A Pilot Study to Evaluate the Feasibility and Potential Effectiveness of the Flexitouch® System Head and Neck Treatment

Protocol# 4030

September 26, 2017

Protocol Version 2.0

Sheila H. Ridner, PhD, RN, Vanderbilt University School of Nursing (Principal Investigator)
Barbara Murphy, MD, Co-I (Oncologist) Mary S. Dietrich, PhD, Co-I (Biostatistics)

Investigator Signature

Protocol Title: A Pilot Study to Evaluate the Feasibility and Potential Effectiveness of the Flexitouch® System Head and Neck Treatment

Protocol Number: 4030
Version: 2.0; 26 September 2017

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 Harmonization Guidelines, Therapeutic Goods Act, institutional research policies and procedures and other appropriate regulatory requirements.

_____
Site Principal Investigator Name (Print)

_____ _____
Site Principal Investigator Signature Date

SYNOPSIS

Title of Study	A Pilot Study to Evaluate the Feasibility and Potential Effectiveness of the Flexitouch® System Head and Neck Treatment
Protocol Date	26 September 2017
Protocol Version	2.0
Name of Sponsor	Tactile Medical™
Investigational Product	Flexitouch® System Head and Neck System
Primary Aim	To determine the feasibility of use of the Flexitouch® Head and Neck System, specifically a) to evaluate implementation fidelity (adherence) and barriers to implementation fidelity, b) to establish safety, and c) to assess satisfaction.
Secondary Aim	To determine the preliminary efficacy of the Flexitouch® Head and Neck System compared to a wait-list control for the following outcomes: a) reduction in swelling/inflammation, b) function (cervical, jaw, and shoulder range of motion), c) symptoms, and d) quality of life changes.
Primary Endpoint	The primary endpoint will occur when subjects complete the 8th week of interventional treatment and provide: a) evaluation of implementation fidelity (adherence) and barriers to implementation fidelity, b) review of adverse events, and c) report satisfaction.
Secondary Endpoint	The secondary endpoint will occur at the same time as the primary endpoint. Secondary outcomes include: a) reduction in swelling/inflammation, b) function (cervical, jaw and shoulder range of motion), c) symptoms, and d) quality of life.
METHODOLOGY	
Study Design	This study is an open label, multi-site, stratified randomized, wait list control, pilot study.
Treatments	Standard home care may include: self-MLD, exercise, skin care, and wearing an appropriate compression garment, if applicable. Interventional treatment: twice daily treatment with Flexitouch® pneumatic compression device and home care regimen, which may include self-MLD exercise, skin care, and wearing an appropriate compression garment, if applicable.
Treatment Duration	The interventional study duration is 8 weeks. The subjects randomized to the investigational group will be seen at baseline and weeks 1, 4 and 8. Subjects randomized to the wait-list group will be seen at baseline and weeks, 1, 4 and 8 while receiving standard of care (SOC) treatment (wait-list control group).
SUBJECT POPULATION	
Number Planned	40 subjects randomized with replacement of up to 10 early withdrawals.

Major Inclusion/Exclusion Criteria	Inclusion Criteria : • Age ≥ 18 years • A previous diagnosis of histologically defined head and neck cancer • A diagnosis of head and neck lymphedema • Must be able and willing to participate in all aspects of the study and provide informed consent prior to study participation • Completed cancer treatment with no evidence of active cancer; all post-surgical swelling must be resolved. • The head and neck garments must fit appropriately. For patients with a tracheostomy, the fit will be assessed to ensure that the garments do not interfere with their tracheostomy. • The subject must have experienced at least one of the following: o Completion of phase 1 lymphedema care in the past 8 weeks o The inability to participate/complete phase 1 care due to: ▪ lack of available therapist/clinic ▪ lack of insurance coverage/funding to support cost of care. Exclusion Criteria : • Uncontrolled hyperthyroidism or parathyroidism (for which endocrinologist recommends against neck compression) • Carotid sinus hypersensitivity syndrome • Symptomatic carotid artery disease, as manifested by a recent transient ischemic attack (within 30 days), ischemic stroke, or amaurosis fugax (monocular visual ischemic symptoms or blindness) • Symptomatic bradycardia in the absence of a pacemaker • Internal jugular venous thrombosis, acute or within 3 months • Increased intracranial pressure or other contraindications to internal or external jugular venous compression • Acute radiation dermatitis, unhealed surgical scar, unhealed or open wound(s), surgical flap less than 6-8 week post-operative • Facial or head and neck dermal metastasis • Acute facial infection (e.g., facial or parotid gland abscess) • Any condition in which increased venous and lymphatic return is undesirable • History of pulmonary edema or decompensated congestive heart failure with in six (6) week of enrollment. • Subject is pregnant or trying to become pregnant
ASSESSMENTS	
Feasibility /Safety	Adherence and barriers monitoring Adverse Event Monitoring (CTCAE) Satisfaction-Subject Self-report Physical Examination

Efficacy	Visits will take place at Vanderbilt University School of Nursing, Vanderbilt Medical Center, or other facility approved location. Any additional sites will see patients in a location as determined by their research environment. Home visits may take place if unexpected circumstances arise that compromise data collection taking place in a timely manner. The following assessments will be completed at predefined times throughout the study.
	• Digital Photos
	• Endoscopy / Revised Patterson Scale
	• Cytokine testing
	• Neck Disability Index
	• Voice Handicap Index
	• Range of Motion Measures
	  o Cervical ROM
	  o Jaw ROM
	  o Shoulder ROM
	• Vanderbilt Head and Neck Symptom Survey
	• Lymphedema Symptom Intensity and Distress Survey
	• Linear Analog Self-Assessment Quality of Life

TABLE OF CONTENTS

1.1 Contact Information

1.2 Sponsor Contact Information

Tactile Medical™
Sunday Hoy, Esq., Director of Clinical Resources and Research
1331 Tyler Street NE, Suite 200
Minneapolis, MN 55413
612-355-5121
shoy@tactilemedical.com

1.3 Study Principal Investigator Information

Sheila Hedden Ridner, PhD, RN, FAAN
Vanderbilt University School of Nursing
525 Godchaux Hall,
461 21st Ave. S.
Nashville, TN 37072
615-322-0831
Sheila.Ridner@Vanderbilt.edu

2.0 Abbreviations

AE	Adverse Event
BP	Blood Pressure
CDT	Complete decongestive therapy
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DVT	Deep vein thrombosis
FT	Flexitouch®
GSS	General Symptom Survey
HIPAA	Health Insurance Portability and Accountability Act
HNC	Head and neck cancer
HNL	Head and neck lymphedema
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional review board
L-SIDS	Lymphedema Symptom Intensity and Distress Survey
MLD	Manual lymph drainage
NDI	Neck Disability Index
REDCap	Research Electronic Data Capture
ROM	Range of motion
SD	Standard Deviation
VHI	Voice Handicap Index
VHNSS	Vanderbilt Head and Neck Symptom Survey

3.1 Introduction

3.2 Background and Rationale:

Secondary head and neck lymphedema (HNL) is a frequent side effect in patients treated for head and neck cancer (HNC) as the primary cancer or factors related to treatment (surgery, radiation, or chemotherapy) either destroy or obstruct lymphatic vessels and damage adjacent soft tissue.[1,4] HNL occurs in over 90% of patients following HNC treatment.[2] HNL may involve external structures (soft tissues of the face, neck and eyes) or internal structures (oral cavity, mucous membranes, larynx and pharynx) but most often both are involved simultaneously.[3] The resultant clinical impact is dependent on the anatomic sites involved and the extent of associated lymphatic dysfunction. Symptoms can range from mild to severe. The most common areas of external swelling and fibrosis are in the submental region and the neck.[2,4] In severe cases, HNL may affect critical physical functions (e.g., respiration, mastication, swallowing, communication and vision). HNL, comparable to lymphedema at other sites, is often associated with psychological distress and degradation to quality of life.[3, 4]

In a recent study of 1,202 HNC patients, the majority of patients reported cosmetic concerns and discomfort. More than one third reported functional complaints, including difficulty swallowing (68%) and difficulty breathing (39%).[2] Internal swelling may be directly related to these symptoms. The most common functional complaint among patients who underwent total laryngectomy was difficulty breathing, often related to tracheostomal obstruction from submental edema.[2]

HNL patients often experience tightness and discomfort in the muscles of the neck and shoulders, which may impede range of motion and function of this muscular groups.[3] Damage to the muscles in the affected region, may occur after radiation, resulting in atrophy, weakness and altered sensation.

Damaged lymphatics result in high-protein fluid collection in the affected tissues. Lymphedema is also associated with chronic inflammation, which may lead to a self-perpetuating and progressive course and exacerbation of symptoms .[5] A study of filariasis disease, whose cardinal signs are lymphedema and massive fibrosis, found elevated TNF-α in early stages and determined that IL-6 and IL-8 were potential biomarkers for acute and chronic (highly fibrotic) stages of the disease.[7] Pre-clinical models suggest cytokine driven pathways are involved in late-effect radiation-induced soft tissue damage and that persistent, elevated levels of some cytokines may foreshadow fibrosis after radiation.[8, 9, 10] Even more relevant are results from, a descriptive, longitudinal study of 93 patients with head and neck cancer, conducted at Vanderbilt University, that followed lymphedema and fibrosis overtime, that found IFNg TNF-α, TGF-β, IL-1b, IL-6, MMP-2, MMP-9, and CRP were associated with lymphedema and fibrosis (confidential personal communication). Inflammation is clearly an area of concern for this patient population. One study (N=9), of individuals with chronic primary or secondary leg lymphedema, found that TNF-α significantly decreased after volume reduction treatment.[10] Thus, manual therapy, may play a role in reduction of inflammatory cytokines and further exploration of such is warranted.

The standard treatment for HNL utilizes modified techniques of in-clinic complete decongestive therapy (CDT), including manual lymph drainage (MLD). Currently, some patients are able to continue simplified versions of these techniques at home, yet, many patients with HNL experience difficulty performing the treatment and/or find the treatment is insufficient in effectively managing their symptoms long-term. Clinicians and patients have therefore identified a need for additional effective options for at home treatment of HNL. In response, Tactile Medical™ has developed a garment for the treatment of HNL utilizing The Flexitouch® System pneumatic compression device (FT). Tactile Medical™ seeks to complete a study designed to evaluate the feasibility and potential effectiveness of the Flexitouch® on swelling/inflammation, symptom burden, and quality of life when used for lymphedema self-care.

3.3 Device Description :

Flexitouch® System (Tactile Medical™, Minneapolis, MN, USA): The Flexitouch® System is a segmental, calibrated, gradient pneumatic compression device that has been cleared for market in the US (K153311) (Appendix A), (US HCPCS code E0652) for the treatment of head and neck lymphedema. The device consists of a specifically designed garment set that covers the head, neck and chest and connects to an advanced pneumatic pump that includes programs specific for head and neck treatment. The Flexitouch® head and neck garment set is constructed of nylon and has up to 14 pneumatic chambers covering the head, neck and chest. The device applies brief applications of dynamic pressure in a wave-like manner to the treatment area. Used in conjunction with the Flexitouch® controller, the head and neck garment set is intended to treat lymphedema affecting the head and neck by stimulating the adjacent axillary lymphatic tributary regions and directing fluid from the affected area to healthy, functioning regions. (See Appendix A)

4.1 Study Objectives/Aims

4.2 Objective: The study will evaluate the feasibility, and preliminary effectiveness of the Flexitouch® head and neck treatment plus standard home care compared to standard home care regimen alone.

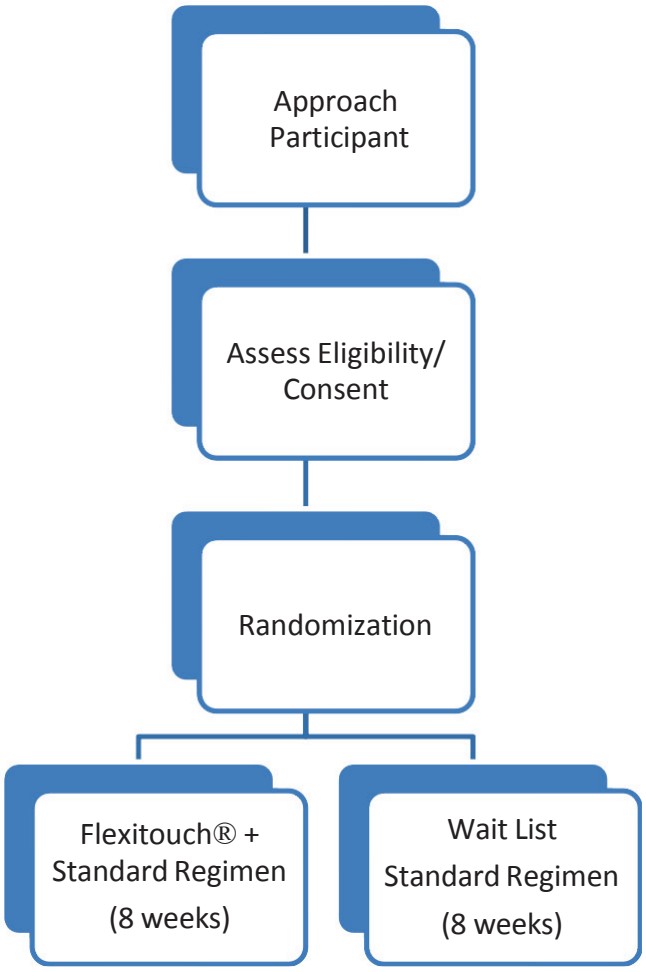
4.3 Primary Aim: To determine the feasibility of use of the Flexitouch® Head and Neck system, specifically a) to evaluate implementation fidelity (adherence) and barriers to implementation fidelity, b) to establish safety, and c) to assess satisfaction.

4.4 Secondary Aim: To determine the preliminary efficacy of Flexitouch® Head and Neck system compared to a wait-list control for the following outcomes: a) reduction in swelling/inflammation, b) function (cervical, jaw, and shoulder range of motion), c) symptoms, and d) quality of life.

5.1 Study Design

This study is an open label, multi-site, stratified by site, randomized, wait list control, pilot study. Vanderbilt University will serve as the multi-site coordinating center.

Within each study site:



5.2 Study Endpoints :

5.2.1 Primary Endpoints: The primary endpoint will occur when subjects complete the 8th week of treatment and provide: a) evaluation of implementation fidelity (adherence) and barriers to implementation fidelity, b) review of adverse events, and c) report satisfaction.

5.2.2 Secondary Endpoints: The secondary endpoints will be a) reduction in swelling/inflammation, b) function (range of motion cervical, jaw, and shoulder), c) symptoms, and d) quality of life.

5.3 Subject Selection

The study sample will be drawn from patients who have received head and neck cancer therapy and have developed HNL secondary to their cancer treatment.

Patients will be recruited from the head and neck cancer clinic at Vanderbilt University and similar clinics at the other investigational sites(s). The patient must have undergone (or attempted and failed) complete decongestive therapy (CDT), or is unable to access CDT as outlined in the inclusion criteria. Only patients who meet the criteria listed below will be considered for the study. A total sample of 40 subjects (20 per group balanced within each site) will be enrolled and those withdrawn for lack of adherence will be replaced, thus we may enroll up to 50 individuals.

5.3.1 Inclusion Criteria :

- Age ≥ 18 years
- A previous diagnosis of histologically defined head and neck cancer
- A diagnosis of head and neck lymphedema
- Must be able and willing to participate in all aspects of the study and provide informed consent prior to study participation
- Complete cancer treatment with no evidence of active cancer; all post-surgical swelling must be resolved.
- The head and neck garments must fit appropriately. For patients with a tracheostomy, the fit will be assessed to ensure that the garments do not interfere with their tracheostomy.
- The subject must have experienced at least one of the following:
    - Completion of phase 1 lymphedema care in the past 8 weeks
    - The inability to participate/complete phase 1 care due to:
        - lack of available therapist/clinic
        - lack of insurance coverage or funding to support cost of care.

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

- Uncontrolled hyperthyroidism or parathyroidism (for which endocrinologist recommends against neck compression)
- Carotid sinus hypersensitivity syndrome
- Symptomatic carotid artery disease, as manifested by a recent transient ischemic attack (within 30 days), ischemic stroke, or amaurosis fugax (monocular visual ischemic symptoms or blindness)
- Symptomatic bradycardia in the absence of a pacemaker
- Internal jugular venous thrombosis, acute or within 3 months
- Increased intracranial pressure or other contraindications to internal or external jugular venous compression
- Acute radiation dermatitis, unhealed surgical scar, unhealed or open wound(s), surgical flap less than 6-8 week post-operative
- Facial or head and neck dermal metastasis
- Acute facial infection (e.g., facial or parotid gland abscess)
- Any condition in which increased venous and lymphatic return is undesirable
- History of pulmonary edema or decompensated congestive heart failure with in six (6) week of enrollment.
- Subject is pregnant or trying to become pregnant

5.3.3 Subject Withdrawal or Early Termination:
Subjects will exit the study if they meet any of the following criteria:

- Subject death
- Subject voluntarily withdraws
- Subject experiences a serious adverse event that in the investigator's clinical judgment necessitates study discontinuation
- Subject acquires any of the exclusion criteria, except
  - In the case of a subject acquiring an infection, they may remain in the study per the discretion of the investigator. Detailed information regarding the infection, nature, treatment, and duration, will be recorded.
- Non-adherence with any study procedures as defined by no use of device during a consecutive 7-day period as documented on the diary or failure to complete required documents.

5.4 Dosage:

Wait-list Control Group: Subjects will continue their home care regimen as defined by their physician/healthcare provider. The home care regimen may include:

- self-MLD
- exercise
- skin care
- wearing an appropriate compression garment.

After 8 weeks, the subject will then receive treatment as outlined below in the investigational group if they so desire.

Investigational Group: Subjects in the investigational group will use the Flexitouch® pneumatic compression device in addition to the home care regimen defined by their treating physician/healthcare provider. The subject will complete two treatment session daily using the Flexitouch® head and neck system for the full 8 weeks of study participation. The twice daily treatment will include the H1 program for the head, neck and chest with an approximate 25-43 minute single cycle time as outlined in the Flexitouch® System User Guide (Appendix A). Instructions for the application of the head and neck garments are located in Chapter 6 of the Flexitouch® System User Guide (Appendix A). The home care regimen may include:

- self-MLD
- exercise
- skin care
- wearing an appropriate compression garment, if applicable

5.5 Study Timetable:

	1- 3months	4-6 months	7-9 months	10-14 months
IRB Review	X			
Enrollment	X	X	X	
Treatment		X	X	
Data Entry		X	X	
Data Analysis			X	
Manuscript Draft			X	
Publication				X

6.1 Study Visit Summaries

6.2 Screening:

The subject will provide written informed consent prior to screening. The study will be explained to each subject. An Informed Consent Form (ICF) will be signed by each subject before study participation as mandated by FDA regulations and the institutional review board (IRB). (See Appendix B) A blank copy of the IRB approved informed consent form must be kept on-site and by Tactile Medical™. A copy of the ICF will be given to the subject to read and take home to consider, if they prefer. All the subject's questions must be answered prior to signing the ICF. Research procedures cannot be performed until the subject provides consent. The signed original for each subject must be kept in the subject's research records. A copy of the signed consent form will be given to each subject.

After informed consent is obtained, screening will commence. (See Appendix C: Screening Form) The subject's head and neck measurements will be taken to assist with garment size selection. For subjects with a tracheostomy, the fit will be accessed further to ensure that the garments do not interfere with their tracheostomy. The head and neck garment measuring guide is included in Appendix A. Should the head and neck measurements indicate the garment will not fit, no further information will be obtained and the subject will be withdrawn. After the garment fit has been confirmed the remaining inclusion and exclusion criteria will be evaluated to ensure that the subject meets all entrance criteria. The subject should not undergo any study specific procedures until after the informed consent process and screening processes are complete.

6.3 Baseline Visit:

The screening and baseline visit can occur on the same day or different days depending on the needs of the subject. At this visit, the subject will undergo the baseline data collection procedures as outlined in the Study Schedule of Activities in section 7.4.

Randomization:

After completing the informed consent process and baseline data collection (including the endoscopy) subjects enrolled at each site will be randomized (1:1) to either the investigational group or wait-list control group via the use of a computer-generated, permuted block program executed by the study biostatistician. Each site will have its own unique randomization list.

Subjects randomized to the investigational group at each site will follow the Study Schedule of Activities table in section 7.4 and will complete the study in 8 weeks. The subjects that are randomized to the waitlist groupat each site will complete all study activities as outlined below in table 7.4. After completing the 8 weeks of the standard regimen, the subjects may choose to receive the same treatment as was implemented in the investigational group. No study data will be completed; however, patients opting to use the device will be seen at weeks 9, 12, and 16 for a documented safety check as outlined in section 7.4.

Research team members will provide the subjects with a self-care kit and provide instructions on how to use the kit. All subjects will leave the initial baseline visit with the self-care kit (Appendices D & E) that includes:

- Subject Diary (intervention group only)
- Self-care checklist
- Dates and Times for their upcoming appointments
- Contact information and instructions to call if any questions

6.4 Follow Up Visit(s):

The subject follow up visits will occur at 1 and 4 weeks (± 3 days). The study staff will collect the checklist and review the subject diary with the intervention patients during each visit to ensure that all entries are complete and understood by the study staff. Any corrections must be made by the subject, and initialed and dated by them. At the visit, the subject will undergo the study procedures as outlined in the Study Schedule of Activities in section 7.4.

6.5 Final Visit:

The final study visit will occur at 8 weeks (± 3 days). At this visit, the subject will undergo the study procedures as outlined in the Study Schedule of Activities in section 7.4. The study staff will collect the checklist and review the subject diary with the subject during each visit to ensure that all entries are complete and understood by the study staff. Any corrections must be made by the subject, and initialed and dated by them.

7.1 Study Procedures

7.2 Data Collection

7.2.1 Vital Signs/Height and Weight:

Vital signs including blood pressure, pulse and weight will be taken at each study visit . Height will be taken only at baseline by the study team. Each measure will be taken twice and averaged.

7.2.2 Laboratory Testing

Women of childbearing potential, defined as premenopausal, intact ovaries and uterus, and not on birth control, will be tested for pregnancy using a self-administrator urine pregnancy test. If the pregnancy test is positive, the subject will be excluded from the study.

7.2.3 Feasibility (Appendix E):

7.2.3.1 Adherence and barriers (Both Groups): Subjects will keep a diary of device use and list barriers to use of device (investigational group). A self-care checklist will be completed each week they are in the study (both groups).

7.2.3.2 Safety (Both Groups) will be evaluated using CTCAE V4.0[11]

7.2.3.3 Pre and Post treatment Survey (Intervention Group Only): Subjects will complete a pre and post treatment survey. The survey will be administered at the baseline visit and at the end of the intervention.

7.2.4 Swelling/Inflammation (Appendix F):

7.2.4.1 Endoscopy with Modified Patterson Scale: The Patterson Scale evaluates internal edema in the pharynx and larynx. The Modified Patterson Scale, with established face validity, includes anatomical sites that may develop internal edema.[12]

7.2.4.2 Cytokines: The study nurse or phlebotomist will draw blood at baseline and at the 8-week visit. The following inflammatory markers will be assessed: IFNg TNF-α, TGF-β, IL-1b, and IL-6. MMP-2, MMP-9, and CRP will also be assessed if testing is available.

7.2.4.3 Digital Photography: At the visits outlined in the Study Schedule of Activities table in section 7.4, subjects will have photos taken of their affected areas to evaluate external swelling/inflammation. These photos will be taken according to the standard procedure as outlined in Appendix F.

7.2.4.4 Grading of External Lymphedema: Trained study personnel will complete a physical examination of the head and neck area. Grading will be documented via the Head and Neck Lymphedema and Fibrosis Assessment criteria.[13]

7.2.5 Function (Appendix G):

7.2.5.1 Neck Disability Index (NDI): This 10-item instrument assesses components of daily life that may be affected by neck pain and dysfunction. Items include pain, personal care, lifting, reaching, headache, concentration, work, driving, sleeping, and recreation. Internal consistency of the 10-item scale is adequate (α= .89 - .92).[14, 15] Factor analysis identified one dimension. Stability of the instrument also is adequate (r = .89). Validity of the NDI was supported by the moderate to strong correlations with self-reported activity improvement following treatment and pain.

7.2.5.2 Voice Handicap Index (VHI): This 30 item instrument taps function, emotion, and physical areas that may be affected by

voice disorders such as those caused by chemo-radiation therapy for HNC.[16] Internal consistency of the 30-item scale is adequate (r=0.95).

7.2.5.3 Cervical and Shoulder ROM: These measurements will be taken according to the instructions provided in Appendix G. The measurements will be taken at intervals outlined in the Study Schedule of Activities table (section 7.4).

7.2.5.4 Jaw ROM: The TheraBite Jaw ROM Scale will be used to measure jaw opening. The Trismus grading criteria from the CTCAE v4.0 also be will be recorded.[11]

7.2.6 Symptoms and Quality of Life (Appendix H)

7.2.6.1 Vanderbilt Head and Neck Symptom Survey plus General Symptom Survey version 2.0 (VHNSS v2.0 plus GSS): The VHNSS v2.0 assesses the prevalence and severity of treatment-related symptoms and their functional impact in patients with head and neck cancer.[17] The VHNSS v.2.0 consists of 50-items within 13 domains including nutrition, swallowing, xerostomia, mucositis, excess mucus, speech, hearing, taste change, smell, dental health, mucosal sensitivity, range of motion, and pain. Items are scored on a numeric scale rating the severity of the symptom from 0 (none) to 10 (severe). The VHNSS v.2.0 takes approximately 10 minutes to complete. VHNSS v2.0 plus GSS includes 12 additional items directed at the systemic effects of therapy. The instrument will be completed by the subjects at the intervals outlined in the Study Schedule of Activities table in section 7.4.

7.2.6.2 Lymphedema Symptom Intensity and Distress Survey (L SIDS-Head and Neck): Lymphedema Symptom Intensity and Distress Survey-Head and Neck, assesses the measurement characteristics of a measure of symptom burden for patients with head and neck lymphedema and is a modified versions of the Lymphedema Symptom Intensity and Distress Survey-Arm.[18]

7.2.7 Quality of Life: The 5-item Linear Analog Self-Assessment will be used to evaluate quality of life. The scale assesses physical, emotional, spiritual, intellectual, and over-all well-being, on a 0-10 scale. It has been successfully used in cancer populations.[19]

7.3 Study Device Application: The garment will be applied initially with the assistance of the study staff. After the study staff has successfully instructed the subject on how to apply the garment, the subject will be asked to apply the garment with limited assistance, complete a treatment session and then remove the garment. After the removal of the garment, the subject will be asked to don and doff the

garment again without assistance. All subjects will be asked to complete one self-administered treatment under the observation of study team members.

7.4 Study Schedule of Activities:

	Screening/ Randomization	Baseline Visit	Follow Up Week 1	Follow Up Week 4	Final Week8
Patient Characteristics					
Medical History	√				
Height		√			
Weight		√	√	√	√
Garment Fitting	√				
Vital Signs (BP, Pulse)*		√	√	√	√
Demographics	√				
Pregnancy Testing*	√			√	√
Fidelity					
Adherence-Diary**			√	√	√
Barriers-Dairy**			√	√	√
Self-care Checklist		weekly			
Safety					
Adverse Events-CTCAEV4.0*			√	√	√
Satisfaction					
Pretreatment survey**		√			
Post treatment survey **					√
Swelling/Inflammation					
Internal-Endoscopy/Patterson Scale		√			√
Digital Photography		√	√	√	√
Grading and Staging*	√	√	√	√	√
Cytokines		√			√
Function					
Range of motion-jaw, shoulder, neck		√		√	√
Patient Reported Outcome-Neck Disability Index		√		√	√
Patient Reported Outcome-Voice Handicap Index		√		√	√
Symptoms					
Vanderbilt H and N Symptom Survey		√		√	√
Lymphedema Symptom Intensity and Distress Scale		√		√	√
Quality of Life					
Linear Analog Self-Assessment		√		√	√

*=safety checks at week 9, 12, &16 for wait-list group opting to use the device
**=intervention group only

8.0 Study Device Accountability (Appendix I):
The site must maintain a device accountability log for the Flexitouch®. Completion of this log will ensure that all study 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, controller disinfected, and final disposition (e.g., returned to sponsor, garments discarded) of all Flexitouch® controllers, and garments will be documented.

Tactile Medical™ must also maintain device accountability documenting all shipments and returns of study devices by serial number, date, and person completing the log. Storage locations for the study devices and garments will be secure (i.e., locked and away from other devices) with access restricted only to investigators and authorized research personnel. At the conclusion of the treatment period, the subject will return the Flexitouch® controller to the study site. Garments may be retained by the subject or discarded. Site personnel will return all controllers and any unused garments to Tactile Medical™ at the completion of the study.

9.1 Risk Analysis and Adverse Events:

9.2 Risk Analysis: The subjects enrolled in the study are not expected to be at any higher or additional risk than those who undergo in-clinic CDT. There is minimal risk with CDT. These risks may include but are not limited to increased swelling and pain.

9.3 Anticipated Adverse Events: Adverse events associated with lymphedema may include increased swelling and pain. The severity of all anticipated events will be graded according to the CTCAE.[15] During the endoscopy it is possible that the following adverse events could occur 1) allergic reactions to the anesthesia or decongestant if these are used 2) problems with heart rhythm 3) nosebleed or other bleeding 4) sore throat 5) fainting 6) headache and 7) chipped teeth.

9.4 Adverse Event Reporting: An adverse event includes any complication whose clinical significance is greater than anticipated, or which occurs with a frequency greater than that which is usually seen for this type of treatment. A serious adverse event is defined as an event that: 1) results in death; 2) is life-threatening (places the subject at immediate risk of death from the experience as it occurred); 3) results in a persistent or significant disability/incapacity (substantial disruption of one's ability to carry out normal life functions); 4) results in medical or surgical intervention; 5) results in or prolongs an existing hospitalization (even if the hospitalization is a precautionary measure for observation); 6) is medically unexpected, regardless of severity. Investigators must report all serious adverse events to Tactile Medical™ within 72 hours. Serious and/or unanticipated adverse events will be reported in writing to the appropriate IRB in accordance with their policy, but not later than five (5) days.

10.0 Deviation from Study Plan: Any deviation from this protocol undertaken to protect the life or physical well-being of a subject in an emergency must be reported to Tactile Medical™ and the respective IRB as soon as possible, but in no event later than five (5) working days

after the deviation occurred. Anticipated deviations from the protocol in a non-emergency situation must be pre-approved by Tactile Medical™ via telephone, email, fax or mail. It is preferred that deviations scheduled to be performed in a non-emergency situation not be conducted until authorized by Tactile Medical™. All protocol deviations must be documented. A deviation that may affect the scientific soundness of the study, or the rights, safety or welfare of the subject must also be reported to the reviewing IRB. Protocol deviations may necessitate the discontinuation of the subject or the site from the study.

11.1 Data/Safety Monitoring & Quality Assurance Procedures: This study will be conducted in accordance with Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) Guidelines, 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. The investigators will permit regular monitoring, audits and site inspections by the IRB, the sponsor, government regulatory bodies and any institution compliance and quality assurance groups of all study related documents (e.g. medical records, source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspection of applicable study related facilities. Clinical trial monitoring may be conducted to ensure compliance to this protocol.

11.2 Site Qualifications: Tactile Medical™ may conduct onsite visits or telephone qualification (pre-study audit) prior to study initiation to verify adequate resources, staffing and a sufficient subject pool.

11.3 Data Collection Procedures: All data storage, transmission and management will be conducted using the Research Electronic Data Capture (REDCap) tool.[20] REDCap is a software toolset and workflow methodology for the secure electronic collection and management of research data. REDCap servers are housed in a data center located in a HIPAA-compliant environment at Vanderbilt with nightly backups. All web-based information transmission is encrypted. REDCap was developed specifically around HIPAA Security guidelines. REDCap has been disseminated for local use at more than 940 other academic/non-profit consortium partners in 75 countries. Vanderbilt leads the REDCap Consortium, which currently supports more than 99,000 projects and 128,000 users. The toolset supports research studies with data management reports, data integrity reports for data cleaning and evaluation, and tracking reports for longitudinal studies. In the event REDCap is unavailable or the patients prefers to use hard copy, hard copy data will be double entered into REDCap.

Each study site will have a site coordinator who will be responsible for ensuring the quality of all data collected at that site and ensuring that the data have been entered into the central study database. All data collected via paper will be double entered and verified by site staff. The raw data will be collected on study specific source document worksheets and/or site specific documentation if REDCap is not available, which includes but are not limited to, medical records and site generated source worksheets.

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

- Subject safety
- That clinical site staff is well informed on 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 AEs are properly reported in a timely manner

Investigator and Institution will permit trial related monitoring, audits, IRB review, and regulatory inspection(s), providing supervised direct access to medical records, source data and documents as appropriate. Monitoring will be performed by Tactile Medical™ and/or designee.

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

- Investigational plan and all amendments
- Signed Investigator Agreement
- IRB approval letter, including a copy of the approved consent forms, progress reports, Adverse Event Report
- IRB roster or Assurance number, if applicable
- All correspondences relating to the conduct of this study between the site and sponsor, IRBs, and study monitor
- Curriculum Vitae and professional license for all study personnel, if applicable
- Site personnel signature and documentation regarding the Investigator's delegation of responsibility
- Clinical Site Visit log
- Protocol/device related training records for all applicable study personnel
- 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
- Reports (see Table 2)

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.

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 2.

Table 2: Investigator Reports

Reports	Submit To	Timeframe
Unanticipated Adverse Device Event	Sponsor and Reviewing IRB	As soon as possible but no later than 10 working days
Withdrawal of IRB Approval	Sponsor	Within 5 working days
Progress	Sponsor and Reviewing IRB	Annually, at a minimum
Final	Sponsor and Reviewing IRB	Within 3 months following the completion or termination of the Investigator's part

Subject study records, correspondence files, all supporting study documentation, and reports must remain on file at the investigational site for a minimum of ten years after the conclusion of this study. All investigators must contact Tactile Medical™ 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™ 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.

11.6 Change to Study Plan:

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

12.1 Statistical Methods and Determination of Sample Size

12.2 Data Management

Collection: All data will be collected using the Research Electronic Data Capture (REDCap) tool.[20] The sites will use hard copy source documents to collect all physical measurements, assessment data, and subjects will complete self-reports questionnaires only if REDCap is not available or patient prefer hard copy. Study staff will keep all hard copies on site and in designated area with subject specific ID numbers.

Storage: Source document forms will be stored in a secure area at each study site. This will be accessible to study staff only and will be assigned a study ID number. At the end of the study the documents will continued to be stored on site or moved to a separate storage facility and held for the required duration.

Data Entry: Data will be added directly into REDCap when collected. If hard copies are used data will be double entered from the source documents into REDCap as soon as REDCap is available. The data will be reviewed for errors and data will be cleaned prior to analysis. All staff at site will be trained by the sponsor, or designee, or study PI on data collection procedures and protocol implementation.

12.3 Statistical Analysis Plan

Minimization of Bias: Stratified randomization to the study groupswithin each study site will be conducted. Given that this is a wait list/control design, blinding is not possible. Each subject will be assigned a study ID number that will be used for identification purposes in the data. The study statistician who will have no contact with any study participants and will conduct all analyses.

Missing Data: Randomly missing item responses within the study survey measures will be handled as specified by the measure developers. Nonrandom missing visit data are informative for this study (i.e., may speak to feasibility) – no imputation will be conducted.

Interim Analysis: Given that this is a feasibility study, no interim analyses will be conducted. The primary reason for early stoppage would be adverse events.

Aims:

Primary Aim: To determine the feasibility of use of the Flexitouch® Head and Neck Garment, specifically a) to evaluate implementation fidelity (adherence) and barriers to implementation fidelity, b) to establish safety, and c) to assess satisfaction.

Secondary Aim: To determine the preliminary efficacy of Flexitouch® Head and Neck Garment compared to a wait-list control for the following outcomes: a) reduction in swelling/inflammation, b) function (range of motion cervical, jaw, and shoulder), c) symptoms, and d) quality of life.

12.4 Statistical Analyses:

Aim 1 (feasibility): Descriptive statistics (percentages) will be used to summarize adherence to the protocol, barriers, adverse effects, and ratings of satisfaction. Comparison of the rates observed within each of the study groups will be compared using likelihood Chi-Square tests however it is expected that >=75% of the total number of participants enrolled in the study as a whole will complete the study. At the end of the study, it is expected that participants in the investigational group will report acceptable levels of satisfaction with the device, as indicated by 80% rating the satisfaction items above neutral.

Aim 2 (preliminary efficacy): Descriptive and graphical summaries of the measures at each time of assessment will summarize the overall and group changes in each of the outcome measures over the *8-week* study period for each of the groups. Mixed effects general linear models will be used to generate estimates of the interactive effect of the Flexitouch® Head and Neck Garment and time in the study on the primary outcomes. Such an interaction effect would be indicate, for example, larger reduction in symptoms for the intervention group than that observed in the wait list control over the same time period. Bias-corrected effect sizes of garment use on the respective changes will be generated from each of the outcomes. While this study is a preliminary study of efficacy and effect sizes, a maximum alpha level of .05 will be used for statements of "statistical" significance.

Safety Analysis: During the time any participant is using the device, safety checks (Adverse Evetns-CTCAEV4.0, B/P, Pulse, and staging) will be made at defined intervals as noted in section 7.3.

Determination of Sample Size: The primary rationale for study size is the proposed funded time of this study and the number of potential subjects that could be recruited during that time. This is not a hypothesis testing study rather it is a preliminary feasibility and efficacy study for generating observed effect sizes. Nevertheless, samples of 20 individuals in each group (total=40) who successfully complete the 8-week protocol will provide 80% statistical power to detect a differential level of change of approximately 0.9SD (effect size). In other words, assuming a baseline Neck Disability Index (NDI) of 20 (SD=10) and that the wait-list control group demonstrates no change from baseline, a reduction in mean NDI to 11 in the garment group would indicate a statistically significant difference (2-sided alpha-0.05). We have no evidence to hypothesize differences of that magnitude however; we do believe that our sample size will provide sufficient data for estimating reasonable effect estimates for future studies.

13.0 Compensation:
Subjects may be compensated for time and travel at an amount determined by each site.

14.0 Publication Plan:

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

15.1 References

1. Smith, B.G. and J.S. Lewin, *Lymphedema management in head and neck cancer.* Curr Opin Otolaryngol Head Neck Surg, 2010. **18**(3): p. 153-8.

2. Ridner, Sheila, et al., *A Prospective Study of the Lymphedema and Fibrosis Continuum in Patients with Head and Neck Cancer.* Lymphatic Research and Biology Volume 14, Number 4, 2016 p. 1.

3. Deng, J., et al., *Preliminary development of a lymphedema symptom assessment scale for patients with head and neck cancer.* Support Care Cancer, 2012. **20**(8): p. 1911-8.

4. Deng, J., et al., *Prevalence of secondary lymphedema in patients with head and neck cancer.* J Pain Symptom Manage, 2012. **43**(2): p. 244-52.

5. Avraham, T., et al., *Radiation therapy causes loss of dermal lymphatic vessels and interferes with lymphatic function by TGF-beta1-mediated tissue fibrosis.* Am J Physiol Cell Physiol, 2010. **299**(3): p. C589-605.

6. Satapathy, A.K., et al., *Human bancroftian filariasis: immunological markers of morbidity and infection.* Microbes Infect, 2006. **8**(9-10): p. 2414-23.

7. Brush J., et al*., Molecular mechanisms of late normal tissue injury.* Semin Radiat Oncol., 2007. **17**(2): p. 121-30.

8. Delanian S., and J.L. Lefaix, *Current management for late normal tissue injury: radiation-induced fibrosis and necrosis.* Semin Radiat Oncol., 2007. **17**(2): p. 99-107.

9. Rubin P., et al., *A perpetual cascade of cytokines postirradiation leads to pulmonary fibrosis.* Int J Radiat Oncol Biol Phys., 1995. **33**(1): p. 99-109.

10. Földi E., et al., *Effect of complex decongestive physiotherapy on gene expression for the inflammatory response in peripheral lymphedema.* Lymphology, 2000. **33**(1): p. 19-23.

11. Common Terminology Criteria for Adverse Events, Version 4.03 (CTCAE v4.03) June 14, 2010.

12. Patterson, J.M., et al., *Measuring edema in irradiated head and neck cancer patients.* Annals of Otology, Rhinology and Laryngology, 2007. **116**(8): p. 559-564.

13. Deng, J., et al., *Preliminary evaluation of reliability and validity of head and neck external lymphedema and fibrosis assessment criteria.* European Journal of Oncology Nursing, 2016. Jun (22): p. 63-70.

14. Vernon H. and S. Mior, *The Neck Disability Index: a study of reliability and validity.* J Manipulative Physiol Ther., 1991. **14**(7): p. 409-15.

15. Hains, F., et al., *Psychometric properties of the neck disability index.* J Manipulative Physiol Ther., 1998. **21**(2): p. 75-80.

16. Jacobson, B.H., et al., *The Voice Handicap Index (VHI): Development and Validation.* American Journal of Speech-Language Pathology, 1997. **6**(3): p. 66-69.
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

17. . Murphy, B. A., Dietrich, M. S., Wells, N., Dwyer, K., Ridner, S. H., Silver, H. J., Gilbert, J., Chung, C. H., Cmelak, A., Burkey, B., Yarborough, W. G., Sinard, R.,

Netterville, J. (Jan 2010). Reliability and validity for the Vanderbilt Head and Neck Symptom Survey (VHNSS): A new tool to assess symptom burden in patients undergoing chemoradiation. *Head and Neck*, *32*(1), 26-37.
18. Ridner, S.H., and M.S. Dietrich, *Development and Validation of the Lymphedema System and Intensity Survey-Arm.* Support Care Cancer, 2015. Oct 23(10): p. 3103-12.
19. Locke D.E., et al., *Validation of single-item linear analog scale assessment of quality of life in neuro-oncology patients.* J Pain Symptom Manage, 2007. **34**(6): p. 628–638.
20. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inf.* 2009;42(2):377-381.