Physiologic responses to varying lymphoedema compression programs with the Flexitouch® System
or
"FlexDose" (**Flex**itouch **Do**sing **S**ystemic **E**valuation)

Protocol # 4010

Version 2.0
13 March 2014

Investigator Signature

Title*:* Dosing Evaluation to Access Treatment Protocol for Lower Extremity Lymphoedema with Flexitouch® System

Protocol Number: 4010

I confirm that I have read this protocol. I will comply with the protocol and the principles of Good Clinical Practices (GCP), the International Conference on Harmonisation Guidelines, Therapeutic Goods Act, institutional research policies and procedures and other appropriate regulatory requirements.

_____

Site Principal Investigator Name (Print)

_____ _____

Site Principal Investigator Signature Date

Table of Contents

1.0 Study Contact Information

1.1 Sponsor Contact Information

Tactile Systems Technology Inc.
Sunday Hoy, Esq., Director of Clinical Resources and Research
1331 Tyler Street NE, Suite 200
Minneapolis, MN 55413
USA
+1.612.355.5121 Office
+1.612.355.5104 Fax
shoy@tactilesystems.com

1.2 Investigator Contact Information

Vaughan Keeley, PhD, FRCP
Consultant in Palliative Medicine
Royal Derby Hospital
Uttoxeter Road
Derby DE22 3NE
United Kingdom
+441332783075 Office
vaughan.keeley@nhs.net

2.0 Common Abbreviations/Acronyms:

BMI	Body Mass Index
BIS	Bioimpedance Spectroscopy
CDT	Complete Decongestive Therapy
CE	*Conformité Européenne*, meaning "European Conformity"
CRF	Case Report Forms
DVT	Deep Vein Thrombosis
EC	Ethics Committee
FDA	Food and Drug Administration
FT	Flexitouch® system
LE	Lower Extremity
LTW	Local Tissue Water
MLD	Manual Lymphatic Drainage
MyMOP	Measure Yourself Medical Outcome Profile
PCD	Pneumatic Compression Device
TSTI	Tactile Systems Technology, Inc
U/S	Ultrasound

3.0 Introduction

3.1 Background and Rationale: Lymphoedema is a chronic, progressive, and debilitating condition arising from congenital abnormalities (primary) or acquired damage (secondary) to the lymphatic system.[1] A healthy lymphatic system works primarily to 1) drain a complex fluid called lymph from the tissues; 2) direct it to structures called lymph nodes which filter out cellular debris, bacteria, and toxins, and then; 3) return it to the major vessels of the venous system.[1] The lymphatic system also serves vital immunological functions such as the production of lymphocytes to defend against infection and disease. Approximately 2-3 liters of lymph is cycled daily from the bloodstream into bodily tissues and, via the lymphatic system, back into the general circulation.[2]

A significant proportion of patients with lymphoedema experience a worsening, ultimately irreversible limb swelling arising from the accumulation of fluids normally regulated by the lymphatic system. Enlargement of extremity proportions may be dramatic and disfiguring. Many suffer impairments in mobility and function due to the weight and bulk of a lymphoedematous limb. Complications include chronic pain, decreased range of motion, compromised immunological function and increased incidence of acute inflammatory episodes and infection.[2,5,6,7] Psychological complications include increased anxiety, depression, negative body image/loss of body confidence, anger, frustration, sexual dysfunction.[8,9]

Lymphoedema is an incurable but treatable condition. Growing awareness of the considerable health, economic and psychosocial consequences of this chronic disability has intensified the search for more effective management strategies.[3,4,10-12]

The goals of lymphoedema therapy are 1) to reduce limb girth; 2) to reduce swelling by encouraging the development of collateral lymph drainage pathways and by stimulating function of intact routes (that is to improve lymph transport from the tissues); 3) to prevent re-accumulation of fluid in interstitial tissues; 4) to prevent or control infection and; 5) to reduce physical disability and psychological sequelae.[1,13,14]

Pneumatic compression devices (PCDs) have been utilized for many years as an adjunct to home lymphoedema care. PCD treatment is intended to assist with limb volume control for patients with lymphoedema. In many cases, the aim is to simulate and potentially replace the conventional self-manual lymphatic drainage (MLD) component during Phase II of Complete Decongestive Therapy (CDT) in patients suffering from lymphoedema. The Flexitouch® system (FT) is an advanced PCD that was developed to aid in lymphoedema management at home.

Though there have been a number of publications on the use of PCD for the treatment of lower extremity lymphoedema, none have had the aim to define the optimal treatment dose with regards to pumping pressure, frequency of treatment session, and duration of the treatment session.[10] Treatment duration in the literature can range from intensive treatment of 6 to 8 hours per treatment session to a less time intensive treatment regimen of as little as 30 minutes to 1 hour per session.[15,16] Additional studies are needed to further address the optimal dose including duration and pressure.[16] Tactile Systems Technology, Inc (TSTI) the makers of the Flexitouch ® system (FT) is dedicated to improving the lives of patients with lymphoedema and chronic swelling conditions through ongoing clinical research to determine optimal treatment.

Compression garments are often part of standard care for patients with lymphoedema. For the purposes of this study that is designed to evaluate the physiologic impact of pneumatic compression device dosing, the compression garment usage will not be formally evaluated. However the compression garments will be standardized across all study patients, mandating knee high compression garments with a pressure of 30–40 mmHg. If it is determined by data collection or clinical assessment that the garments variable is influencing the FT effect then the type and use of garment will be further controlled in future studies.

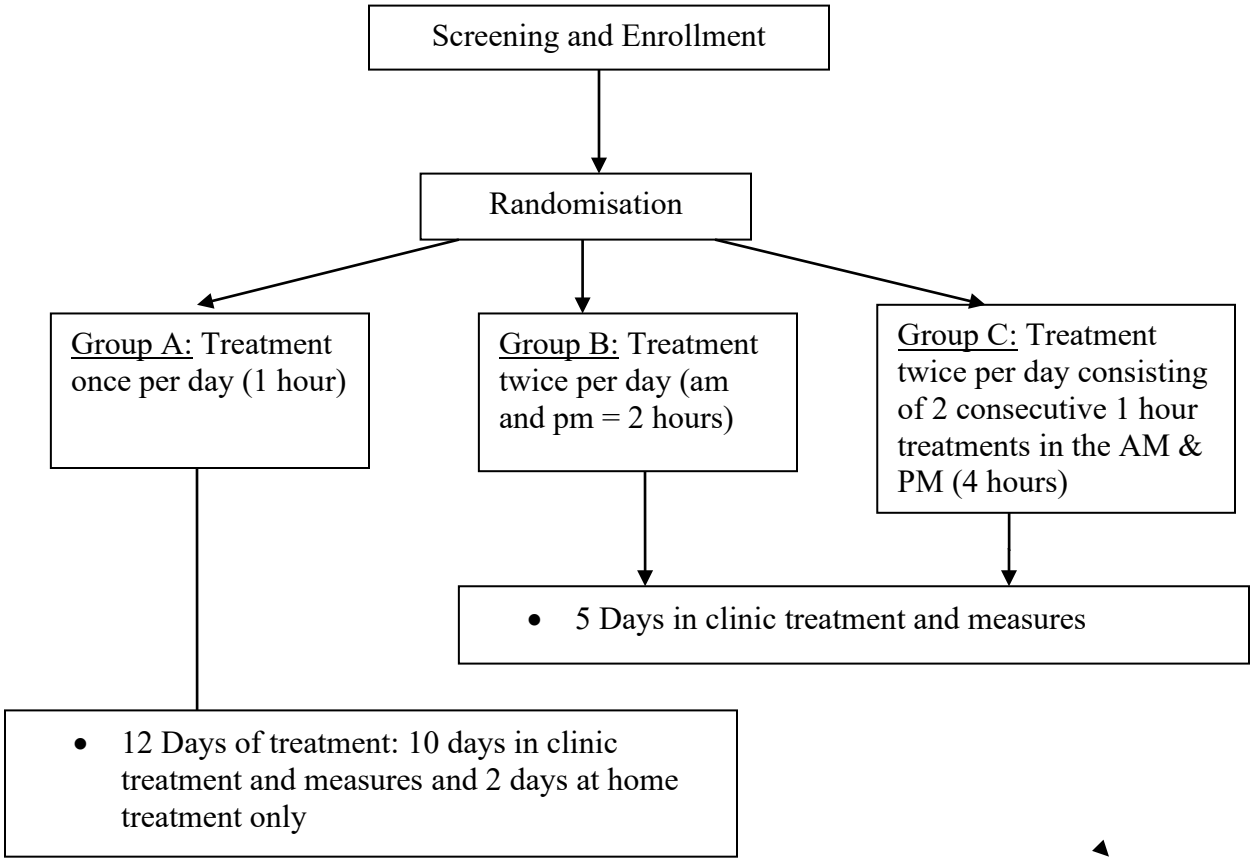
3.2 Device Description and Intended Use:

Flexitouch® system (Tactile Systems Technology, Inc., Minneapolis, MN, USA): The FT is a programmable, segmental, gradient pneumatic compression device which has been cleared by the FDA for market in the US (K013061, K120972), by Heath Canada for market in Canada (88415) and by European Union for market in Europe (CE 0459) for the treatment of lymphoedema, primary lymphoedema, post mastectomy oedema, oedema following trauma and sports injuries, post immobilization oedema, and venous insufficiencies. Additionally, the device has been cleared to market in the US by the FDA (K062818) for reducing wound healing time as well as the treatment and assistance in healing stasis dermatitis, venous stasis ulcers, arterial ulcers and diabetic leg ulcers (Appendix A).

4.0 Study Objectives: The study objectives have been selected in this proof of principle study in order to determine if there is a difference in treatment effect across the 3 study groups when treating lower extremity lymphoedema using the Flexitouch® system.

5.0 Study Design

5.1 Overview of Study Design: This study is a 3 arm, prospective, randomised, proof of principle clinical trial to determine the optimal treatment duration for achieving a measurable physiologic effect on lower extremity lymphoedema with the Flexitouch® system (FT) as determined by bioimpedance, perometry, tonometry, ultrasound, local tissue water assessment, symptom burden and subject interview.. Each intervention arm will include 10 completed subjects for a total of 30 completed subjects.



5.2 Endpoints The endpoints for this study include:

- Intra/extra cellular fluid changes (bioimpedance)
- Limb fluid volume changes (whole and segmental) (perometry and bioimpedance)
- Superficial tissue characteristics (induration/depth and thickness of fascia) using ultrasound and tonometry.
- Tissue water assessment utilizing Moisture Meter D and Ultrasound
- Symptom assessment (MyMOP)
- Qualitative interviews
- Activity level between and post treatment (pedometer and patient log)

5.3 Safety Endpoints: Safety endpoints will include incidence and severity of complications. A clinician will assess any signs and symptoms of acute infection, DVT, cellulitis, pain or any other need for medical intervention and the possible need for a subject to discontinue the study.

6.0 Study Population, Selection, Withdrawal/early exit

6.1 Study Population: This is a community based trial. The study population will be drawn from patients who are seeking or have previously sought treatment of primary or secondary lower extremity lymphoedema. Only patients who meet the inclusion criteria listed below will be considered for participation.

6.1.1 Inclusion Criteria: Subjects may participate in this study if they meet **all** of the criteria described below:

- Subjects must be ≥ 18 years old
- Subjects must have a diagnosis of primary or secondary Stage 2 unilateral or bilateral lower extremity lymphoedema.
- Must currently be using adequate compression garment(s) as determined by the clinician:
    - Garments must be at least 20mmHg and no more than 3 months old and must be worn upon rising and removed at bedtime.
- Subjects must have clinically relevant excess limb swelling as determined by clinician "pitting test".
- Must be able to attend all required in-clinic treatment visits

6.1.2 Exclusion Criteria: Subjects will be ineligible for this study if they meet any of the criteria described below:

- 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.
- Active infection or inflammation
- Active thrombophlebitis (within the last 2 months)
- History of pulmonary embolism (within the last 2 months)
- Documented history of deep chronic venous insufficiency or deep venous obstruction with a reflux duration of > 2 second in the deep system, and any history of deep vein thrombosis (DVT)
- History of pulmonary edema
- History of congestive heart failure
- History of chronic kidney disease with a glomerular filtration rate (GFR) of less than 30 mls per minute.
- Patients with poorly controlled asthma (i.e. those with severe persistent symptoms throughout the day, night time awakenings

several times per week, use of a beta2 agonist inhaler several times per day and those whose normal activity is extremely limited).

- Symptomatic or severe peripheral artery disease, defined by current lifestyle-limiting claudication or critical limb ischemia
- Presence of an open wound or ulcer of any etiology
- Diagnosis of lipoedema and lipolymphoedema*
- Currently using an in home pneumatic compression device
- Metal implants that would interfere with bio impedance equipment
- Individual with pacemaker or other implanted electronic devices
- Inability or unwillingness to remove bandaging from treatment regimen while participating in the study.
- Pregnancy
- Any condition where increased venous and lymphatic return is undesirable
- Inability or unwillingness to participate in all aspects of study protocol and/or inability to provide informed consent
- Currently participating in another clinical trial
- Currently using diuretics
- BMI > 40

6.1.3 Exit/Discontinuation Criteria: Subjects may exit the study prior to completion of all study visits if they meet any of the following criteria. The data collected as part of the study will be included in the intent to treat analysis.

- Subject death
- Subject voluntarily withdraws
- Subject experiences a serious adverse event that in the investigator's clinical judgment necessitates study discontinuation
- Subject acquires any of the exclusion criteria during treatment phase of the study

** Clinical assessment of lipoedema and lipolymphoedema will be completed to assure that the subject meets enrollment criteria. Lipoedema is a type of lipodystrophy, which can cause enlargement of the legs and be confused with lymphoedema. It is a clinical diagnosis with no specific diagnostic tests available. The typical pattern of lipoedema is excess fat deposition in the lower part of the body from the hips to the ankles, commonly with a history of bruising and tenderness. Patients also exhibit asymmetrical weight loss on dieting with weight being lost in the upper part of the body rather than the legs. Pure lipoedema is non pitting.*

Lipolymphoedema is the term used when patients with lipoedema develop superadded oedema. This typically forms around the ankles and feet and is pitting in nature. The diagnosis of lipolymphoedema is made by applying the

diagnostic criteria for lipoedema but with the presence of pitting oedema in the ankles and feet.

6.2 Recruitment and Randomisation

6.2.1 Recruitment Plan: Subjects will be recruited from patients either seeking or who have previously sought treatment at a clinic for lymphoedema. Desired enrollment/follow-up time (first subject in to last subject out) is 20 weeks. If additional recruitment is required to meet enrollment, referring general practitioners and potential reference clinics may be solicited for subjects. Patient advocacy/support groups may also be notified of the study opportunity. Subject recruitment materials may be provided for referring physicians' waiting rooms including posters, flyers, brochures, etc. If additional recruitment is required, direct to public advertisements in local newspapers may be utilized.

6.2.2 Randomisation Scheme: After completing the informed consent, subjects will be randomly assigned equally to one of three groups. Randomisation will follow the computer generated scheme. A master copy of the scheme will be kept at TSTI.

The site(s) will be provided with sealed envelopes containing the device assignment for each potential subject. Each envelope will be numbered sequentially from 01 to 030. Randomisation envelopes and/or subject IDs cannot be used more than once. After the subject signs the informed consent agreeing to participate in the study, the appropriate study staff will obtain the next sequential sealed randomisation envelope and open it while the subject is present.

The randomisation assignment cannot be changed or chosen by the subject or the investigator. The randomisation envelope should be placed in the subject binder.

6.3 Study Timetable:

Task	25 Weeks				
	1-5	6-10	10-15	15-20	21-25
EC/Regulatory	X	X			
Enrollment		X	X	X	
Treatment		X	X	X	X
Data Entry		X	X	X	X
Data Analysis				X	X

7.0 Treatment Plan and Study Procedures:

7.1 Dosage and Rationale: All subjects enrolled will receive treatment to the study leg using the FT study device. The treatment will be received in clinic and the garments applied by a trained clinician with the exception of Group A's weekend treatment which will be done by the patient in their home.

Subjects will be randomised into one of three groups. Following randomisation and study arm assignment the subjects will receive treatment according to study arm assignment:

Group A: subjects will receive 12 consecutive days of treatment utilizing the following treatment regimen. The first 5 days will be in clinic (Monday through Friday) followed by self administered at home treatment for 2 days (Saturday and Sunday). The last 5 days of treatment will be in clinic ending the treatment phase on day 12 (Monday through Friday).

- One lower extremity treatment per day using program L1 with the pressure set to "normal" applying the full garment set.

Groups B & C subjects will receive 5 consecutive days of treatment in clinic (Monday through Friday) utilizing the following treatment regimens.

- Group B: Two lower extremity treatments per day (am and pm) using program L1 with pressure set to "normal" applying the full garment set.
- Group C: Two consecutive treatments 2 times a day (am and pm) using program L1 with pressure set to "normal" applying the full garment set.

In the case of bilateral lymphoedema, the leg with the largest volume will be considered the study leg. The contralateral (non study) leg will be treated in the same manner that it was being treated prior to entering the study. Limb volume measures for both legs will be collected.

At the screening visit, each subject's compression garment(s) will be assessed for clinical adequacy (Class: ≥ 20mmHg; Age: 3 months or less) by the Principal Investigator. Subjects will be instructed to wear the compression garment(s) every day during wakeful time. Garments may be remove while bathing and overnight. The clinician will remove the subject's compression garment during device treatment. This treatment regimen is consistent with standard home care compression garment(s) treatment.

7.2 Subject Data Requirements: The following data will collected from all subjects:

Key: B = Before Treatment A= After Treatment D = During Visit	Screening	Baseline/ Initial Treatment (D1)	Treatment (≠ D1, 5 & 12)	Day 5(All Groups) and Day 12 (Group A)
Medical History	**D**			
Bio Impedance		**B A**	**B A**	**B A**
Perometer		**B A**	**B A**	**B A**
Duplex U/S	**B**			
Interface Pressure		**B**	**B**	**B**
Ultrasound		**B**		**A**
Tonometry		**BA**	**BA**	**BA**
Moisture Meter D		**B A***	**B A***	**B A***
Subject Interview				**D**
MyMOP		**D**		**D**
Activity Level		**D**	**D**	**D**
BMI		**D**	**D**	**D**
Adverse effects		**A**	**A**	**A**
Compliance		**D**	**D**	**D**

*Group C: Will have moisture meter done before the first treatment session, after the first treatment session, and then after the final treatment session of the day = 3 times total during treatment visits.

7.3 Laboratory Testing Procedures: After provision of informed consent, women of child bearing potential will be tested for pregnancy at the site specific clinical laboratory according to site standard procedures. If the pregnancy test is positive, subjects will be excluded from the study. Potential subjects suspected to have renal dysfunction will undergo a blood test to determine the glomerular filtration rate (GFR). Those subjects with a GFR of less than 30mls per minute would be excluded from the study.

7.4 Clinical Study Procedures: Pre-screening of subjects will be conducted by study staff either by phone or in person. Potential subjects will meet with study staff in-person for the consent process.

7.4.1 Informed Consent: Informed consent must be obtained from all subjects prior to randomisation and participation in clinical studies as mandated by Federal Regulations and/or the qualifying Ethics Committee (EC). A blank copy of the EC-approved informed consent form must be kept on-site and by the sponsor. The signed original for each subject must be kept in the subject's medical

records and copy of the signed informed consent will be provided to the subject.

A copy of the consent will be given to the subject to read and take home to consider if they prefer. All the subject's questions will be answered, prior to signing the informed consent. No research procedures will be performed until subject signs the consent. A signed copy of the consent will be provided to the subject. After completing the informed consent, subjects will be randomly assigned equally to one of 3 groups.

7.4.2 Duplex Ultrasound: This test will be done at the time of the screening visit to rule out a significant deep vascular obstruction or venous insufficiency as determined by a reflux of > 2 second. If the subject had a duplex U/S done within the last two months the results may be reviewed and utilized for inclusion or exclusion into the study. The test has no associated risks. A water soluble gel is placed in a handheld transducer, which directs high-frequency sound waves to the arteries or vein being tested. Subject should experience no pain or discomfort.

7.4.3 Bioelectrical Impedance: A Bioimpedance Spectroscopy (BIS) device will also be used to quantify changes in intra- and extra-cellular fluid at each visit. BIS utilizes the characteristics of frequency dependent current flow to detect fluid changes. Measurements are generated by a low frequency electrical signal transmitted to the patient from the device through skin surface electrodes. The measurement is imperceptible to the subject and is not confounded by weight or muscle changes that may occur in the limbs. Appendix B contains the study procedure for bioimpedance.

7.4.4 Limb Volume Measurement: Limb volume measures will be taken at each visit for both legs of the subject. The site will conduct limb volume measurements using an optoelectronic system (Pero-System, Perometer, Appendix C). The perometer utilizes infra red light beams to measure limb volume more rapidly than the circumferential tape measure method. These systems have been validated against circumferential measures to a correlation coefficient of .977 in leg subjects.[17] The perometer can be used for whole leg or segmental (upper/lower) measurements. Perometer measurement will be taken twice on each leg and the average used.

7.4.5 Tonometry: Tissue assessment/fibrosis will be evaluated with use of a tonometer at anatomically defined locations on the affected leg and on the trunk. The Tonometer is a mechanical device that gives

an indication of the resistance of tissue to compression. It is used in lymphoedema to give an estimate of the extent of pitting and fibrotic induration. Tonometry readings of the affected areas will be compared to readings taken pre-treatment intervention. Appendix D contains the Tonometer operating instructions and the body points for this trial.

7.4.6 Tissue Ultrasound (U/S): Tissue ultrasound will be used to measure skin thickness and oedema in fixed areas of the limb and trunk at Day 1 (pre-treatment) and at the day 5 (All Groups) and day 12 (Group A) post FT treatment. Measurements will be obtained at defined anatomic locations. The aim of this is to measure and assess for changes in the tissue in the treated limb and trunk. A positive correlation has been observed between skin thickness and oedema in the affected lymphoedema arm. In addition, increases in skin thickness may also be related to development of fibrosis or other skin changes. The use of ultrasound has been suggested in the literature as another simple, reliable means to evaluate therapeutic outcomes.[18]

7.4.7 Other Measures:

Local tissue water (LTW) measures will be obtained with a Moisture Meter D™ (Delfin Technologies, Finland). This device and technology has been demonstrated to provide a measure of LTW and its change based on measurements of the skin's tissue dielectric constant at a frequency of 300 MHz. The method has been widely used in clinical studies to evaluate LTW and its change under a variety of conditions.[19-22] (Appendix E)

Interface pressure will be obtained with the PicoPress®. This technology was designed to be used to determine the pressure exerted under both static and dynamic compression. The PicoPress® transducer allows for dynamic pressures readings.[23] Appendix F

Symptom assessment will be obtained by using the Measure Yourself Medical Outcome Profile (MyMOP). This questionnaire was created to be a patient-generated or individualized outcomes questionnaire. It was designed to be problem specific but also include general wellbeing questions. Patient symptoms can be emotional, social or physical (Appendix G). At the conclusion of study treatment visits the subject-reported treatment comfort and effectiveness will be assessed by asking the subject targeted questions. (Appendix H)

Activity level will be monitored through the use of a pedometer and a subject diary. The subject wear a pedometer during the treatment phase of the study to record the number of steps accumulated throughout the day. The diary is intended to capture additional information regarding the subject's activity level such as type of activity.

7.4.8 Screening Visit: At this visit, the patient will be asked to provide written informed consent and inclusion and exclusion criteria will be evaluated to ensure that the patient meets all entrance criteria. See section 7.2 for a schedule of events.

After the informed consent process is complete, the subject will be randomised into one of 3 study groups. The baseline visit must occur on a Monday. Study staff and the subject will make every attempt to schedule all study visits at the same time of day.

At this visit, the subject will withdraw all at home lymphoedema treatments with the exceptions of wearing appropriate compression garments and maintaining proper skincare. Subjects cannot use limb bandaging at any time during the study.

The subject will leave the screening visit with:

- Schedule for all study visits with the first treatment visit starting on a Monday.
- Pedometer and instruction to start wearing the morning of the first treatment visit
- Diary to record daily activity and instructions to start documenting the morning of the first treatment visit
- Contact information and instructions to call if any problems arise

7.4.9 Baseline Visit/Initial Treatment: At the time of the baseline/initial treatment visit the subject will undergo the study procedures according to the table in section 7.2.

During the visit the subject will undergo treatment according to which group they were randomised. For Groups B and C which receive FT treatment twice a day the subject must have at least 2 hours and no more than 6 hours between the am and pm treatment sessions. The compression garment must be worn between the am and pm treatment sessions.

7.4.10 Treatment Visits (Group A: Day 2 to 5; 8 to 12; Group B & C: Day 2 to 5): The subject will be examined, receive FT

treatment according the treatment group assigned and the study parameters according to the table in section 7.2 will be completed and recorded by appropriately trained study staff.

7.5 Investigational Device Accountability

The site must maintain a device accountability log. Completion of this log will ensure that all investigational devices are properly tracked and accounted for throughout the study from the time they are received by the institution to the time they are returned to the study sponsor or other designated site. Device location, Subject ID assigned, date Subject returned to site (if assigned to Group A subject), controller disinfected, and final disposition (e.g., returned to sponsor, garments discarded) of all pneumatic compression devices and garments will be documented. The sponsor must also maintain device accountability documenting all shipments and returns of investigational devices by serial number, date, and person completing the log. Storage locations for the investigational devices and garments will be secure (i.e., locked and away from other devices) with access restricted only to investigators and authorized research personnel.

Sanitation Procedure:

At the conclusion of each treatment session the clinic will disinfect the controller and store the subject's garments which must be clearly labeled with subject identification information until the next treatment to ensure that the garments are not used on other study subjects. Group A will be taking a controller and their FT garments home for the weekend. Upon return that site must disinfect the controller before using in clinic. The subject garments should be stored like all other subject assigned study garments. The garment(s) **CANNOT** be reused on multiple subjects and should be appropriately discarded upon study completion.

8.0 Statistical Plan

8.1 Study Design: This study is a prospective, randomised, proof of principle clinical trial to determine the optimal treatment duration and frequency between three options for treating lower extremity lymphoedema with the Flexitouch® system (FT). Optimal treatment duration will be determined by a nested series of physiologic and clinical changes induced by FT treatment within three key outcomes categories: (a) fluid dynamics (as assessed by bioimpedance, perometry, and local tissue water assessments); (b) tissue characteristics/fibrosis (by ultrasound and tonometry measurements); and (c) patient-reported outcomes (quantified by symptom assessment tools, treatment assessments, treatment adherence, and subject interview.) Patient demographics will be summarized and compared between the randomised groups.

8.2 Efficacy Analysis

Analysis will be undertaken for the following groups:

Group A: One lower extremity treatment per day using program L1 with the pressure set to "normal" utilizing the full garment set over 12 days. Total number of treatment hours=12.

Group B: Two lower extremity treatments per day (am and pm) using program L1 with pressure set to "normal" utilizing the full garment set over 5 days. Total number of treatment hours=10.

Group C: Two consecutive treatments 2 times a day (am and pm) using program L1 with pressure set to "normal" utilizing the full garment set over 5 days. Total number of treatment hours=20.

This study is planned to have a maximum of 30 completed subjects, 10 in each group with unilateral or bilateral primary or secondary leg lymphoedema. Each subject will receive the FT as per the groups described above. This small sample size will not offer a powered statistical analysis for any single outcome measurement, but is designed to estimate treatment effects for each proposed endpoint for evaluation in a subsequent clinical trial. This study is designed to determine both which measurement endpoints are most sensitive to the variable dosing protocols and to determine which endpoint should be defined as the primary end-point in a larger investigation of compression "dosage". The study will be used to find the effect size for comparisons between the doses and from this to estimate a suitable sample size for a definitive study.

Subjects with missing data for the study outcomes will be included in the intention to treat analysis. However, the study will continue to enroll until there are 10 subjects in each arm that complete all study visits. After 30 patients have been randomised, those patients who fail to complete all treatment visits will be replaced until all data are available for 10 subjects in each study group. Data from the subjects who fail to complete will be used to determine the adherence to therapy in each randomised group.

Study analysis will be conducted for "within day" change as well as "between day" change. "Within day" change is defined as a comparison of pre-treatment measures against post-treatment measures following the last treatment of the day. "Between day" change is defined as a comparison of pre-treatment outcomes on treatment day 1 compared to post-treatment outcome measures on the final treatment day (day 12 for group A, day 5 for groups B and C).

This study will evaluate FT-induced changes in three types of outcome measurements categorized as:

(a) fluid dynamics (measured via bioimpedance; moisture meter; and perometry);

(b) subcutaneous tissue density (a presumed surrogate marker of tissue fibrosis measured via tonometry)

(c) patient reported outcomes addressing symptoms, treatment satisfaction; and treatment adherence (measured via MYMOP; patient survey and adherence diary).

Although this is a pilot study with multiple outcomes, the outcome measurement order as listed above indicates a *pre hoc* identification of the order of significance of the outcome measures (change in fluid dynamics > change in tissue fibrosis > change in patient outcomes) in this short-term dose-finding trial.

8.2.1 Analysis of Fluid Dynamics/Change

Bioimpedance measurement

It is hypothesized that changes in the intracellular and extracellular fluid ratios as measured by multifrequency bioimpedance will yield the most relevant pilot data indicative of treatment success. At present there is no indication of the magnitude of the effect expected using bioimpedence. However, since this is a comparative study, any difference in ECF/ICF change will be evaluated between the three groups. This will be determined using a linear mixed model with repeated measures.

For the within day measures the change in ECF/ICF will be calculated, and used as the dependent variable. Assigned group and day of visit will be forced into the model to allow for comparisons between groups and changes over time ECF/ICF ratio at baseline, BMI, time of day measurements are taken, activity level (number of hours upright and ambulatory), age, number of hours utilizing compression garment, will be tested for inclusion in the model.

To evaluate the between day outcome the change in ECF/ICF from baseline (pre-treatment) will be calculated for each follow up visit (post-treatment), with assigned group and day of visit forced into the model. Identical confounding variables will be used as for the within day analysis.

Final analysis will examine the change in ECF/ICF ratio from baseline to end of final treatment using the same model as above.

Local Tissue Water

Local Tissue Water (LTW) will be assessed prior to and post-treatment at each visit as for the bioimpedance data. The analysis will therefore be undertaken in a similar way to the bioimpedance data.

Perometry
Perometry will used to estimate limb volume pre and post treatment. The analysis will therefore be undertaken in an identical way as for the bioimpedance measurements.

8.2.2 Analysis of Subcutaneous Tissue Density/Fibrosis

Subcutaneous tissue density and fibrosis are being assessed using one method, namely tonometry. Tonometry will be assessed at two or 3 time points depending on study group, at baseline (prior to first treatment), and after the final treatment on day 5 and day 12 if applicable. A repeated measures mixed linear model will be used to determine the changes in subcutaneous density at these time points. Randomised group will be forced into the model. Other covariates considered for inclusion in the model will include BMI, time of day measurements are taken, activity level (number of hours upright and ambulatory), age and number of hours utilizing compression garments.

8.2.3. Analysis of Patient Reported Outcomes.

Patients' self-reported symptoms and change in symptoms are recorded using the MYMOP questionnaire. Analysis will be undertaken to compare the intensity of the self-reported symptoms using a repeated measures analysis, with BMI, activity level (number of hours upright and ambulatory), age and number of hours utilizing compression garments.

8.3 Adherence to Therapy

Adherence will be evaluated by investigating the number and reasons for withdrawal for patients who fail to complete the pre-specified number of treatments and visits along with compression garment compliance and at home device usage for Group A.

9.0 Safety and Adverse Events

9.1 Risk Analysis: The subjects enrolled in the study are not expected to be at any higher or additional risk than those who use non-study pneumatic compression devices. There is risk with using any pneumatic compression device. These may include, but are not limited to risk of explosion if the device is used in the presence of flammable gases, risk of electrical shock if

the device is immersed in water or if the housing is broken and subject attempts to service the unit.

Pneumatic compression devices are contraindicated for use in the presence of pulmonary edema, thrombophlebitis, congestive heart failure, deep vein thrombosis, episodes of pulmonary embolisms, acute cancer, acute infection, and inflammationor other conditions where increased lymphatic return in undesirable. Clinical trials have not been completed to show the safety of using the FT garments during pregnancy and therefore should not be used.

There are minimal side effects expected from the treatment subjects will receive in this study. The expected risks are often a failure to respond to the treatment intervention and are not related to the treatment itself. In some cases, side effects due to lymphoedema can be serious, long lasting, or may be permanent. The risks listed below are symptoms of lymphoedema and may be experienced by all subjects with lymphoedema:

Likely:

- Pain or discomfort
- Increased swelling

Less Likely:

- Cellulitis – Infection of the skin which may include swelling, redness, and tenderness of the infected tissue
- Development of or increased edema in the truncal and/or genital region.

Ultrasound, bio-impedance and moister meter are procedures with minimal risk involved.

9.2 Adverse Events Reporting: All adverse events (related or not related to the device treatment) that occur throughout the conduct of the study will be reported. An adverse event is defined as any undesirable experience associated with the use of a medical product.

Anticipated Adverse Events

Adverse events associated with lymphoedema may include, but are not limited to: cellulitis, deep vein thrombosis, increased swelling.

All adverse events are to be reported to TSTI at the time of occurrence or when the Investigator becomes aware of the adverse event (e.g., at the follow-up evaluation).

TSTI may request that additional information such as operative notes, discharge summaries, lab reports, and a physician's summary of the event, be provided to TSTI as supporting documentation for any reported adverse event.

In the event of a subject death, a death summaries and autopsy reports will be provided to TSTI.

Serious Adverse Events

A serious adverse event is any adverse event that affects subject health or safety, that is life threatening, results in disability or permanent damage, or requires intervention to prevent permanent impairment/damage, or an event that results in hospitalization (initial or prolonged) or causes congenital or anomaly/birth defect, or results in death.

It is the responsibility of the Principal Investigator to notify their EC of any adverse events, as required. Serious adverse events will be reviewed by TSTI and the final determination as to whether or not an event is related to the device or treatment will be made by TSTI. If a serious adverse event is deemed related by TSTI, TSTI will report the event to the appropriate regulatory body and to all reviewing EC and participating investigators within 10 working days after TSTI first receives notice of the event, as required.

The protocol is specifically designed to minimize risks through careful subject selection (reference section 5.1.1 Inclusion Criteria and 5.1.2 Exclusion Criteria), rigorous adherence to a standardized schedule of treatment visits and routine clinical monitoring by TSTI representatives.

9.3 Subject Withdrawal: Subjects may voluntarily withdraw at any time, for any reason. Reasons for withdrawal will be recorded if the subject is willing to share this information. Subjects will be withdrawn from the study if they experience a serious adverse event or for any other reason set forth in section 5.1.3 or if in the investigator's judgment the subject develops an unrelated illness which will significantly affect assessment of the subject's clinical condition. The data from the withdrawn subjects will be included in the intent to treat analysis.

Withdrawn subjects will be replaced according to the following process:

- After all randomisation assignments have been assigned via the randomisation scheme. The site will review the subject withdrawal list and replace the subject according the sequence of subject withdrawal. For example: If first subject withdrawal is from Group A then the second from Group C. The next eligible subject would be enrolled in Group A followed by Group C. This will continue until there are 10 subjects completed in each study group for a total of 30 completed subjects.

10.0 Deviations from the Clinical Protocol: Any deviation from this Clinical Protocol undertaken to protect the life or physical well-being of a subject in an emergency

situation must be reported to the sponsor and the respective EC as soon as possible, but in no event later than five (5) working days after the emergency occurred. Anticipated deviations from this plan in a non-emergency situation must be pre-approved by the sponsor via telephone, e-mail, fax, or mail. It is preferred that deviations scheduled to be performed in a nonemergency situation not be conducted until written authorization via fax, mail, or e-mail is provided by the sponsor. All protocol deviations must be documented. Deviations that may affect the scientific soundness of the study, or the rights, safety or welfare of the subjects must also be reported to the reviewing EC according to their reporting requirements. Protocol deviations may necessitate the discontinuation of the subject from the study.

11.0 Subject Compensation: The sponsor agrees that it is responsible for the reasonable and necessary costs of diagnosis, care and treatment of any undesirable side effects, adverse reactions, illness or injury to a subject in the Investigation which are determined to result from participation in the Investigation, except for cost as a result of (i) any failure of Institution, Site Principal Investigator or any of the employees or agents of the Institution, Principal Investigator or Co-Investigator, to conduct the investigation in compliance with the clinical protocol, (ii) violation of any law, including the Health Insurance and Portability Act (HIPAA) (iii) any negligent or willful acts or omissions of Institution, Site Principal Investigator or Co-Investigator (iv) any misuse of the device by the Institution, or Site Principal Investigator or any Co-Investigator or any of the employees or agents of the Institution, Site Principal Investigator or Co-Investigator or (v) medical problems caused by failure of the subject to follow study instructions. Subjects may be provided reasonable reimbursement for time and/or parking/travel costs arising out of their participation in the trial. Subjects will not be otherwise compensated for their participation in the study.

12.0 General Study Information

12.1 Technical Support: Training and support for study procedures will be provided by the Sponsor contact listed in Section 1.1 or designee.

12.2 Discontinuation of the Study: The study may be terminated if:

- That the rate of severe adverse events in any arm of the study is such that the Ethics Committee decides continued participation would compromise subject safety. If deemed necessary by the Ethics Committee, a follow-up safety analysis will be performed for all subjects.
- Target subject accrual has not met, and cannot meet subsequent trial objectives.

Upon study termination by Sponsor, Sponsor will compensate Institutions for actual Study costs incurred through the close out of the Study, in accordance with the terms of the study contract.

12.3 Record Retention: Records must be maintained for a period of at least ten years after the date on which the study is completed or terminated. Investigator or Institution shall notify Sponsor at least thirty (30) days prior to any planned archiving or destruction of records related to this study. The recordings from the patient interviews will be transcribed and the recording then deleted. The transcription will be maintained with the study records.

12.4 Quality Assurance Procedures: This study will be conducted in accordance with Good Clinical Practice and International Conference on Harmonization Guidelines, NHS Trusts, 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. The investigators will permit regular monitoring, audits and site inspections by the EC, the sponsor, government regulatory bodies and any institution compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspection of applicable study related facilities. Regular trial monitoring will be conducted to ensure compliance to this protocol.

12.5 Materials Provided by the Sponsor: Sponsor will provide administrative study materials along with the FT controllers and garments, PicoPress® and pedometers.

12.6 Materials Provided by the Site: Institution will provide assessment equipment (scales, lab tests, perometer, bio impedance equipment, tonometer, clinical and support staff) needed to complete the trial.

13.0 Administrative Study Information

13.1 Pre-Study Site Visit: The study sponsor may conduct onsite visits or telephone qualification (pre-study audit) prior to study initiation to ensure to verify adequate resources, staffing and a sufficient subject pool.

13.2 Ethics Committee Review: Prior to subject enrollment and study initiation, the appropriate Ethics Committee and National Competent Authority (if applicable) must approve the clinical study. It is the responsibility of the investigator to provide the Ethics Committee with all necessary information to satisfy the individual institution's requirements.

13.3 Clinical Site Monitoring: Clinical sites will be monitored for compliance with the clinical protocol, investigator agreement, and applicable regulatory 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 a 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, EC review, and regulatory inspection(s), providing direct access to source data and documents as legally appropriate. Monitoring will be performed by study sponsor and/or local study monitor. Monitoring will review subject source documentation and Case Report Forms for accuracy, completeness, and compliance with Good Clinical Practice procedures. Monitoring site visits will be performed at approximately quarterly intervals. Additional site visits may be scheduled at the discretion of the Sponsor upon review of the monitoring reports. In addition to site visits, a screening log will be submitted to Sponsor or designee by the sites as requested (by fax or e-mail). This screening log will be reviewed with the site for plan vs. actual recruitment purposes.

13.4 Investigator Records and Reports: Records to be maintained by the investigator in a designated study file include:

- Investigational plan and all amendments
- Signed Investigator Agreement
- EC approval letter, including a copy of the approved consent forms, progress reports, Adverse Event Report
- EC roster or Assurance number, if applicable
- All correspondences relating to the conduct of this study between the site and sponsor, ECs, 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
- Investigational device inventory information including the date, quantity and serial number of all devices and received identification of all subjects who received treatment, and final disposition of the devices.
- Screening log
- Financial Disclosure documentation for the Investigator and Co-Investigators, if applicable
- Reports (see Table 1)

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 (if applicable), etc.
- Records pertaining to a subject's death during the investigation

Investigators are required to prepare and submit to the sponsor 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 Table 1.

Table 1: Investigator Reports

Reports	Submit To	Timeframe
Unanticipated Adverse Device Event	Sponsor and Reviewing EC	As soon as possible but no later than 10 working days
Withdrawal of EC Approval	Sponsor	Within 5 working days
Progress	Sponsor, Monitor and Reviewing EC	Annually, at a minimum
Final	Sponsor and Reviewing EC	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 or when it is no longer needed to support a marketing application, whichever is later. All investigators must contact Tactile Systems 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 Systems 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.

13.5 Changes Necessary After Study Initiation: Should changes in the study plan or protocol become necessary in the course of the clinical trial, those specific changes will be discussed and agreed upon by the Sponsor, its acting representative if appropriate, Investigator, and appropriate EC

approval obtained before the changes are implemented. All changes must be documented.

14.0 References

1. Szuba A, Rockson SG. Lymphedema; Classification, diagnosis and therapy. *Vasc Med* 1998; 3: 145-156.
2. Moffatt CJ, Franks PJ, Doherty DC, Williams AF, Badger C, Jeffs E, Bosanquet N, Mortimer PS. Lymphedema: an underestimated health problem. *Q J Med* 2003; 96: 731-738.
3. Tiwari A, Cheng KS, Button M, Myint F, Hamilton G. Differential diagnosis, investigation, and current treatment of lower limb lymphedema. *Arch Surg* 2003; 138 (2): 152-161.
4. Gomide LB, Matheus JPC, Candido dos Reis FJ. Morbidity after breast cancer treatment and physiotherapeutic performance. [Review Article]. *Int J Clin Pract* 2007; 61 (6); 972-982.
5. Fleissig A, Fallowfield LJ, Langridge CI, Johnson L, Newcombe RG, Dixon JM, Kissin M, Mansel RE. Post-operative arm morbidity and quality of life. Results of the ALMANAC randomized trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. *Breast Cancer Res and Treatment* 2006; 95: 279-293.
6. Velanovich V, Szymanski W. Quality of life of breast cancer patients with lymphedema. *Am J Surg* 1999; 177: 184-188.
7. Morgan, Franks, & Moffatt, (2005).Health related quality of life with lymphedema: a review of the literature. *International Wound Journal*, 2 (1), 47-62.
8. Williams A.F., Moffatt C.J., Franks P.J. (2004) A phenomenological study of the lived experiences of people with lymphedema. *International Journal of Palliative Nursing*, 10, 279-286.
9. Ridner, S.H., MKcMahon, E., Dietrich, M.S., Hoy S. (2008) Home-Based lymphedema treatment in patients with cancer-related lymphedema or non cancer-related lymphedema. *Oncology Nursing Forum,* 35, 671-680.
10. Brennan MJ, Miller LT. Overview of treatment options and review of the current role and use of compression garments, intermittent pumps, and exercise in the management of lymphedema. *Cancer* 1998; 83 (12 Suppl American): 2821-2827.
11. Kligman L, Wong RK, Johnston M, Laetsch NS. The treatment of lymphedema related to breast cancer: a systematic review and evidence summary. *Support Care Cancer.* 2004 Jun; 12(6):421-31.
12. Harris SR, Hugi MR, Olivotto IA, Levine M. Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer Clinical practice guidelines for the care and treatment of breast cancer: 11. Lymphedema. *CMAJ.* 2001; 164(2):191-199.
13. Badger C, Preston N, Seers K, Mortimer P. Physical therapies for reducing and controlling lymphedema of the limbs. *The Cochrane Database of Systematic Reviews* 2004, Issue 3. Art NO: CD003141.pub2. DOI: 10.1002/14651858.CD003141.pub2.
14. Cohen SR, Payne DK, Tunkel RS. Lymphedema: Strategies for Management. *Cancer* 2001; 92 (4) (Suppl): 980-987.
15. Cheville A, McGarvey CL, Petrek JA, Russo SA, Taylor ME, Thiadens SR. Lymphedema Management. Seminars in Radiation Oncology. 2003:13 (3) 290-301
16. Comerota A, Aziz. The Case For Intermittent Pneumatic Compression. *Journal of Lymphoedema* 2009; 4(2):57-64.
17. Mayrovitz HN, Sims N, Macdonald J. Assessment of limb volume by manual and automated methods in patients with limb edema or lymphoedema. *Adv Skin Wound Care* 2000;13(6):272-276.
18. Mellor RH, Bush NL, Stanton AWB, Bamber JC, Levick JR, Mortimer PS. Dual-frequency ultrasound examination of skin and subcutis thickness in breast cancer-related lymphoedema. *The Breast Journal* 2004;10(6):496-503. FH

19. Nuutinen J, Ikaheimo R, Lahtinen T. Validation of a new dielectric device to assess changes on tissue water in skin and subcutaneous fat. *Physiol Meas*. 2004, 25: 447-454.
20. Laaksonen DE, Nuutinen J, Lahtinen T, Rissanen A, Niskanen LK. Changes in abdominal subcutaneous fat water content with rapid weight loss and long-term weight maintenance in abdominally obese men and women. *Int J Obes Relat Metab Disord*. 2003, 27: 677-683.
21. Mayrovitz HN. Assessing local tissue edema in postmastectomy lymphoedema. *Lymphology*. 2007. 40:87-94.
22. Mayrovitz HN, Davey S, Shapiro E. Local tissue water assessed by tissue dielectric constant: anatomical site and depth dependence in women prior to breast cancer treatment related surgery. *Clin Physiol Funct Imaging*. 2008. 28: 337-342.
23. Partsch H, Mosti G. Comparison of three portable instruments to measure compression pressure. *International Angiology*. 2010. 29:426-430.

15.0 Appendices