A Feasibility Study Evaluating the Impact Flexitouch® Plus with Connectivity has on Compliance in Patients with Breast Cancer-Related Lymphedema (BCRL)

Protocol Number: 4090

February 11, 2021
Protocol Version 4.0

Principal Investigator Signature Page

A Feasibility Study Evaluating the Impact Flexitouch Plus with Connectivity has on Compliance in Patients with Breast Cancer-Related Lymphedema (BCRL)

Protocol Number: 4090

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

Study Title	A Feasibility Study Evaluating the Impact Flexitouch Plus with Connectivity has on Compliance in Patients with Breast Cancer-Related Lymphedema (BCRL)
Protocol Date	February 11, 2021
Protocol Version	4.0
Protocol Number	4090
Name of Sponsor	Tactile Medical™
Device	Investigational Flexitouch Plus with Cellular Connectivity (FT-CC)
Study Objective	To demonstrate the feasibility of using the FT-CC to actively monitor device use data to: • Determine if patient reminders impact the rate of compliance, • Identify the impact device compliance has on arm girth, quality of life, and symptoms.
Primary Endpoint	• Compare the rate of compliance in patients treated with PASSIVE FT-CC and ACTIVE FT-CC
Exploratory Endpoints	• Assess the impact device compliance has on arm girth • Determine the impact device compliance has on measures of quality of life (QOL) and symptom assessment: o Lymphedema Quality of Life Tool (LYMQOL ARM) o Short Form-36 (SF-36) o Lymphedema Symptom Intensity and Distress Survey-Arm (LSIDS-A)
Study Design	This is a multi-center, on label, prospective, randomized, two-arm feasibility study.
Treatment(s)	Eligible patients will be randomized to one of the following groups for 60 days: • **ACTIVE FT-CC – Text message reminders will be sent if subject does not use the device for 2 consecutive days** • **PASSIVE FT-CC – Text message reminders will not be sent to subjects**
Eligibility	**Inclusion Criteria:** 1. Female 18 years of age or older 2. Diagnosis of unilateral breast cancer-related lymphedema 3. Willing and able to give informed consent (remotely or in-person) 4. Willing and able to comply with the study protocol requirements and all study-related visit requirements, including the ability to participate remotely 5. Willing and able to receive text messages from sponsor **Exclusion Criteria:** 1. In-home use of pneumatic compression device (PCD) within previous 3 months

	2. Phase-one complete decongestive therapy (CDT) within previous 1 month or planned phase-one CDT during study participation *Phase-one CDT defined as professionally administered manual lymphatic drainage (MLD) and/or multi-layer short stretch compressive bandaging.* 3. Inability to be fit for PCD garments 4. Heart failure (acute pulmonary edema, decompensated acute heart failure) 5. Acute venous disease (acute thrombophlebitis, acute deep venous thrombosis, acute pulmonary embolism) 6. Active skin or limb infection/inflammatory disease (acute cellulitis, other uncontrolled skin or untreated inflammatory skin disease) on the arms or trunk 7. Currently receiving treatment for cancer with curative intent. 8. Any circumstance where increased lymphatic or venous return is undesirable 9. Currently pregnant or trying to become pregnant 10. Known inability to receive cell phone connection where FT-CC therapy will be administered
Treatment Duration	60 days
Number Planned	30 Randomized Subjects

TABLE OF CONTENTS

1.0 Contact Information

1.1 Sponsor Contact Information

Tactile Medical™
Suzanne Hansel, Clinical Trial Manager
3701 Wayzata Blvd, Suite 300
Minneapolis, MN 55416
612-540-5325
shansel@tactilemedical.com

1.2 Site Principal Investigator Information

The sponsor will maintain a document with contact information for all investigators participating in the study. The information maintained will include full names, addresses, telephone numbers, and, if available, email addresses and mobile phone numbers for the site principal investigators and Institutional Review Board (IRB) chairperson.

2.0 Abbreviations

Abbreviation	Term
AE	Adverse Event
BCRL	Breast Cancer-Related Lymphedema
CDT	Complete Decongestive Therapy
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
CTA	Clinical Trial Agreement
DCF	Data Clarification Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FT	Flexitouch Plus
FT-CC	Flexitouch Plus with Cellular Connectivity
GCP	Good Clinical Practice
HCPCS	Healthcare Common Procedure Coding System
ICF	Informed Consent Form
IRB	Institutional Review Board
LSIDS-A	The Lymphedema Symptom Intensity and Distress Survey-Arm
LYMQOL ARM	Lymphedema Quality of Life Tool
MLD	Manual Lymphatic Drainage
NSR	Nonsignificant Risk
PCD	Pneumatic Compression Device
PHI	Protected Health Information
PI	Principal Investigator
QoL	Quality of Life
SAE	Serious Adverse Events
SF-36	Short Form-36
UADE	Unanticipated Adverse Device Effect

3.0 Introduction

3.1 Background and Rationale

Lymphedema is a chronic debilitating disease marked by accumulation of protein rich fluid in the interstitium of the skin. Breast cancer-related lymphedema (BCRL) is a common complication from breast cancer treatment, with reported frequencies ranging from 6% to 65% (1). This insufficiency in the lymphatic system leads to limb edema in early stages and progresses to thickened skin or fibrosis over time. As a result, persons afflicted with lymphedema are prone to develop impaired extremity function, recurrent episodes of soft tissue inflammation and infection, lymphorrhea, unsatisfactory cosmesis, and a variety of psychological and social issues (2).

There is currently no cure for lymphedema, thus treatment focuses on symptom management and improved patient-reported outcomes. Using a multimodal approach, accepted interventions include: limb elevation, MLD, compression therapy, skin hygiene, and in very severe cases, lymphatic exchange (3). Pneumatic Compression Devices (PCDs) are a fairly recent addition to the armamentarium clinicians offer patients in the treatment of lymphedema. Studies have demonstrated continual use of PCDs is associated with a significant patient-reported improvement in overall symptoms, decreased limb-girth, decreased limb volume, increased elasticity of tissues, and fewer episodes of infection (4-7).

Adherence to prescribed, at-home self-care is a critical factor in the treatment of lymphedema (8-9). Research shows PCD compliance diminishes over time (10). This study seeks to determine if active monitoring of device use information and patient reminders affects compliance. Additionally, there is limited data on how various compliance rates impact health outcomes. Therefore, this study also seeks to identify the impact compliance rates have on swelling, quality of life, and symptoms.

3.2 Device Description

The Flexitouch Plus system (FT) (Tactile Medical™, Minneapolis, MN, USA) is an advanced pneumatic compression device clinically proven to stimulate the lymphatic system and is cleared for market in the USA (K203178, K170216, HCPCS code E0652). The device helps direct and move excess fluid from an impaired lymphatic region to healthy regions, where fluid can be absorbed and processed naturally by the body. Flexitouch Plus garment chambers inflate sequentially with each chamber inflating before the adjacent distal chamber fully deflates. This creates a dynamic wave of therapy that directs fluid into the lymphatic capillaries while maintaining distal pressure to prevent distal backflow.

The Flexitouch Plus system consists of two primary components: the controller unit and garments.

The controller unit is a programmable pneumatic compressor with four connector outlets. Each connector has eight outflow ports that garment hoses plug into. Air passes through the hoses, delivering treatment through the sequential inflation and deflation of up to 32 air chambers in the garments. By selecting the appropriate treatment program, calibrated gradient pressure is delivered to the chambers and assists in moving excess fluid out of the affected limb(s).

The air-chambered garments are made of soft, pliable fabric. They are designed to fit the contours of the body by wrapping around the limb(s) and attaching with hook and loop fasteners. A variety of upper and lower extremity treatment options are available. The pressure setting is variable between "decreased," "normal," and "increased." Individual chamber pressures may also be individually adjusted.

The novel FT-CC is identical to the Flexitouch Plus with the exception of an addition of a cellular communication module to the controller unit which transmits device usage data to a cloud-based database accessible to the study sponsor. This data will be used by the sponsor to send automated text messages to subjects randomized to the FT-CC ACTIVE group that have not used their device for 2 consecutive days.

The FT-CC will be labeled, "CAUTION – Investigational Device, Limited by Federal Law to Investigational Use" and each unit will have a unique serial number. The FT-CC is investigational only in that it has the cellular communication module; in all other aspects, including cleared intended use, FT-CC is the same as the currently marketed FT.

4.0 Study Objective

The objective of the study is to demonstrate the feasibility of using the FT-CC to actively monitor device use data to:

- Determine if patient reminders impact the rate of compliance
- Identify the impact device compliance has on arm girth, quality of life, and symptoms.

5.0 Study Design

This is a multi-center, on label, prospective, randomized, two-arm, feasibility study (Figure 1) comparing the PASSIVE FT-CC to ACTIVE FT-CC. A multi-center design is used to expedite the enrollment period and provide a broader sample of the study population. Randomization was incorporated into the study to determine if ACTIVE FT-CC affects device use.

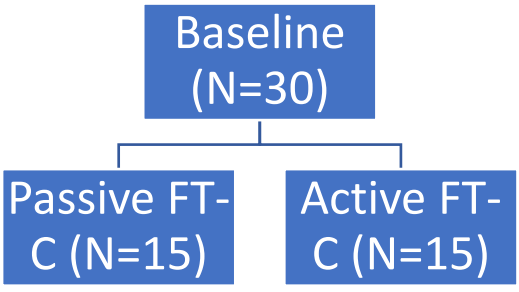

Figure 1. Study Design

5.1 Endpoints

5.1.1 Primary Endpoint

Compare the rate of compliance in patients treated with PASSIVE FT-CC and ACTIVE FT-CC

5.1.2 Exploratory Endpoints

To assess the exploratory endpoints, subjects will be categorized as partially compliant and compliant (Table 1). These endpoints will be analyzed using the following compliance categories.

Table 1. Compliance Category Definitions

Compliance Category	Definition
Partially Compliant	FT-CC used on average 1-4 days per week
Compliant	FT-CC used on average 5-7 days per week

- Assess the impact device compliance has on arm girth
- Determine the impact device compliance has on measures of QoL and symptoms assessment:
  - Lymphedema Quality of Life Tool (LYMQOL ARM)
  - Short Form-36 (SF-36)
  - The Lymphedema Symptom Intensity and Distress Survey-ARM (LSIDS-A)

5.1.3 Outcome Measures

Primary and exploratory endpoints will be based on the outcome measures as described in Table 2.

Table 2. Outcome Measures

Endpoint	Outcome Measure
Compliance	• Compare rate of compliance (# of days used/total study days) to prescribed treatment between FT-CC PASSIVE and FT-CC ACTIVE Subjects at 30 and 60 days
Change in Arm Girth	• Comparison between baseline and day 30/60 arm girth measurement
Quality of Life	• Comparison between baseline, 30 day, and 60 day surveys
Symptom Assessment	• Comparison between baseline, 30 day, and 60 day surveys

5.2 Subject Selection

The target population includes patients who have unilateral BCRL. Only patients who meet the criteria below will be considered for the study. A total sample of 30 subjects will be randomized.

5.2.1 Inclusion Criteria

1. Female 18 years of age or older
2. Diagnosis of unilateral breast cancer-related lymphedema
3. Willing and able to give informed consent (remotely or in person)
4. Willing and able to comply with the study protocol requirements and all study-related visit requirements, including the ability to participate remotely
5. Willing and able to receive text messages from sponsor

5.2.2 Exclusion Criteria

1. In-home use of PCD within previous 3 months

2. Phase-one CDT within previous 1 month or planned phase-one CDT during study participation
   Phase-one CDT defined as professionally administered MLD and/or multi-layer short stretch compressive bandaging.
3. Inability to be fit for PCD garments
4. Heart failure (acute pulmonary edema, decompensated acute heart failure)
5. Acute venous disease (acute thrombophlebitis, acute deep venous thrombosis, acute pulmonary embolism)
6. Active skin or limb infection/inflammatory disease (acute cellulitis, other uncontrolled skin or untreated inflammatory skin disease) on the arms or trunk
7. Currently receiving treatment for cancer with curative intent.
8. Any circumstance where increased lymphatic or venous return is undesirable
9. Currently pregnant or trying to become pregnant
10. Known inability to receive cell phone connection where FT-CC therapy will be administered

5.3 Point of Enrollment and Randomization

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

Randomization codes will be generated by a statistician 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 assignment will be obtained from the electronic data capture (EDC) database and assigned sequentially as soon as a subject is considered enrolled.

If a subject does not meet all the eligibility criteria or meets any of the exclusion criteria but is randomized in error, or incorrectly started treatment, the Investigator should inform Tactile Medical immediately.

5.4 Subject Discontinuation or Withdrawal

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.
- **Discretion of the Principal Investigator**

Subjects may be withdrawn at the investigator's discretion in the event of changes in the subject's health, or other reasons based on the investigator's clinical judgment.

When a subject withdraws prior to completing the study, the reason for withdrawal will be recorded.

5.5 Randomization Assignment and Treatment Duration

Eligible patients will be randomized (1:1) to one of the following groups for 60 days:

- ACTIVE FT-CC – Text message reminders will be sent if subject does not use device for 2 consecutive days
- PASSIVE FT-CC – Text message reminders will not be sent to subjects

The FT-CC prescription will be a daily 60-minute U1 unilateral treatment at normal pressure. Settings and programs may be modified by the discretion of the investigator, if needed, and these modifications will be documented. If subjects are assigned to the ACTIVE FT-CC group and their device is not used for 2 consecutive days, they will receive a text message reminding them to use their device. If subjects are assigned to the PASSIVE FT-CC group, they will not receive text message reminders.

If subjects assigned to the ACTIVE FT-CC group are not able to receive text messages due to cellular connectivity or text transmission issues, alternate methods may be used to remind the subject to use their device and will be documented on the Case Report Form (CRF).

5.6 Study Timeline

The expected study duration is approximately 10 months with 2-3 months spent on activation, 5 months enrolling and following subjects, and 2 months completing the data analysis.

6.0 Study Assessments

In an effort to reduce potential exposure to COVID-19, all study assessments are intended to be performed in a contactless manner (i.e., telephone, video conference, etc). If an assessment is done in-person, the reason will be documented, (e.g., required for adverse event assessment, requested by subject, risk for COVID-19 eliminated, assessment performed in conjunction with another clinic visit, etc.).

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 and responses to data queries according to the Clinical Trial Agreement (CTA).

All data entry, storage, transmission, and management will be conducted using iMedNet, a 21 code of federal regulations (CFR) Part 11 compliant EDC system. When all data have been validated, signed, and locked, the database will be locked and available for analysis.

All devices and testing procedures outlined are standard of care or approved/cleared for use by the Food and Drug Administration (FDA) with the exception of FT-CC. Tactile Medical will provide qualified trainers to train the subject on how to use the FT-CC.

6.1 Screening/Baseline Visit

If a patient appears eligible to participate based on medical history, they will be contacted or approached to assess interest. If the subject is interested in learning more, an ICF will be provided to them (in-person, electronically, or via mail) and the subject will be given adequate time to review and ask questions. If the subject decides to participate and provides documented informed consent, they will undergo the following assessments:

- Obtain medical history
- Administer a serum or urine pregnancy test for all female subjects of child-bearing potential (if this is required, it will be done at the clinic)
- Height and weight
- Medication Review
- Lymphedema evaluation
- Lymphedema treatment review
- Arm Girth
- Randomization
- LYMQOL ARM
- SF-36
- LSIDS-A
- FT-CC Garment Measurements

6.2 Day 0 – Training

FT-CC training should occur within 21 days of the Screening/Baseline visit. The training may occur remotely using electronic means (i.e., telephone, video conference, etc), or in-person. Training will be performed by qualified Tactile Medical personnel.

6.3 Day 30 (±7 days) Follow-Up Visit

The subject will be contacted for the following assessments:

- Weight (only required if they have access to a scale and can self-report)
- Medication Review
- Lymphedema Treatment Review
- Arm Girth
- LYMQOL ARM
- SF-36
- LSIDS-A
- Adverse Event (AE) & Device Observation Assessment

6.4 Day 60 (±7 days) Follow-Up Visit

The subject will be contacted for the following assessments:

- Weight (only required if they have access to a scale and can self-report)

- Medication Review
- Lymphedema Treatment Review
- Arm Girth
- LYMQOL ARM
- SF-36
- LSIDS-A
- AE & Device Observation Assessment

After the subject has completed their Day 60 follow-up visit, they will be exited from the study and the FT-CC device will be collected. Return of the FT-CC may be done by the subject returning the controller to the clinic or by shipping it back from their home in a box provided by Tactile Medical.

6.5 Study Schedule of Activities

The study schedule of activities is shown below (Table 3).

Table 3. Schedule of Study Activities

Assessments	**Screening/Baseline**	**Day 0 - Training**	**Day 30**	**Day 60**
Visit Window	***N/A***	***Within 21 days after Screening/Baseline***	***±7 Days***	***±7 Days***
Informed Consent	X			
Demographics & Medical History	X			
Pregnancy Test (if applicable)[1]	X			
Inclusion/Exclusion Assessment	X			
Height and Weight	X[2]		X[3]	X[3]
Medication Review	X		X	X
Lymphedema Evaluation	X			
Lymphedema Treatment Review	X		X	X
Arm Girth	X		X	X
Randomization	X			
Quality of Life Assessments (LYMQOL ARM, SF-36)	X		X	X
Symptom Assessment (LSIDS-A)	X		X	X
FT-CC Garment Measurements	X			
FT-CC Training		X		
AE & Device Observation Assessment			X	X

[1]If pregnancy test is required, it will be performed in the clinic
[2]Height collected at Screening/Baseline visit only; height and weight collected via self-report for subjects with access to scale or from subject's most recent medical history
[3]Weight collected via self-report if subject has access to a scale at home

7.0 Study Procedures

7.1 Informed Consent

Subjects will sign an ICF 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 all 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, including if the process was performed in-person or remotely.

7.2 Demographics & Medical History

Demographics will be collected including the date of birth, ethnicity, race, and sex.

Significant medical history, including lymphedema history, will be collected.

7.3 Pregnancy Test

Women of childbearing potential will be tested for pregnancy according to the site-specific procedures during the Screening/Baseline visit. If the pregnancy test is positive, the subject will not be enrolled in the study.

7.4 Height and Weight

Height and weight will be collected during the Screening/Baseline visit via self-report for subjects who have access to a scale or from the subject's most recent medical history. Weight will be collected during follow-up visits via self-report if the subject has access to a scale.

7.5 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)

7.6 Lymphedema Evaluation

Research personnel will confirm a diagnosis of unilateral breast cancer-related lymphedema by review of the subject's medical records.

7.7 Lymphedema Treatment Review

During each visit, with the exception of the training visit, the subject will also be asked questions regarding their use in the last 7 days of the FT-CC (Day 30 and 60 only), compression garments, and other prescribed lymphedema treatment.

7.8 Arm Girth

The subject will be provided with a tape measure to make an arm girth measurement on the anterior forearm 6 cm below the midline of the antecubital fossa on the affected arm (see Figure 2). If a family member or care provider is able to do this measurement for the subject, the same person should perform the measurement at all visits.

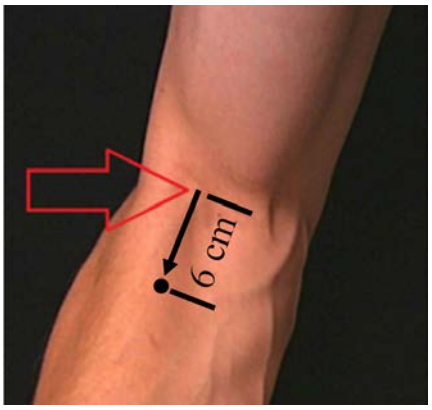

Figure 2. Arm girth to be measured on the anterior forearm 6 cm below (distal to) the midline of the antecubital fossa.

7.9 Randomization

If the subject meets all of the inclusion criteria and none of the exclusion criteria, they will be randomly assigned to ACTIVE FT-CC or PASSIVE FT-CC.

Randomization will occur via entering the randomization CRF in the EDC system. The randomization assignment should not be shared with the research subject.

The randomization assignment cannot be changed or chosen by the subject or the investigator.

7.10 Quality of Life Assessments

7.10.1 LYMQOL ARM

The LYMQOL ARM is an assessment tool designed for measuring quality of life (QoL) in patients with upper limb lymphedema. It is a 21-item questionnaire which has been designed and validated in patients with chronic edema and covers four domains: function, appearance, symptoms, and mood, and in addition, has an overall QoL score (11). The subject will have a unique user account and can complete the assessment online via secure connection to the study database. If subject is not able to complete the questionnaire electronically, they can also be mailed to them for completion.

7.10.2 SF-36

The SF-36 is an assessment of functional status and quality of life. This questionnaire 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.

7.11 Symptom Assessment

The LSIDS-A is a 30-item validated assessment tool designed for measuring arm lymphedema and its associated symptoms in patients with breast cancer-related lymphedema (12). The subject will have a unique user account and can complete the assessment online via secure connection to the study database. If a subject cannot complete the questionnaire electronically, a paper version may be mailed to them for completion.

7.12 FT-CC Garment Measurements

The subject's chest, arm inseam, biceps, and hips will be measured to determine the appropriate size for the arm-shoulder and trunk garment.

7.13 FT-CC Training

After all baseline assessments have been performed, the subject will be contacted by a Tactile Medical trainer to schedule a training visit on how to use the FT-CC. This training may occur virtually, at the clinic, or in the subject's home. Training may be conducted up to 21 days after the baseline visit.

7.14 AE & Device Observation Assessment

AE assessment will occur after randomization and continue throughout the study.

Reportable events, as defined below, will be recorded in the subject's medical record and on the CRFs. All device related AEs will be assessed by the Tactile study team for reporting through the Tactile Medical Complaint System.

7.14.1 AE

An adverse event is any untoward medical occurrence in a clinical research study subject which may or may not be related to the use of the medical device under investigation.

Adverse events will be reported to the IRB in accordance with IRB policy.

7.14.2 Serious Adverse Event (SAE)

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

- Death;
- 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 must report all Serious Adverse Events (SAEs) to Tactile Medical within 10 working days of becoming aware of the event. SAEs will be summarized in writing and reported to the IRB in accordance with IRB policy.

7.14.3 Unanticipated Adverse Device Effect (UADE)

A UADE is a serious adverse effect on the health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the product labeling, published literature, or Investigational Plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Investigators must report all UADEs to Tactile Medical within 10 working days of becoming aware of the event. UADEs will be summarized in writing and reported to the IRB in accordance with IRB policy.

7.14.4 Device Observations

Device observations will be recorded and reported to Tactile Medical and assessed by the Tactile study team for reporting through the Tactile Medical Complaint system.

7.14.5 Adverse Event Severity

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

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

8.0 **Accountability**

The FT-CC and FT garments will be provided at no cost to the subject and be utilized with the assistance of study personnel. The FT-CC and FT garments will be shipped directly to the subject and will be returned to Tactile Medical upon study exit. The subject may ship the controller back to Tactile Medical (Tactile Medical will provide a box and label) or return the FT-CC to the site. Tactile Medical will provide all shipping records to the site to enable appropriate accountability of study devices. The record will include the receipt, location, use, and final disposition of all controllers and garments. Subjects may keep the FT garments at the end of the study. Study devices will be stored in a secure area with

restricted access. At the conclusion of the study all FT-CCs will be returned to Tactile Medical.

9.0 Risk Analysis

This study does not present risks above and beyond those normally associated with the use of the Flexitouch Plus.

Theoretically, massage and mechanical compression could mobilize dormant tumor cells in some patients; however, this is expected to have limited impact on prognosis such that the benefits of reduction in morbid edema will likely outweigh those theoretical risks.

Pneumatic compression is a minimal risk therapy with nominal complications or adverse events. Known reactions to sequential pneumatic compression therapy include:

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 device is not maintained or used properly)

Risk analysis assessments determined the probability of occurrence for these potential device risks are at the lowest level. Thus, the residual risks for these types of hazards is acceptable with the benefits to treating patients outweighing the risks.

Use of the Flexitouch Plus may not improve lymphedema symptoms, such as:

- Increased edema
- Pain or discomfort
- Redness, swelling/inflammation, and blistering
- Skin breakdown, including pressure ulcers
- Cellulitis infection
- Stasis dermatitis

The addition of cellular connectivity does not introduce any new risks to the patient regarding treatment. Risk is limited to a potential cybersecurity breach given its cellular connection; however, the device data that is being transmitted does not contain any protected health information (PHI).

If the subject is randomized to the FT-CC arm, they must consent to receiving text messages from Tactile Medical. The text messages will not include any of the subject's PHI.

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 Principal Investigator and the 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.

10.0 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 a 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 study, so that no unneeded sensitive information is being collected.

11.0 Deviations from Study Plan

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

12.0 Regulatory Assessment

The investigational device used in this study meets the requirements of a nonsignificant risk (NSR) device given the FT-CC is used for its intended purpose and:

- Is not an implant
- Is not used to support or sustain human life
- Is not of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health
- Does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject

Per 21 CFR 812, an NSR study is not required to follow all IDE regulations nor have an IDE application approved by FDA before proceeding. An NSR study must follow the abbreviated requirements at 21 CFR 812.2(b) which address labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion. There is no need to make progress reports or final reports to FDA. In addition, Sponsors and IRBs do not have to report the IRB approval of an NSR device study to FDA. The IRB serves as the FDA's surrogate for review, approval, and continuing review of the NSR device studies. The IRB application should state that the study is NSR and be supported with the rationale in the preceding paragraph. An NSR device study may start as soon as the IRB reviews and approves the study, without prior approval by FDA.

Importantly, the investigational software present on the FT-CC was built in accordance with 820.30 Design Controls, with the controller and garments being manufactured in full compliance with 21 CFR 820.

13.0 Quality Assurance Procedures

This study will be conducted in accordance with Good Clinical Practice (GCP), 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 study. As required by 21 CFR 56 and the Declaration of Helsinki, the protocol, amendments, and ICF will be reviewed and approved, according to 21 CFR §50 and §56, by each center's IRB. This investigational device meets the requirements of a nonsignificant risk (NSR) device; therefore, the study will follow the abbreviated requirements of 21 CFR 812.2(b).

13.1 Site Qualification

Tactile Medical personnel will conduct a Qualification Visit onsite or by telephone to verify the resources, staffing, and subject pool are adequate to ensure successful enrollment and study completion.

13.2 Site Initiation

Tactile Medical personnel will conduct a Site Initiation Visit onsite or by telephone to ensure all required regulatory documents are accurate and complete, and site personnel have been adequately trained on the protocol. An activation letter will be sent to the Principal Investigator once the site is approved to enroll subjects.

13.3 Monitoring

Clinical sites will be monitored, remotely or onsite, for compliance with the clinical protocol, investigator agreement, and applicable regulations throughout the study. Prior to each visit, the investigator will receive a confirmation letter outlining the scheduled dates and activities.

Regular site contact will be maintained to ensure:

- Subject safety;
- Clinical staff are informed of regulations and sponsor requirements;
- The clinical protocol is followed;
- Data is gathered in a complete and timely manner;
- Problems with data or data collection are addressed appropriately and in a timely manner;
- Adverse events are properly reported in a timely manner; and
- Each onsite visit is recorded on the Site Visit Log.

After each visit, the investigator will receive a follow-up letter summarizing site progress as well as any outstanding items that need to be addressed.

In addition to monitoring 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 planned versus actual recruitment.

The Principal Investigator and Institution agree to permit study 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 a Tactile Medical clinical research associate (CRA) and/or designee.

Source verification includes reviewing subject source documentation and Case Report Forms (CRFs) for accuracy, completeness, and compliance with GCP.

13.4 Data Safety Monitoring

The Principal Investigator (PI) 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 PI and clinical investigators. As this has always been the policy of the PI, the researchers and study team are under specific instructions to make the PI aware of all adverse events, expected or unexpected; therefore, the responsibility for reporting adverse events is shared with the PI and the research team.

Additionally, a periodic review may be completed by a designated member of the Sponsor's 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 AEs and/or SAEs, and number of significant deviations from the protocol. At the conclusion of the review, the reviewer may provide recommendations pertaining to study continuation, modification, or termination of the study or investigational site.

13.5 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, and adverse event reports;
- IRB roster or Assurance number, if applicable;
- All correspondence relating to the conduct of this study between the site and sponsor, IRB, and study monitor;
- Curriculum Vitae and professional license for all study personnel, if applicable;
- Financial Disclosure for all Investigators, if applicable;
- Site personnel signature and documentation regarding the investigator's delegation of responsibility;
- Site visit log;
- Protocol/device related training records for all applicable study personnel;
- Device accountability log;
- Device observations;
- Screening log; and
- Reports (shown below).

The Principal Investigator is required to prepare and submit to Tactile Medical, or its designees, complete, accurate, and timely reports on this investigation as required by regulations (Table 6).

Table 6. Required Reports

Reports	Submit To	Timeframe
SAE or UADE	Sponsor and Reviewing IRB	Sponsor: Within 10 working days of becoming aware of the event; IRB: In accordance with IRB procedure.
Withdrawal of IRB Approval	Sponsor	Within 5 working days
IRB determination that study is classified as Significant Risk (SR)	Sponsor	Immediately upon notification from the IRB
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

The following records must be maintained for each subject enrolled:

- Original, signed and dated ICF, as well as documentation of the process of consent;
- Completed CRFs, DCFs, and source document worksheets, 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 must remain on file at the 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.

15.0 Changes 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 Tactile Medical personnel and the investigator, and IRB approval will be obtained before any changes are implemented. All changes must be documented.

16.0 Statistical Methods

16.1 Sample Size Determination

No power calculations were used to derive a sample size for this study given this study seeks to identify which health outcomes should be used for a larger randomized controlled trial in the future. The desired target sample size for this feasibility study is 10 analyzable data sets for each group. It is estimated that up to 30 subjects will need to be enrolled to achieve 60 day follow-up data on 20 subjects.

16.2 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 the result of 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 feasibility nature of the study suggests that the statistical focus will be on estimation and hypothesis generation. Thus, formal statistical tests of hypotheses are not planned.

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

17.0 Publication Plan

All information obtained during the conduct of the study will be considered confidential and 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 and Publication Plan.

18.0 References

1 Perdomo M, Davies C, Levenhagen K, Ryans K. Breast cancer edge task force outcomes: Assessment measures of secondary lymphedema in breast cancer survivors. *Rehabilitation Oncology.* 2014; 32:22-35.

2 Zaleska M, Olszewski WL, Durlik M. The effectiveness of intermittent pneumatic compression in long-term therapy of lymphedema of lower limbs. *Lymphatic Research Biology.* 2014; 12:103-9.

3 Langbecker D, Hayes SC, Newman B, Janda M. Treatment for upper-limb and lower-limb lymphedema by professionals specializing in lymphedema care. *European Journal of Cancer Care*. 2008; 17:557-64.

4 Fife CE, Davey S, Maus EA, Guilliod R, Mayorovitz HN. A randomized controlled trial comparing two types of pneumatic compression for breast cancer-related lymphedema treatment in the home. *Support Care Cancer.* 2012; 20:3279-86.

5 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. *Lymphatic Research Biology*. 2015; 13:208-14.

6 Blumberg SN, Berland T, Rockman C, et al. Pneumatic compression improves quality of life in patients with lower-extremity lymphedema. *Annals of Vascular Surgery*. 2016; 30:40-4.

7 Muluk SC, Hirsch AT, Taffe EC. Pneumatic compression device treatment of lower extremity lymphedema elicits improved limb volume and patient-reported outcomes. *European Journal of Vascular Endovascular Surgery*. 2013; 46:480-7.

8 Ridner SH, McMahon E, Dietrich MS, Hoy S. Home-based lymphedema treatment in patients with cancer-related lymphedema or noncancer-related lymphedema. *Oncology Nursing Forum*. 2008; 35:671-80.

9 Palmer S. Barriers and facilitators to successful lymphedema therapy: the role of adherence. *Lymph Link*. 2006; 18:1-5.

10 Brown JC, Cheville AL, Tchou JC, Harris SR, Schmitz KH. Prescription and adherence to lymphedema self-care modalities among women with breast cancer-related lymphedema. *Support Care Cancer*. 2014; 22:135-43.

11 Keeley V, Crooks S, Locke J, et al. A quality of life measure for limb lymphedema (LYMQOL). *Journal of Lymphoedema*. 2010; 5:26-37.

12 Ridner SH, Dietrich MS. Development and validation of the lymphedema symptom and intensity survey-arm. *Support Care Cancer*. 2015; 23:3103-12.