A Feasibility Study Evaluating Flexitouch® Plus with Novel Simultaneous Therapy Cycle Software in Patients with Unilateral Breast Cancer-Related Lymphedema (BCRL)

Protocol Number: 4070
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May 15, 2019
Protocol Version 2.0

Investigator Signature

Protocol Title: A Feasibility Study Evaluating Flexitouch Plus with Novel Simultaneous Therapy Cycle Software in Patients with Unilateral Breast Cancer-Related Lymphedema (BCRL)

Protocol Number: 4070

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 Flexitouch Plus with Novel Simultaneous Therapy Cycle Software in Patients with Unilateral Breast Cancer-Related Lymphedema (BCRL)
Protocol Date	15 May 2019
Protocol Version	2.0
Protocol Number	4070
Name of Sponsor	Tactile Medical
Investigational Product	Flexitouch Plus (FT) with Novel Simultaneous Therapy Cycle Software (FT-SW)
Study Objective	To demonstrate the treatment equivalency of the Flexitouch Plus with novel simultaneous therapy cycle software and the standard Flexitouch Plus in patients with unilateral BCRL.

Endpoints	To compare the effects of the Flexitouch Plus (FT) to Flexitouch Plus with novel simultaneous therapy cycle software (FT-SW) in unilateral BCRL patients after one treatment by evaluating:
	• Flow of lymph in the affected and contralateral limb using near infrared-fluorescence (NIRF) imaging
	• Swelling in the affected and contralateral limb as assessed by:
	  ○ Perometry (LymphaTech 3D Scanner)
	  ○ Local tissue water (MoistureMeterD)
	• Skin changes
	  ○ Skin thickness (Ultrasound)
	• Safety

Study Design	This is a prospective, randomized, two-arm feasibility study.
Treatments	Eligible patients will be randomized to receive one of the following treatments: • **Flexitouch Plus (FT)** • **Flexitouch Plus with Novel Simultaneous Therapy Cycle Software (FT-SW)** The compression treatment will be conducted on the affected limb.
Inclusion/Exclusion	**Inclusion Criteria:** 1. Female 18 years of age or older 2. Diagnosis of unilateral breast cancer-related lymphedema 3. Stage I or early Stage II lymphedema without severe fibrosis at the time of enrollment 4. ≥ 5% volume difference between affected and unaffected arm as verified via perometry (LymphaTech 3D scanner) 5. Willing and able to give informed consent 6. Willing and able to comply with the study protocol requirements and all study-related visit requirements **Exclusion Criteria:** 1. In-home use of pneumatic compression device (PCD) within previous 3 months

	2. Therapist or self-administered manual lymph drainage (MLD) within previous 1 week 3. Mastectomy or lymph node removal on side without lymphedema 4. Bilateral lymphedema 5. Heart failure (acute pulmonary edema, decompensated acute heart failure) 6. Acute venous disease (acute thrombophlebitis, acute deep venous thrombosis, acute pulmonary embolism) 7. Active skin or limb infection/inflammatory disease (acute cellulitis, other uncontrolled skin or untreated inflammatory skin disease) on the arms or trunk 8. Active cancer (cancer that is currently under treatment, but not yet in remission) 9. Poorly controlled kidney disease (glomerular filtration rate < 30 mls per minute), hypoproteinemia, pulmonary hypertension, hypothyroidism, cyclic edema, or Munchausen Syndrome 10. Body Mass Index (BMI) >50 11. Any circumstance where increased lymphatic or venous return is undesirable 12. Currently pregnant or trying to become pregnant 13. Allergy to iodine
Treatment Duration	A single treatment lasting: • FT-SW: Approximately 40 minutes **OR** • FT: Approximately 60 minutes
Number Planned	20 subjects randomized (minimum of 10 in each arm) with replacement of up to 5 early withdrawals.

TABLE OF CONTENTS

1.0 Contact Information

1.1 Sponsor Contact Information

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1.2 Principal Investigator Information

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1.3 Clinical Investigator Information

The sponsor will maintain a document with contact information for all investigators participating in the study. The information maintained will include full name, addresses, telephone, 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
BMI	Body Mass Index
CFR	Code of Federal Regulations
CMI	Center for Molecular Imaging
CRA	Clinical Research Associate
CRF	Case Report Form
CTA	Clinical Trial Agreement
DCF	Data Clarification Form
ESAS-R	Edmonton Symptom Assessment System
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FT	Flexitouch Plus
FT-SW	Flexitouch Plus with Novel Simultaneous Therapy Cycle Software
GCP	Good Clinical Practice
ICG	Indocyanine Green
IMM	The Brown Foundation Institute of Molecular Medicine
IND	Investigational New Drug
IRB	Institutional Review Board
LTW	Local Tissue Water
PCD	Pneumatic Compression Device
mg/kg	milligram/kilogram
MLD	Manual Lymphatic Drainage
mm	millimeter
MMD	MoistureMeterD™
NIRF	Near Infrared-Fluorescence
NSR	Nonsignificant Risk
PI	Principal Investigator
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan

Abbreviation	Term
TDC	Tissue Dielectric Constant
US	Ultrasound
USA	United States of America
HCPCS	Healthcare Common Procedure Coding System
UADE	Unanticipated Adverse Device Effect
µg	microgram
µg/ml	micrograms/millimeter
UTHealth	University of Texas Health Science Center at Houston

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 (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).

Lymphedema may be inherited (primary) or caused by injury to the lymphatic vessels (secondary). While the exact cause of primary lymphedema is unknown, it generally occurs due to congenital malformations with the onset of symptoms presenting at birth, during puberty, or well into adulthood. Secondary lymphedema typically results from trauma to the lymphatic system, surgery, radiation therapy, obesity, and chronic venous insufficiency (3-4). Breast Cancer-Related Lymphedema (BCRL) is a common complication from breast cancer treatment, with reported frequencies ranging from 6% to 65% (5).

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, manual lymphatic drainage, compression therapy, skin hygiene, and in very severe cases, lymphatic exchange (6). 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 (7-10).

The efficacy of PCD therapy depends on the applied force (pressure) mobilizing stagnant edema fluid, time of compression to move fluid to the root of the limb, and elasticity of skin and subcutaneous tissue. Thus, adherence to prescribed, at-home self-care is a critical factor in the treatment of lymphedema (11-12). One of the most robust findings in adherence literature concerns aspects of the therapy itself – the more complex and complicated a therapeutic regimen is (e.g., treatment duration), the less likely patients are to adhere to all aspects of prescribed care (12).

To address non-adherence, the FT was updated with the novel simultaneous therapy software to shorten treatment time. Currently, the FT takes approximately 1 hour of treatment to provide clearing of the trunk, chest, and arm. With the novel simultaneous therapy cycle software engaged, the device will run two simultaneous therapy cycles. Thus, the simultaneous therapy cycle program will provide the same number therapy cycles as a traditional FT while reducing treatment time.

The purpose of this study is to demonstrate equivalency in treatment effect between the novel simultaneous therapy cycle software and the standard FT.

3.2 Device Description

3.2.1 Flexitouch Plus (FT)

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

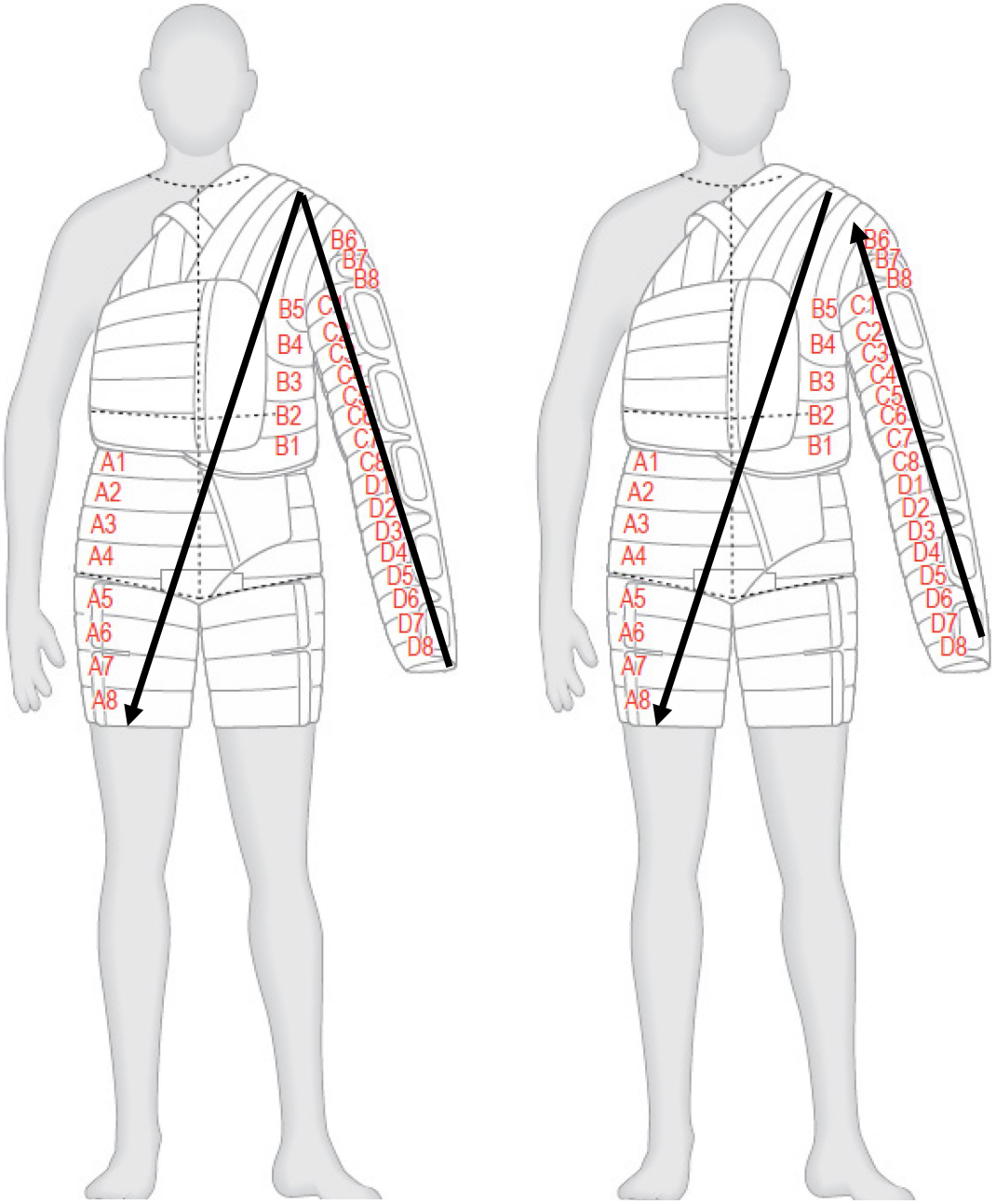
The FT consists of two primary components: a controller unit and garments. The controller unit has connector outlets for garment hoses to plug into such that air can pass through the hoses and deliver treatment through sequential inflation and deflation of air chambers within the garments. The garments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

The device is intended to provide Manual Lymphatic Drainage (MLD) therapy for approximately 1 hour treatment duration. Indications for use include lymphedema, primary lymphedema, post-mastectomy edema, edema following trauma and sports injuries, post immobilization edema, venous insufficiency, reducing wound healing time, and treatment and assistance in healing stasis dermatitis, venous stasis ulcers, or arterial and diabetic leg ulcers.

3.2.2 Flexitouch Plus with Novel Simultaneous Therapy Cycle Software (FT-SW)

The investigational device utilized in this study is the FT-SW. The software was developed for use with the current-generation FT and allows the device to run two simultaneous waves of therapy. As shown in Figure 1, the novel software provides the same number of therapy cycles as a traditional FT, however 2 simultaneous waves are applied instead of one. Application of these simultaneous waves results in a reduction in treatment time. The intended use, indications, and garments for the FT-SW are identical to the FDA cleared FT system.

The FT-SW will be labeled, "CAUTION – Investigational Device, Limited by Federal Law to Investigational Use" and will have the unique 10 character serial number.



FT: 1 wave = 1 cycle **FT-SW: 2 simultaneous waves = 1 cycle**

Figure 1. FT and FT-SW

3.2.3 NIRF Imaging

The investigational imaging techniques of near-infrared fluorescence (NIRF) are focused on addressing unmet clinical diagnostic needs in lymphatic imaging through point of care, non-radioactive, clinical imaging diagnostic platform based on image intensifier technology. NIRF imaging has been used under the investigational new drug (IND) experience by the

Principal Investigator (PI) to map lymphatic structure and visualize lymphatic function in hundreds of patients without adverse effects. This method of imaging has shown efficacy in detecting impaired lymphatic function with dermal backflow, defined as abnormal fluorescent signal observed in networks of lymphatic capillaries and/or in the extravascular space, presenting as one of the earliest signs of lymphedema onset (13-15).

NIRF lymphatic imaging provides real-time imaging of the lymphatic anatomy and its function. Following intradermal injections of 25 micrograms of indocyanine green (ICG) in 0.1 cc sterile saline, a dim laser diode light of 785 nm is illuminated on the tissue surface. The light penetrates the tissues and excites the ICG and the resultant fluorescence emanates from tissues and is collected using an intensified camera system.

4.0 Study Objective

The objective of the study is to demonstrate equivalency in treatment effect, as determined by objective measurements, between the novel simultaneous therapy cycle software and the FDA-cleared FT.

5.0 Study Design

This is an acute, prospective, randomized, two-arm, feasibility study (Figure 2) comparing the FT-SW to FT.

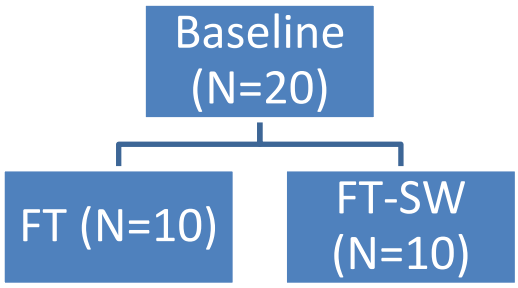


Figure 2. Study Design

5.1 Endpoints

To compare the effects of FT to FT-SW in BCRL patients after one treatment based upon:

- Lymphatic activation in the affected and contralateral limb using the investigational technique of near infrared-fluorescent (NIRF) imaging
- Swelling in the affected and contralateral limb as assessed using:
  - Perometry (LymphaTech 3D Scanner)
  - Local tissue water content (MoistureMeterD)
- Skin changes on the affected and contralateral limb as assessed by:
  - Skin thickness (Ultrasound)
- Safety

Table 1. Outcome Measures

Endpoint	Outcome Measure
Lymphatic activation	• Proportion of subjects who show an increase in the number of functional vessels and/or area of dermal backflow per NIRF imaging of the affected and contralateral arm when comparing post-treatment values to pre-treatment values • Proportion of subjects who show an increase of lymphatic propulsion events immediately after treatment
Changes in Swelling	• Proportion of subjects who show a decrease in arm perometry (limb volume) when comparing post-treatment values to pre-treatment values for the affected and contralateral arm • Proportion of subjects who show a decrease in local tissue water at target sites when comparing post-treatment values to pre-treatment values for the affected side • Mean change in perometry and local tissue water post-treatment will be compared for all sites
Skin Changes	• Proportion of subjects who show a decrease in skin thickness at target site when comparing post-treatment values to pre-treatment values for the affected side • Mean change in skin thickness post-treatment will be compared for all sites
Safety	• Adverse events will be presented in data listings

5.2 Subject Selection

The target population includes patients who have received breast cancer therapy and developed unilateral lymphedema secondary to their cancer treatment. Patients will be recruited from the clinical investigator's patient population.

5.2.1 Inclusion Criteria:

1. Female 18 years of age or older
2. Diagnosis of unilateral breast cancer-related lymphedema
3. Stage I or early stage II lymphedema without severe fibrosis at the time of enrollment
4. $\geq$ 5% volume difference between affected and unaffected arm as verified via perometry (LymphaTech 3D scanner)
5. Willing and able to give informed consent
6. Willing and able to comply with the study protocol requirements and all study-related visit requirements

5.2.2 Exclusion Criteria:

1. In-home use of PCD within previous 3 months
2. Therapist or self-administered manual lymph drainage (MLD) within previous 1 week
3. Mastectomy or lymph node removal on side without lymphedema
4. Bilateral lymphedema
5. Heart failure (acute pulmonary edema, decompensated acute heart failure)

6. Acute venous disease (acute thrombophlebitis, acute deep venous thrombosis, acute pulmonary embolism)
7. Active skin or limb infection/inflammatory disease (acute cellulitis, other uncontrolled skin or untreated inflammatory skin disease) on the arms or trunk
8. Active cancer (cancer that is currently under treatment, but not yet in remission)
9. Poorly controlled kidney disease (glomerular filtration rate < 30 mls per minute), hypoproteinemia, pulmonary hypertension, hypothyroidism, cyclic edema, or Munchausen Syndrome
10. BMI >50
11. Any circumstance where increased lymphatic or venous return is undesirable
12. Currently pregnant or trying to become pregnant
13. Allergy to iodine

5.3 Point of Enrollment and Randomization

Subjects will be considered enrolled in the study once the Informed Consent Form 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 database and assigned sequentially as soon as an eligible subject completes the pre-treatment measurements.

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 on treatment, the Investigator should inform Tactile Medical immediately.

Up to 5 enrolled subjects may be replaced if the subject is withdrawn prior to completion of the study. If a subject withdraws from participation in the study, his or her randomization code cannot be reused.

5.4 Treatment Assignment and Duration

Patients with unilateral BCRL will be randomized (1:1) to receive one of the following treatments in the affected limb:

- Approximately 60 minutes of treatment with Flexitouch Plus (FT); or
- Approximately 40 minutes of treatment with Flexitouch Plus with Novel Simultaneous Therapy Cycle Software (FT-SW)

5.5 Study Timeline

The expected study duration is approximately 8 months with 2-3 months spent on activation, 3 months enrolling subjects, and 2 months completing the data analysis.

6.0 Study Assessments

Case Report Forms (CRFs) and Data Clarification Forms (DCFs) will be used for data collection and query handling. The Investigator will ensure the accuracy, completeness, and timeliness of the data recorded and responses to data queries according to the Clinical Trial Agreement (CTA). NIRF data collected and recorded by the Investigator, and perometry data collected and recorded by LymphaTech, will be obtained and reconciled against study data.

All data entry, storage, transmission, and management will be conducted using iMedNet, a 21 CFR Part 11 compliant electronic data capture (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 FDA with the exception of FT-SW and NIRF imaging (which is approved by the FDA for investigational use in humans under an existing IND #102,765). Prior to taking endpoint measurements, delegated personnel will receive training and will demonstrate proficiency.

6.1 Screening/Baseline

If a patient appears eligible to participate based on medical history, he or she will be approached to participate in the study and consented if interested in participating. All consented subjects will undergo the following procedures:

- Obtain medical history
- Administer a serum or urine pregnancy test for all female subjects of child-bearing potential (for imaging purposes, the pregnancy test should be done ≤ 36 hours prior to NIRF imaging)
- Vital signs – historic values within past 7 days may be used
- Subject survey – Edmonton Symptom Assessment System (ESAS-R)
- Lymphedema evaluation
- Perometry via LymphaTech 3D scanner to determine volume of affected and unaffected arm
    - If the subject's volume difference is <5% between affected and unaffected arm, they will be considered a screen failure and will not continue in the study
- Mark Anatomical Sites
- ICG Injections
- The following assessments will be performed on the affected and unaffected arm in the order listed
    - MoistureMeterD (MMD) to assess local tissue water (LTW) content
    - Ultrasound to assess skin thickness
    - NIRF imaging to assess lymphatic activation
- Randomization

6.2 Randomization

Randomization will occur after all of the screening/baseline assessments are complete. The study personnel performing study assessments will remain blinded to the treatment assignment.

6.3 Treatment

The randomized treatment assignment will be administered to the affected limb. The personnel administering the treatment will not perform any study assessments as they will be unblinded to the treatment.

6.4 Post-Treatment Testing

After the subject has completed treatment, the Flexitouch garments will be removed. The following assessments will be performed on affected and unaffected arm in the order listed and should begin within approximately 15 minutes of the completion of treatment:

- Perometry via Lymphatech 3D Scanner to determine volume
- MoistureMeterD (MMD) to assess local tissue water (LTW) content
- Ultrasound to assess skin thickness
- NIRF imaging to assess lymphatic activation
- Subject surveys
    - ESAS-R
    - Treatment Perception Survey
- Adverse Event Assessment

6.5 24-Hour Follow-up

Subjects will return to the clinic or be contacted via telephone 18-28 hours after ICG injection for assessment of adverse events.

7.0 Study Schedule of Activities

The study schedule of activities is shown below (Table 2).

Table 2. Schedule of Activities

Procedures	Day 0 (Acute Study)			24 hour follow-up
	Screening	Treatment	Post-Treatment	
Informed Consent	X			
Demographics & Medical History	X			
Inclusion/Exclusion Assessment	X			
Pregnancy Test (if applicable)	X			
Vital Signs	X			
Subject Surveys	X		X	
Lymphedema Evaluation	X			
Perometry (LymphaTech 3D Scanner)	X		X	
Mark Anatomical Sites	X			
ICG Injection	X			
LTW (MoistureMeterD)	X		X	
Ultrasound	X		X	
NIRF Imaging	X		X	
Randomization	X			
FT or FT-SW Treatment		X		
Adverse Event Assessment	X	X	X	X

8.0 Study Procedures

8.1 Informed Consent

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

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

8.2 Demographics & Medical History

Demographics will be collected including the age at time of participation, ethnicity, race, and sex.

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

8.3 Pregnancy Test

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

8.4 Vital Signs

Height and weight will be collected to confirm subject's BMI is <50.

8.5 Subject Surveys

Prior to treatment the subject will complete the ESAS-R. After treatment and assessments are completed, the subject will complete the ESAS-R and a Treatment Perception survey.

8.6 Lymphedema Evaluation

Research personnel will confirm the presence of Stage I or early Stage II lymphedema and severity of fibrosis at Screening/Baseline. The clinical stage of lymphedema will be evaluated by a clinician using the following definitions:

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

Severity of fibrosis, to distinguish between early and late Stage II lymphedema, will be based on the definitions below:

Table 3. Fibrosis Assessment

None	No fibrotic tissue
Minimal	Able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up), <20% of affected limb noted to have fibrotic tissue
Moderate	Able to slide skin, unable to pinch skin, 20-40% of affected limb noted to have fibrotic tissue
Severe	Unable to slide or pinch skin, >40% of affected limb noted to have fibrotic tissue

8.7 Perometry

Perometry will be performed on both limbs before and after treatment. The LymphaTech 3D Scanner will be utilized by appropriately trained research personnel in accordance with the instructions for use provided by LymphaTech.

8.8 Marking Anatomical Sites

Have the subject pull-up/remove clothing if covering arms. Using a pen or marker, with the subject in a seated or standing position with arms completely relaxed at sides, mark the skin at the locations outlined in Figures 3-5 on affected and unaffected sides.

If a subject experiences pain at a targeted measurement site, an alternate location may be measured, recorded, and used for the duration of the study.

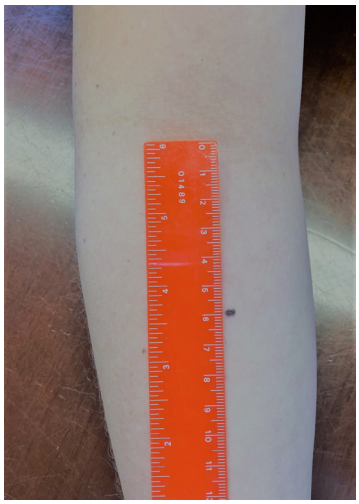


Figure 3. Site A is on the anterior forearm 6 cm below (distal to) the midline of the antecubital fossa.

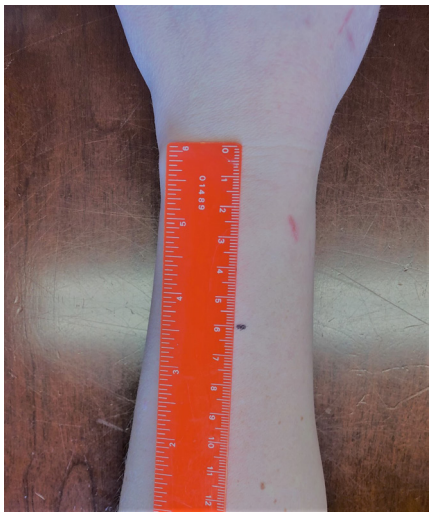


Figure 4. Site B is 6 cm above (proximal to) the dorsal aspect of the wrist (midline).

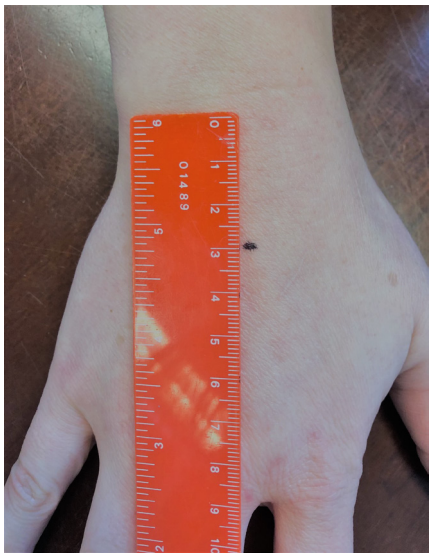


Figure 5. Site C is 3 cm distal to the midline dorsal aspect of the wrist.

8.9 ICG Injections

ICG (25 mg vial) will be reconstituted with 10 ml sterile water provided by the manufacturer; further dilutions will be made in saline to achieve the final concentration of 0.32 ml, or 250 µg/ml ICG. Up to 16 intradermal injections, each consisting of 0.1 mL or less, using conventional 30 or 31-gauge needles may be administered by a clinician. However, typically each subject will only receive 8 intradermal injections in the arms and the additional 8 injections may be administered if the clinician identifies areas of lymphatic drainage that may not be covered by the typical injections. Subjects will typically receive 2 injections in the

dorsum of each hand and 2 in each medial wrist. Subjects will not receive more than 400 µg of ICG.

Vital signs (blood pressure, heart rate, temperature) and redness or inflammation at the injection sites will be monitored and recorded at baseline (pre-injection of ICG) and at 15 and 30 minutes after the initial injection. Study subjects will be contacted between 18 and 28 hours after ICG administration to ensure no adverse events have occurred

8.10 MoistureMeterD Measurements

Local tissue water (LTW) measures will be obtained using the FDA-cleared MoistureMeterD™ (MMD) with the M25 (2.5 mm) and L50 (5.0 mm) probes (Delfin Technologies, Finland). This non-invasive, rechargeable, battery-operated 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 as a highly sensitive measurement of water content and edema in the skin and subcutis (16-19). There are no risks associated with the use of this data collection device. In addition, data collected from this device will not be used in the diagnosis or treatment of lymphedema.

The MMD measurements will be performed on the affected and unaffected side before and after treatment. Measurements may only be conducted by research personnel with documented training showing the individual was able to independently and accurately conduct the measurements.

The following measurement procedures will be followed to assess the upper extremity tissue dielectric constant (TDC) values as indices of skin/tissue water:

- Ensure the subject remains in a seated position with the arms relaxed
- Turn on the MoistureMeter D unit, select the correct probe size on the display, and wait for the word "wait" to disappear from the display before taking any measurements.
- Measure and record the TDC values at sites A, B, and C (See Figures 3-5) by firmly placing the probe on the marked site such that the entire probe depresses the skin and leaves a slight indentation.
- All measurements will be made in duplicate using the L50 (5 mm) probe alternating in a consistent fashion (A, B, C, A, B, C) to ensure tissue water is not displaced at the time the second measurement is taken.
- Clean the L50 probe with an antiseptic cleansing towel or ethanol and return to the storage case.
- Repeat steps 1 through 5 (in duplicate) using the M25 (2.5 mm) probe.
- Turn off the MoistureMeterD unit, clean the M25 probe with an antiseptic cleansing towel or ethanol, and return both the probe and MoistureMeterD unit to the storage case.

8.11 Ultrasound

Tissue ultrasound measurements will be collected from the affected and unaffected arms using a 4-13 MHz linear transducer with the probe placed longitudinally on

the tissue. Measurements may only be conducted by a study team member with documented training. Field size and gain may be adjusted as necessary to optimize image quality and boundary definition.

Ultrasound measurements will be taken to assess the thickness of the epidermis (skin) and the thickness of the subcutaneous layer from the epidermis (skin) to the muscular fascia. When the dermo-hypodermal junction is clearly identified, the full skin thickness (epidermis and dermis) from the anterior echogenic border of the epidermis to the posterior echogenic border of the dermis may be measured in B-mode. Subcutaneous tissue thickness is measured as the distance between the posterior echogenic border of the dermis and the anterior echogenic border of the muscular fascia. When the dermo-hypodermal junction or the muscular fascia is not clearly identified, measurements will not be performed, and the reported result will be classified as a "blurred border."

The following measurement procedures will be followed to assess skin thickness:

- Ensure the subject remains in a seated position with the arms relaxed
- Measure and record skin and subcutaneous thickness measurements at sites A, B, and C (See Figures 3-5)

Additional guidance on ultrasound measurements and analysis will be provided in an ultrasound user guide.

8.12 NIRF Imaging

After all injections are made and the water content and skin thickness measurements are made, NIRF imaging will commence. From the images of each region, the lymphatic activation (anatomy and propulsion) will be quantified as follows:

- Intact, fluorescent lymphatic vessels observed before and after the treatment will be recorded as an increase in vessels, decrease in vessels, or no change. The two-dimensional, projected area or extent of dermal backflow, before and after treatment, will be quantified using ImageJ (NIH, Bethesda, MD) by adjusting the brightness of the images to 20% of the maximum pixel value and measuring the area of regions of interest drawn around fluorescent areas not associated with intact and well-defined (i.e., "normal") lymphatic vessels.
- The rate of lymphatic propulsion events observed immediately before and after treatment will be quantified by counting the total number of propulsion events observed and dividing by the total observation time at each region of interest.

Prior to injection and after NIRF imaging is complete, digital photographs of the arms will be acquired. Images of the front and back of the arms will be acquired with the subject standing up and the arms held out away from the sides.

8.13 Randomization

If the subject meets all of the inclusion criteria and none of the exclusion criteria, they will be randomly assigned to FT or FT-SW. The appropriate unblinded staff

member will obtain the randomization assignment by entering the appropriate randomization CRF in the EDC system.

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

8.14 Treatment

After all pre-treatment assessments have been performed, the subject will undergo the treatment that they have been randomized to. The personnel administering the treatment will not perform any study assessments as they will be unblinded to the treatment. If the subject has been randomized to the FT-SW, treatment will begin approximately 20 minutes after they enter the room where treatment is being performed to ensure the blinded study staff remain unaware of the treatment allocation.

8.15 Adverse Event Assessment

Adverse event assessment will occur during the acute study period and ~24 hours after the acute study.

Reportable events, as defined below, will be recorded on the subject's case report forms (CRFs).

8.15.1 Adverse Event (AE)

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

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

8.15.2 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 work days of becoming aware of the event. SAEs will

be summarized is writing and reported to the IRB in accordance with IRB policy.

8.15.3 Unanticipated Adverse Device Effect (UADE)

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 Unanticipated Adverse Device Effects (UADEs) to Tactile Medical within 10 work days of becoming aware of the event. UADEs will be summarized in writing and reported to the IRB in accordance with IRB policy.

8.15.4 Device Observations

Device observations will be recorded and reported to Tactile Medical. Device observations include device failures, device malfunctions, use errors, device issues, and user preferences, as defined below:

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

9.0 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.
- **Adverse Event**

Subject experiences an adverse event that in the investigator's clinical judgement necessitates discontinuation of their participation in this study.

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

When a subject withdraws prior to completing the study, the reason for withdrawal will be documented in the subject's record, and up to five replacement subjects may be enrolled to complete the cohort.

10.0 Accountability

The FT, FT-SW, garments, MMD, and LymphaTech 3D Scanner (with iPad) will be provided at no cost to the site and applied/utilized with the assistance of study personnel. The site will maintain a record of device accountability to ensure all study devices are properly tracked and accounted for throughout the study. The record will include the receipt, location, use, disinfection, and final disposition of all controllers and garments. Study devices will be stored in a secure area with restricted access. At the conclusion of the study, the FT, FT-SW Controllers, MMD, and LymphaTech 3D Scanner (with iPad) will be returned to Tactile Medical.

A record of lot number and expiration date will be maintained for all ICG used during the study to complete the investigational NIRF imaging. Information related to the NIRF system used for the imaging session, including the name(s) of the system operator(s) and performance verification, will also be documented.

11.0 Risk Analysis and Adverse Events

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

11.1 Risk Analysis

11.1.1 Pneumatic Compression

Pneumatic compression is a minimal risk therapy with minimal known complications or adverse events. However, as with any treatment, there is the possibility of undesirable events such as a local skin reaction to the device materials. The subject will be made aware of known complications and adverse events at time of consent and monitored closely throughout the study.

In addition, since the FT-SW simulates manual lymphatic drainage, the lymphangions in the existing lymphatics will be stimulated to contract more frequently and the interstitial fluid may be propelled up the limb in a more rapid manner with the FT system. To minimize any risk associated

with the moderate increase in fluid reduction, patients with heart failure are excluded from the study.

There are nominal possible adverse effects associated with the therapy. The expected adverse effects that are experienced by patients using this device are often due to the natural history of the primary disease, or a failure to achieve an adequate response to the compressive therapeutic intervention, and are thus not related to the therapy itself. In some cases, lymphedema adverse events can be serious, long lasting, or may be permanent. The risks listed below are symptoms or signs of lymphedema and may be experienced by all subjects with lymphedema:

Likely:

- Pain or discomfort
- Increased swelling

Less Likely:

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

11.1.2 NIRF Imaging

Participants may have an allergic reaction to ICG that can include itchiness and/or swelling; there is a rare possibility of a severe reaction, including death. Two anaphylactic deaths have resulted from IV injection of ICG at the maximal approved dose (2 mg/kg). Because we will inject a maximum dose of 400 µg of ICG, the risk of severe adverse event is extremely low. Members of the research team will be present during the entire imaging procedure and physicians will be nearby to provide antihistamines or other interventions if needed. To minimize discomfort from intradermal injections, subjects may have a topical anesthetic agent (ethyl chloride spray) applied to the injection sites prior to administering ICG.

To generate the fluorescent signal for NIRF imaging, the subject's arms and sides will be illuminated with the diffused output of a 785 nm laser diode. Risks associated with Class IIIB/IV lasers are not applicable for this study, since the fluence rate at which the laser diode is operated (≤ 1.9 mW/cm2) constitutes no skin hazard. However, participants will be instructed in general laser safety precautions as applicable to their participation and will be required to wear laser safety goggles during NIRF imaging. Additional laser safety goggles will be available for other individuals in the room if they wish to wear them.

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

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

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

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

13.0 Deviation from Study Plan

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

14.0 Quality Assurance Procedures

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

14.1 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.

14.2 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 has been adequately trained on the protocol. An activation letter will be sent to the Principal Investigator once the site is approved to enroll subjects.

14.3 Onsite Monitoring

Clinical sites will be monitored 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 site staff are well 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 site visits, a screening log must be submitted to Tactile Medical as requested (by fax or e-mail). This screening log should be reviewed with site staff to assess planned versus actual recruitment.

The Principal Investigator and Institution agree to permit trial related monitoring, audits, IRB review, and regulatory inspection(s); providing direct access to source data and documents, as appropriate. Monitoring and source verification will be performed by 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.

14.4 Data Safety Monitoring

The Principal Investigator will be responsible for the monitoring of study data and subject safety. Due to the small number of research subjects, the most comprehensive and effective method of monitoring will be an individual case review by the 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.

CRFs containing all monitoring information will be completed by the PI, clinical investigator(s), or designee and reviewed by the PI or clinical investigator(s). CRFs will be kept in a secure location.

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 trial or investigational site.

14.5 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 4).

Table 4. 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 informed consent form, 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 Change to Investigational Plan

Should changes in the study plan or protocol become necessary during the course of the clinical research study, proposed changes will be appropriately reviewed and approved by 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

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 3.54.0 or higher.

17.0 Publication Plan

The data collected as part of this research is intended to be used for new product development and marketing claims. As the study contains trade secret product enhancements, data is intended to be kept "on file" with no plan for publication of the data.

18.0 References

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