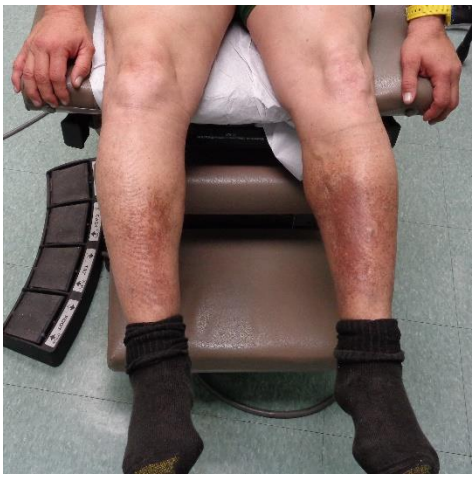

Figure 6. Leg photograph example.

Additionally, if a subject has areas of hyperpigmentation, ulcers, or excessive swelling, a close-up photo of that area should be taken. The image number(s) from the digital camera should be recorded on the subject's source documentation.

7.7 Prescribed Care & Treatment Protocol

At each visit, current lymphedema treatment, including Flexitouch treatment, will be reviewed and recorded.

7.8 Medication Review

At each clinic visit, use of the following medications will be documented:

- Beta blockers
- Diuretics
- Oral steroids
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

7.9 QoL Questionnaires

The LYMQOL is an assessment tool designed for measuring QoL in patients with lower limb lymphedema.[9] It is a 25 item questionnaire which has been designed and validated in patients with chronic edema and covers 4 domains: function, appearance, symptoms, and mood and in addition has an overall QoL score. This tool has been designed and validated for patients with chronic lymphedema in one or both legs to measure QoL. (Appendix A)

The Short Form-36 (SF-36) is an assessment of functional status and quality of life. The SF-36 is a validated QoL tool that has been widely utilized and has been found to be appropriate for use in evaluating health related quality of life impacts. The SF-36 consists of 36 questions that evaluate eight health concepts including physical functioning, role functioning-physical, bodily pain, general health, vitality, social functioning, role functioning – emotional, and mental health. (Appendix B)

7.10 Flexitouch Compliance Assessment & Subject Diary

At each phone call and clinic visit, subject compliance will be assessed by collecting the following information:

- Days Flexitouch used in past week
- Days compression garments used in past week
- Difficulty in following treatment
- Difficulty in putting on Flexitouch garments
- Difficulty using Flexitouch controller
- Pain or discomfort experienced when using Flexitouch
- Position treatment being done in

If the subject reports difficulty following treatment, putting on the Flexitouch garment, difficulty using the Flexitouch controller, or is experiencing pain or discomfort when using Flexitouch, the site may refer the subject to Tactile Medical clinical services for assistance in addressing the issue(s).

In addition, the subjects will be provided with a Subject Diary at their Screening/Baseline visit and be instructed to begin completing the diary when they start using their device after their training visit. The subject will be asked to keep a daily record of their use of Flexitouch, Actitouch (if prescribed), and compression stockings. (Appendix C) Subjects should bring their diary into each study visit for review and collection.

If the subject is noncompliant or partially compliant in device use, (see Table 1), the site should identify barriers to compliance and determine if additional device training by the site or Tactile personnel is warranted. If noncompliance continues, the Investigator may initiate the subject's withdrawal from the study.

At the 4 week in-clinic follow-up visit, if a subject is not using their Flexitouch an average of 3 times per week, they will be considered a screen failure.

If the subject experiences a complication (e.g., active infection, DVT) that requires temporary discontinuation of device use and 4 weeks of continuous treatment is not possible before the final in-clinic visit takes place, the subject should be withdrawn from the study.

Additionally, a device history log may be downloaded periodically from Flexitouch Plus units.

7.11 Lymphedema and Venous Related HCU, Device-Related Adverse Events, & Device Observations

At each phone call and clinic follow-up visit, assessment of lymphedema and venous related HCU, device-related adverse events, and device observations will occur and be recorded in Clindex, per the following definitions.

7.11.1 Lymphedema and Venous Related HCU

Lymphedema and venous related visits that required HCU (includes clinic visits, hospitalization, walk-in clinic/urgent care, and ER visits).

7.11.2 Device-Related Adverse Events

Any untoward medical occurrence in a subject that is associated with the use of the Flexitouch device.

7.11.3 Device Observations

All subject-reported user errors, device failures, malfunctions, or device issues.

7.12 Flexitouch Administration & Training

After the subject's screening/baseline visit, Tactile Medical personnel will perform in-home device training. The date of device training (Day 0) will be used to determine the timing of subsequent follow-up visits.

7.13 Study Schedule of Activities

Assessments	Screening/Baseline	Training / Day 0	Week 1 (Phone Call)	Week 4	Week 8	Week 12	Week 18 (Phone call)	Week 24	Week 32 (Phone call)	Week 40 (Phone call)	Week 52
Visit Window	***N/A***	***N/A***	***+7 Days***	***±7 Days***	***±7 days***	***±7 days***	***±14 days***	***±14days***	***±14 days***	***±14 days***	***±14 days***
Informed Consent	X										
Inclusion/Exclusion	X										
Demographics	X										
Medical History/Status	X[1]										
Vital Signs[2] (Height, Weight)	X			X	X	X		X			X
Skin Assessment	X			X	X	X		X			X
Limb Circumference	X			X	X	X		X			X
Photograph (Leg)	X			X	X	X		X			X
Prescribed Care & Treatment Protocol	X		X	X	X	X	X	X	X	X	X
Medication Review	X		X	X	X	X	X	X	X	X	X
Quality of Life Assessments	X					X		X			X
Subject Diary	X[3]			X	X	X		X			X
Flexitouch Compliance			X	X	X	X	X	X	X	X	X
HCU, Adverse Events, & Device Observations			X	X	X	X	X	X	X	X	X
Flexitouch Training		X									

[1]Includes Lymphedema History
[2]Height and weight collected at Screening/Baseline, weight collected at all subsequent visits
[3]Dispense and train subject on subject diary completion

8.0 Study Device Accountability

To participate in the study, the Flexitouch must be covered by a payer. The Flexitouch will be provided to the subject and tracked according to normal business practices. Subjects' whose payer requires rental of the Flexitouch will be excluded from the study.

9.0 Risk Analysis and Adverse Events

9.1 Risk Analysis

This study does not present risks above and beyond those normally associated with the use of this market cleared product. Pneumatic compression is a minimal risk therapy with minimal known complications or adverse events. However, as with any treatment, there is the possibility of undesirable events such as a local skin reaction to the device materials. The subject will be made aware of known complications at time of consent and monitored closely throughout the study.

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 principal investigator will oversee all safety aspects of the study and report all adverse events to the IRB per the IRB's reporting requirements. Should a subject choose to terminate his or her participation in the study, they will be treated according to the standard of care that applies at the point of withdrawal.

9.2 Adverse Events

This study will collect device-related adverse events. A device related adverse event is defined as any untoward medical occurrence in a subject that is associated with the use of the Flexitouch device. If this device-related event is serious, investigators must report the event to Tactile Medical within 72 hours and to their IRB per their policy. A serious adverse event is defined as an event that, 1) results in death; 2) is life-threatening (places the subject at immediate risk of death from the experience as it occurred; 3) results in a persistent or significant disability/incapacity (substantial disruption of one's ability to carry out normal life functions); 4) results in medical or surgical intervention; 5) results in or prolongs existing hospitalization; 6) is medically unexpected, regardless of severity.

10.0 Deviation from Study Plan

All deviations will be documented 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, 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) CFR (21 CFR 56) and the Declaration of Helsinki, the study protocol, amendments, and Informed Consent form will be reviewed and approved, according to 21 CFR §50 and §56, by each study center's IRB.

11.1 Site Qualification

Tactile Medical personnel must conduct on-site Qualification Visits or a telephone qualification assessment to verify that there are adequate resources, staffing, and a sufficient subject pool to ensure successful enrollment and study completion.

11.2 Data Collection Procedures

Raw data will be collected on appropriate source document worksheets, or site-specific appropriate forms which include but are not limited to, clinic charts and site-generated source document worksheets. If the site staff chooses to use site-specific data collection forms it may be beneficial for these to be reviewed by Tactile prior to use. Data collection shall be entered into the validated and secure Clindex electronic data capture systems.

11.3 Clinical Site Monitoring

Clinical sites will be monitored for compliance with the clinical protocol, investigator agreement, and applicable regulations. Regular contact will be maintained to ensure:

- Subject safety
- That clinical site staff is well informed of regulations and sponsor requirements
- That the clinical protocol is followed
- That data is gathered in an accurate, complete and timely way
- That problems with data or data collection are addressed appropriately and in a timely manner
- That adverse events are properly reported in a timely manner

Investigator and Institution will permit trial related monitoring, audits, IRB review, and regulatory inspection(s), providing direct access to source data and documents as appropriate. Monitoring and source verification will be performed by Tactile Medical Clinical Research Associates (CRAs) and/or designee. Source verification includes reviewing subject source documentation and Case Report Forms (CRFs) for accuracy, completeness, and compliance with GCP procedures. In addition to site visits, a screening log must be submitted to Tactile Medical as requested (by fax or e-mail). This screening log should be reviewed with site staff to assess plan vs. actual recruitment.

11.4 Data Safety Monitoring

A periodic review may be completed by a designated member of the Scientific Advisory Board. The frequency of the review will be determined on a number of parameters including but not limited to: the rate of enrollment, number of complications, and number of significant deviations from the protocol. At the conclusion of the review the reviewer may provide recommendations that pertaining to study continuation, modification or termination of the trial, or a specific investigational site.

11.5 Reports and Records

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

- Investigational plan and all amendments
- Signed Investigator Agreement/Research Contract
- IRB approval letter, including a copy of the approved consent forms, progress reports, Adverse Event Report
- IRB roster or Assurance number, if applicable
- All correspondences relating to the conduct of this study between the site and sponsor, IRBs, and study monitor
- Curriculum Vitae and professional license for all study personnel, if applicable
- Site personnel signature and documentation regarding the Investigator's delegation of responsibility
- Clinical Site Visit log
- Protocol/device related training records for all applicable study personnel
- Screening log
- Reports (Table 4)

The following records must be maintained for each subject enrolled:

- Signed and dated informed consent forms
- Completed CRFs, queries, and source document worksheets (if applicable)
- Complete medical records including procedure reports, lab reports (as applicable), etc.

Investigators are required to prepare and submit to Tactile Medical or its designees complete, accurate, and timely reports on this investigation as required by regulations. The types of reports to be submitted are summarized in the table below.

Table 4: Investigator Reports

Reports	Submit To	Timeframe
Serious Adverse Event (SAE)	Sponsor and Reviewing IRB	Sponsor: 72 hours IRB: per their procedure
Withdrawal of IRB Approval	Sponsor	Within 5 working Days
Progress	Sponsor and Reviewing IRB	Annually, at a minimum
Final	Sponsor and Reviewing IRB	Within 3 months following the completion or termination of the Investigator's part

Subject study records, correspondence files, all supporting study documentation, and reports must remain on file at the investigational site for a minimum of ten years after the conclusion of this study. All investigators must contact Tactile Medical personnel prior to destroying or archiving off-site any records and reports pertaining to this study to ensure that they no longer need to be retained on-site. Additionally, Tactile Medical personnel must be contacted if the Investigator plans to leave the investigational site to ensure that arrangements for a new Investigator or records transfer are made prior to the Investigator's departure.

12.0 Change to Investigational Plan

Should changes in the study plan or protocol become necessary in the course of the clinical trial, proposed changes will be appropriately reviewed and approved by Tactile Medical personnel, Investigator, and appropriate IRB approval obtained before the any changes are implemented. All changes must be documented.

13.0 Statistical Methods and Determination of Sample Size

13.1 Statistical Analysis Plan

The analysis will be completed by a qualified statistician or analyst. The Sponsor will establish and maintain the trial database.

13.2 Determination of Sample Size

The study is planned to have up to 300 subjects enrolled. Each subject will undergo treatment as prescribed, using the Flexitouch system or Flexitouch Plus. This sample of convenience was selected based on the investigator's previous pilot study and experience with this patient population.

14.0 Compensation

Study subjects may be compensated for their time and travel for participating in this study.

15.0 Publication Plan

All information obtained during the conduct of the study will be considered to be confidential and is the property of Tactile Medical. Written permission from Tactile Medical personnel must be obtained before disclosing any information related to this study. All publications (e.g. manuscripts, abstracts, and slide presentations) based on this study must be submitted to Tactile Medical for review and approval before submission or according to the individual site clinical trial agreement.

16.0 References

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7. Wilburn O, Wilburn P, Rockson SG. A pilot, prospective evaluation of a novel alternative for maintenance therapy of breast cancer-associated lymphedema [ISRCTN76522412]. BMC Cancer. 2006;6:84.
8. Cannon S. Pneumatic compression devices for in-home management of lymphedema: two case reports. Cases J. 2009;2:6625.
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17.0 Appendices

Appendix A: Lymphedema Quality of Life Tool (LYMQOL)
Appendix B: SF-36 Health Survey v.2 (SF-36)
Appendix C: Subject Diary

Appendix A: Lymphedema Quality of Life Tool (LYMQOL)

LYMQOL (Source Document)
Assessment of Quality of Life Changes on Lower Extremity Lymphedema Patients using an Advanced Pneumatic Compression Device at Home
Protocol #5010

Subject ID: ___ ___ ___ - ___ ___ ___ **Visit Date:** ____/_____/_____
(ddMMMyyyy)

LYMQOL LEG
Lymphoedema Quality of Life Tool

This questionnaire has been designed and validated for patients with chronic oedema/ lymphoedema of one or both legs to measure quality of life.
Please tick the box that best describes how you feel about each of the questions.

If any of the items are not applicable to you, please write N/A in the relevant answer box(es)

(Q1) How much does your swollen leg affect the following activities?	**Not at all**	**A little**	**Quite a bit**	**A lot**
a) your walking				
b) your ability to bend, e.g. to tie shoelaces or cut toenails				
c) your ability to stand.				
d) your ability to get up from a chair.				
e) your occupation				
f) your ability to do housework				

	Not at all	**A little**	**Quite a bit**	**A lot**
(Q2)Does the swelling affect your leisure activities/ social life?				

Please give examples of this .....

.....

	Not at all	**A little**	**Quite a bit**	**A lot**
(Q3) How much do you have to depend on other people?				
(Q4) How much do you feel the swelling affects your appearance?				
(Q5) How much difficulty do you have finding clothes to fit?				
(Q6) How much difficulty do you have finding clothes you would like to wear?				
(Q7) Do you have difficulty finding shoes to fit?				
(Q8) Do you have difficulty finding socks/ tights/ stockings to fit?				
(Q9) Does the swelling affect how you feel about yourself?				
(Q10)Does it affect your relationships with other people?				
(Q11) Does your lymphoedema cause you pain?				

LYMQOL (Source Document)

Assessment of Quality of Life Changes on Lower Extremity Lymphedema Patients using an Advanced Pneumatic Compression Device at Home
Protocol #5010

Subject ID: ___ ___ ___ - ___ ___ ___

	Not at all	A little	Quite a bit	A lot
(Q12) Do you have any numbness in your swollen leg(s)?				
(Q13) Do you have any feelings of "pins & needles" or tingling in your swollen leg(s)				
(Q14) Does (do) your swollen leg(s) feel weak?				
(Q15) Does (do) your swollen leg(s) feel heavy?				

In the past week….	Not at all	A little	Quite a bit	A lot
(Q16) Have you had trouble sleeping?				
(Q17) Have you had difficulty concentrating on things, e.g. reading?				
(Q18) Have you felt tense?				
(Q19) Have you felt worried?				
(Q20) Have you felt irritable?				
(Q21) Have you felt depressed?				

(Q22) Overall, how would you rate your quality of life at present?
Please mark your score on the following scale:

0 1 2 3 4 5 6 7 8 9 10
poor **excellent**

Thank you for completing this form.
If you have any comments or queries about it, please discuss these with your study coordinator

Questions 16 to 21 have been reproduced with permission from the EORTC.
These questions are only a part of the QLQ-C30 Questionnaire.

Signature of person completing _____ Date: ___/___/___
Day Month Year

Appendix B: SF-36 Health Survey v.2 (SF-36)

Subject ID: ___ ___ ___ - ___ ___ ___ **Initial Report Date:** ____/_____/_____ (ddMMMyyyy)

Study Visit: ☐ Baseline Visit ☐ Week 12 Visit ☐ Week 24 Visit
(*select one*)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

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

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

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

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

Subject ID: ___ ___ ___ - ___ ___ ___

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

Subject ID: ___ ___ ___ - ___ ___ ___

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

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time 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)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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

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

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

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

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

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. 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 <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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

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

Subject ID: ___ ___ ___ - ___ ___ ___

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

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

Signature of person completing:_____ **Date:**_____/_____/_____
Day Month Year

Thank you for completing these questions!

Appendix C: Subject Diary

SUBJECT DIARY

Subject ID: _______________

Prescription:

Flexitouch___________ **Actitouch**___________ **Compression Stockings**___________

MONTH:_________________

	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Check treatments used each day	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings
Check treatments used each day	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings
Check treatments used each day	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings
Check treatments used each day	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings
Check treatments used each day	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings	☐ None ☐ Flexitouch ☐ Actitouch ☐ Compression Stockings

SUBJECT SIGNATURE:____ **DATE:**______________________

Reminder: Your next appointment is scheduled for: ________________________ Version 3.1, July 2019