A Randomized Trial of an Advanced Pneumatic Compression Device vs. Usual Care for Head and Neck Lymphedema

Protocol Number: 8030
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December 8, 2021
Protocol Version 2.0

Investigator Signature

Protocol Title: A Randomized Trial of an Advanced Pneumatic Compression Device vs. Usual Care for Head and Neck Lymphedema

Protocol Number: 8030

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

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Site Principal Investigator Name (Print)

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Site Principal Investigator Signature Date

SYNOPSIS

Study Title	A Randomized Trial of an Advanced Pneumatic Compression Device vs. Usual Care for Head and Neck Lymphedema
Protocol Date	December 8, 2021
Protocol Version	2.0
Protocol Number	8030
Name of Sponsor	Tactile Medical™
Study Design	This study is an open label, multi-site, randomized trial comparing the use of an advanced pneumatic compression device (APCD) to Usual Care.
Treatment Groups	Eligible patients will be randomized to receive one of the following treatments: ➢ APCD: Daily self-administered treatment with the Flexitouch® Plus system (FT) ➢ Usual Care: Complete Decongestive Therapy (CDT) directed by a lymphedema therapist and any additional adjunctive measures as prescribed by the lymphedema therapist
Study Objective	To compare the effectiveness of an APCD to Usual Care in the management of lymphedema and fibrosis (LEF) in head and neck cancer (HNC) survivors.
Primary Aims	<u>Aim 1:</u> To compare the short-term and long-term effectiveness of self-administered APCD therapy versus Usual Care in HNC survivors with treatment naive LEF on anatomical measures of internal and external LEF. Baseline measures will be obtained at the start of therapy. Short-term effectiveness will be evaluated at 2 months and long-term effectiveness will be evaluated at 4 and 6 months. Hypothesis: the APCD therapy will be associated with greater short-term and long-term reduction in anatomical measures of LEF. <u>Aim 2:</u> To compare the short-term and long-term effectiveness of self-administered APCD therapy versus Usual Care in HNC survivors with treatment naive LEF on patient reported biopsychosocial outcome measures impacted by LEF. Outcome measures will include: 1) symptom burden, 2) symptom burden and functional impairment, 3) quality of life (QOL), 4) work and activity, 5) perceived self-management capacity, 6) body image, and 7) diet modifications. Baseline measures will be obtained at the start of therapy. Short-term effectiveness will be evaluated at 2 months and long-term effectiveness will be evaluated at 4 and 6 months. Hypothesis: the APCD therapy will be associated with greater short-term and long-term improvement in patient reported biopsychosocial outcomes.
Primary Endpoints	To compare the short (2 months) and long-term (4 & 6 months) effectiveness of self-administered APCD therapy to Usual Care in HNC survivors with treatment naïve LEF. <u>Anatomical Measures:</u> 1. Internal lymphedema o Assessment of upper aerodigestive tract (UADT) via endoscopy with direct or indirect visualization (Modified Patterson Scale) o Computed Tomography (CT) Imaging (CT Lymphedema and Fibrosis Assessment Tool [CT-LEFAT]) 2. External lymphedema

	○ Assessment using Head and Neck Cancer Related Lymphedema and Fibrosis Grading (HN-LEFG) criteria ○ Digital Photography (30 section grid) <u>Patient Reported Biopsychosocial Measures:</u> 1. Symptom Burden: Lymphedema Symptom Intensity and Distress Survey – Head and Neck (LSIDS-H&N v2.0) 2. Symptom Burden and Functional Impairment: Vanderbilt Head and Neck Symptom Survey plus General Symptom Survey (VHNSS plus GSS) 3. QOL: 5-item Linear Analog Self-Assessment 4. Work and Activity: Work Productivity and Activity Impairment Questionnaire (WPAIQ) 5. Perceived self-management compacity: Perceived Medical Condition Self-Management Scale (PMCSMS) 6. Body image: Body Image Quality of Life Inventory (BIQLI) 7. Diet modifications: Automated Self-Administered 24-Hour Dietary Assessment Tool (ASA24®)
Treatment Duration	The duration of study will include the screening period, randomization, and therapeutic intervention. From the time patients sign consent until they initiate treatment is less than 1 month. The intervention phase will last 6 months.
Inclusion/Exclusion Criteria	**Inclusion Criteria:** 1. Age ≥ 18 years 2. Pathologically confirmed cancer of the head and neck (larynx, pharynx, oral cavity, paranasal sinuses, major salivary glands, and HNC of unknown primary) 3. Completed curative intent cancer therapy with no evidence of active cancer at time of study enrollment 4. A diagnosis of either internal or external head and neck lymphedema 5. At least one core lymphedema associated symptom of ≥ 4 out of 10 at the time of study screening 6. Must be able and willing to participate in all aspects of the study and provide informed consent prior to study participation 7. Must be able to speak and understand English **Exclusion Criteria:** 1. Previous APCD or Usual Care treatment for HNC LEF 2. Acute facial infection (e.g., facial or parotid gland abscess) 3. Known carotid sinus hypersensitivity syndrome 4. Symptomatic carotid artery disease, as manifested by a recent (within 30 days prior to consent) transient ischemic attack, ischemic stroke, or amaurosis fugax (monocular visual ischemic symptoms or blindness) 5. Internal jugular venous thrombosis (within 3 months prior to consent) 6. Patient is pregnant or trying to become pregnant
Number Planned	250 randomized patients

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2.0 Abbreviations

Abbreviation	Term
APCD	Advanced Pneumatic Compression Device
ASA24	Automated Self-Administered 24-Hour Dietary Assessment Tool
BIQLI	Body Image Quality of Life Inventory
CDT	Complete Decongestive Therapy
CFR	Code of Federal Regulations
CMS	Centers for Medicare & Medicaid Services
CT	Computed Tomography
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CT-LEFAT	Computed Tomography Lymphedema and Fibrosis Assessment Tool
eCRF	electronic Case Report Form
ePRO	electronic Patient Reported Outcomes
FT	Flexitouch Plus system
GCPs	Good Clinical Practices
HN-LEFG	Head and Neck Cancer Related Lymphedema and Fibrosis Grading
HNC	Head and Neck Cancer
HPV	Human Papilloma Virus
ICF	Informed Consent Form
IRB	Institutional Review Board
LEF	Lymphedema and Fibrosis
LSIDS-H&N	Lymphedema Symptom Intensity and Distress Survey – Head and Neck
NIRFLI	Near-Infrared Fluorescence Lymphatic Imaging
PI	Principal Investigator
PMCSMS	Perceived Medical Condition Self-Management Scale
PRO	Patient Reported Outcome
QOL	Quality of Life
RCT	Randomized Controlled Trial
Sub-I	Sub-Investigator
UADT	Upper Aerodigestive Tract
VHNSS plus GSS	Vanderbilt Head and Neck Symptom Survey plus General Symptom Survey
VUMC	Vanderbilt University Medical Center
WPAIQ	Work Productivity and Activity Impairment Questionnaire

3.0 Introduction

3.1 Importance of Problem

Approximately 53,260 Americans will develop head and neck cancer (HNC) in 2020 and an estimated 10,750 patients will die of these cancers.[1] For patients with locally advanced disease, aggressive multi-modality therapy has been shown to improve local control and survival but at the expense of significant acute and late treatment effects.[2] There has also been an increase in human papilloma virus (HPV) associated and oropharyngeal cancers and oral cavity cancers.[3-6] As a result of improved treatment outcomes and changing epidemiology, there has been an increase in the number of HNC survivors, many destined to live for protracted periods of time with the side effects from cancer and its therapy.[7-10] A common but under recognized late effect of HNC treatment is secondary lymphedema and fibrosis (LEF).[7]

LEF occurs when either lymphatic structures or surrounding soft tissues are damaged or blocked. LEF manifests as soft tissue swelling and fibrosis.[11] The sequalae vary based on the site of tissue involvement. HNC associated LEF may involve external structures (e.g., face, neck and shoulders, and internal structures (e.g., larynx and pharynx).[7,12] Involvement of external sites may lead to alternations in skin color or texture, pain and discomfort, stiffness and decreased range of motion in the neck and shoulders, and body image issues.[13,14] Involvement of internal structures including the pharynx and larynx results in functional deficits such as altered speech and shortness of breath due to airway obstruction.[14,15] Of note, LEF is a common cause of acute and long term dysphagia resulting in dietary adaptations, long term feeding tube dependence, and increased risk for aspiration pneumonia. Without early identification and timely therapy, soft tissues affected by lymphedema can become increasingly fibrotic and contracted. This can result in profound function loss with disability. For example, patients with fibrosis and contractures of the neck (e.g., neck fibrosis) may have chronic pain, pronounced postural abnormalities, and severe function loss due to decreased range of motion (ROM) in the neck (e.g., inability to drive or dress). Trismus secondary to fibrosis of the muscle of mastication results in limiting oral intake, inability to maintain oral care, speech abnormalities, and difficulty with intubation.[14,16] Our data indicate that increasing LEF severity is associated with increasing symptom burden, functional impairments, and decreased QOL.[14] In a prospective longitudinal study describing the incidence, biological mechanisms, and impact of LEF in HNC patients, *one hundred percent of patients followed for 18-months post-cancer treatment experienced LEF at some point along the time course of their disease, treatment, or recovery.*[17] *Furthermore, the severity was in the moderate to severe range in the majority of patients.* Evidence supports the hypothesis that early identification of LEF followed by aggressive lymphedema therapy may improve patient outcomes in lymphedema patient populations.[18,19]

3.2 Conceptual Framework

In non-pathological conditions, the blood capillaries and lymphatic system provide for fluid exchange at the blood capillary-interstitial-lymphatic-interface.[20,21] Filtration pressures at the arterial side of a capillary force fluid and protein into the interstitium. Although re-absorption pressures pull some of the fluid back into the capillary at the venous side, the majority of filtered fluid and protein are removed by the lymphatics.[20-23] The face and neck contains an extensive network of lymphatic channels and over 300 lymph nodes (1/3 of lymph nodes within the body).[20-23] Cancer, surgery, and radiation may disrupt lymphatic structures, blocking lymph flow and resulting in soft tissue edema.[25-27] This stagnant edema results in an inflammatory response. If edema is not reduced in a timely manner, chronic inflammation leads to non-reducible fibrofatty scarring. This in term further damages lymphatics creating a self-perpetuating cycle of soft tissue damage. Both usual care CDT and Advanced Pneumatic Compression Devices (APCD) move lymphatic fluid from the extracellular spaces thereby decreasing edema and the associated inflammation. By interrupting the cycle, they can not only halt the progression of soft tissue damage, but they can also impact the symptoms and functional impairment associated with LEF.

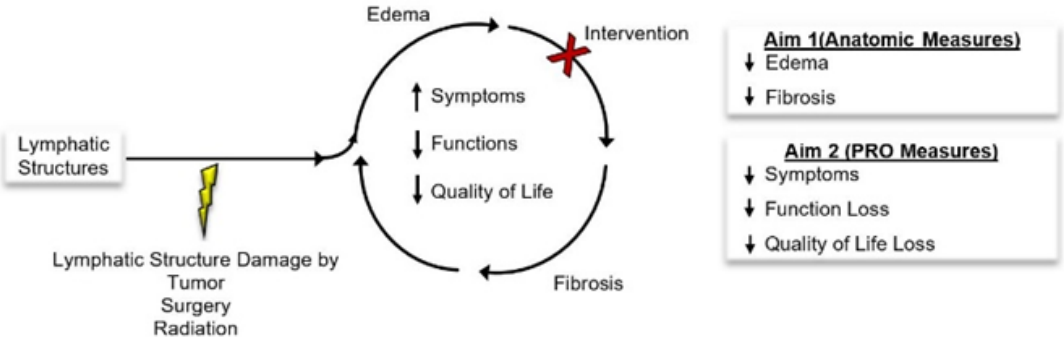


Figure 1. Conceptual Framework for Impact of FT on LEF and Associated Outcomes

3.2.1 Usual Care

The cornerstone of lymphedema management is usual care two-phase complete decongestive therapy (CDT). Phase 1 is most commonly performed by a physical or occupational therapist with specialized training and certification in lymphedema management.[28] Phase 2 is long term self-care.[28,29] Initial Therapy (Phase 1 Care): This phase includes: consultation with a lymphedema therapist, patient education, therapist administered manual lymph drainage, compression garments or bandages where indicated, skin care techniques, and a program of exercises and postural recommendations. The goal is to reduce visible or palpable LEF and control associated symptoms. The duration of the initial therapy varies with LEF severity and therapeutic response. Though 5 therapy sessions per week are recommended, a 2017 study of 107 lymphedema therapists reported a mean of 3.71 therapy sessions per week being most common.[30] Self-Care

(Phase 2 Care)**:** During the self-care phase, patients must conduct a life-long program of disease management that mimics the program undertaken by the lymphedema therapist as delineated above with compression and lymphatic massage as integral components. Unlike other chronic diseases there are no routine or annual follow-ups to monitor the patient after Phase 1 care. Patients are expected to contact their primary care provider should LEF exacerbations or infections arise during Phase 2 care. They would then be referred back for Phase 1 CDT.

Treatment algorithms for HNC associated lymphedema are based on clinical experience and data from other anatomical sites of lymphedema. A systematic review evaluating treatment modalities for HNC lymphedema published in 2019 identified 26 studies including: usual care CDT (n=10), alternative or complementary studies (n=7), non-liposuction surgical techniques (n=6), and liposuction (n=3). No studies addressed APCDs and none assessed internal lymphedema or fibrosis as outcomes.[31] The most informative data was generated through a retrospective review conducted at MD Anderson in which 733 out of 1200 lymphedema patients were evaluable for treatment response.[32] Patients were divided into two cohorts: 1) those who underwent CDT at the MD Anderson Cancer Center (n=86; 12%) or 2) those who received instruction for self-administered home CDT (n=647; 88%). Patients in the second cohort either "could not or declined" therapist administered Phase 1 CDT.[31] External lymphedema was assessed by composite surface tape measurements. For patients in cohort 1, the frequency and duration of therapy sessions varied from between 2-5 sessions per week over 2-4 weeks. Patients exhibited a 60% response rate (no p values given) for external lymphedema, suggesting that CDT was effective for some, but not all patients. Patients in cohort 1 demonstrated greater improvement at follow-up (p=0.014) compared to those in cohort 2 who conducted self-care only.

3.2.1.1 Barriers to Usual Care

Barriers to Initial Therapy (Phase 1):1) High Cost of Therapy: Lymphedema therapy is provided in a one-on-one fashion as it requires extensive manual interventions such as lymphatic massage and commonly lasts 90 minutes.[33] One therapy session at Vanderbilt-Ingram Cancer Center costs $344 (not including supplies). Thus, weekly costs range from $688 to $1,032 and total costs over 8-weeks exceed $8,000. 2) Lack of Insurance Coverage for Therapy: A cross-sectional study of 103 HNC patients found 8% did not have insurance coverage.[14] For those with insurance, lymphedema therapy may not be covered. Costly copayments and claim denials are common. Data also indicate that most third-party payers may fail to cover the recommended number of sessions needed to achieve maximum reduction of swelling and symptom relief in this population. 3) Lack of Access to General Lymphedema Therapy Services: Lymphedema management

services, especially for HNC survivors, are often difficult to obtain.[34-35] There are limited numbers of certified lymphedema therapists. Most are located in urban areas. Data revealed that 37% of patients resided in rural areas without lymphedema services.[14] 4) Lack of Certified Lymphedema Therapists: Lymphedema therapists require additional training to adequately treat patients with HNC associated LEF. Few have this training. Wait-lists range from weeks to months.[28] 5) Time Burden to Patients and Caregivers: Following a rigorous and time-consuming HNC therapy, patients and families feel compelled to concentrate time and effort on return to work and other important activities that were suspended during treatment. Lymphedema therapy is often seen as a nonessential activity. 6) Transportation Difficulties: Patients with HNC LEF often depend on others to bring them to treatment. 7) Profitability: Basic lymphedema certification requires several weeks of training beyond what is provided in graduate rehabilitation therapy education.[28] This training can cost thousands of dollars in direct and indirect (loss of income) costs. Management of head and neck lymphedema requires additional time-consuming courses which results in added expense. Centers for Medicare & Medicaid Services (CMS) requires lymphedema therapy be conducted one-on-one.[33,36] This is in distinction to orthopedic therapy where one therapist treats two to three non-Medicare patients simultaneously.[36] Thus, the earning potential of a lymphedema therapist is limited when compared to the provision of other therapies. The high cost of training and reduced earning potential has limited the number of practitioners and directed lymphedema services to tertiary care centers where reimbursement is higher and a loss-leading service is better tolerated.[37] Taken together, an alternative approach to usual Phase 1 care such, as self-administered home-based APCD treatment, warrants investigation to address these barriers that contribute to Phase-1 treatment failure.

Barriers to Self-Care (Phase 2): Lymphedema therapists set therapeutic goals and stop Phase 1 therapy once those goals are met. Previous studies have indicated that approximately 50% of patients did not conduct Phase 2 self-care activities for their LEF after initial lymphedema therapy due to the following barriers. 1) Lack of Guidelines or Protocols: Standardized LEF self-management protocols have yet to be developed and tested for feasibility, safety and efficacy in the HNC population.[14] 2) Lack of Monitoring: LEF is an evolving process that may regress, redevelop, or progress to fibrosis over time during Phase 2 self-care.[11,14,16] However, there are no protocols for monitoring patients after lymphedema therapy is completed to identify and address changing therapeutic needs secondary to progressing LEF. 3)

Limited Knowledge, Lack of Training on Skills and Techniques for Self-Care: Many HNC survivors with LEF state despite education from therapists, there remained lack of required knowledge and skills and they were unable to replicate techniques needed for self-management; thus, they felt self-care did not work and required re-education.[7] 4) Lack of Motivation: A previous study found patents did not conduct Phase 2 self-care activities due to lack of personal motivation and/or social motivation (social/family support).[7] 5) Low Self-Efficacy: Previous research has highlighted that low self-efficacy (efficacy of self-care) was a predominant issue among HNC survivors with LEF.[7] 6) Difficulty Integrating into Daily Routine: After completion of Phase-1 lymphedema therapy, patients desire to return to their previous life and to work full time. They specify that it is difficult to integrate self-care into established daily, busy routine. 7) Symptom Burden: LEF therapy would optimally be initiated early post-cancer-treatment as patients continue to experience high levels and severity of symptoms that may impact adherence including fatigue, neurocognitive deficits, anxiety, and depression. These barriers often lead to failed self-care and poor patient outcomes.

3.2.2 Advanced Pneumatic Compression Devices

Two types of pneumatic compression devices (billing codes E0651 and E0652) are used in the treatment of limb lymphedema. Both have multiple outflow ports on the compressor that release pressurized air from the outflow ports lead to corresponding segments on the appliance/garment. The segments inflate and deflate based upon the specified pressures and cycle times. A segmented device *without calibrated gradient pressure* (E0651) is one in which either the same pressure is present in each segment or there is a predetermined pressure gradient in successive segments. *An advanced segmented device with calibrated gradient pressure (E0652) is characterized by manual control on at least three outflow ports that can deliver an individually determined pressure to each corresponding appliance segment. The only known compression device FDA cleared for treatment of head and neck LEF is the advanced Flexitouch Plus system* (Tactile Medical)*, classified as E0652*. It is differentiated from all other pumps because it has flat, curved chambers and peristaltic pressure flow. This device more closely replicates human massage techniques than do other compression devices as it produces gentle, dynamic “stretch and release” mechanism of action to stimulate lymphatic function similar to manual lymphatic drainage massage rather than a “squeeze and hold” mechanism of action which tends to simply displace interstitial fluid as do other pumps.

3.2.2.1 Flexitouch Plus system (FT)

The Flexitouch Plus system (Tactile Medical, Minneapolis, MN, USA) is an APCD clinically proven to stimulate the lymphatic system and is cleared for market in the USA (K170216, HCPCS code E0652). The device helps direct and move excess fluid from an impaired lymphatic region to healthy regions, where fluid can be absorbed and processed naturally by the body.

FT garment chambers inflate sequentially with each chamber inflating before the adjacent distal chamber deflates. This creates a dynamic wave that directs fluid into the lymphatic capillaries while maintaining distal pressure to prevent distal backflow.

The Flexitouch Plus system consists of two primary components, the controller unit and garments. The controller unit is a programmable pneumatic compressor with four connector outlets. Each connector has eight outflow ports that garment hoses plug into. Air passes through the hoses, delivering treatment through the sequential inflation and deflation of up to 14 air chambers covering the head, neck, and chest. The air chambered garments are made of soft, pliable fabric. They are designed to fit the contours of the body by wrapping around the affected area(s) and attaching with hook and loop fasteners.

3.2.2.2 FT for treatment of HNC associated LEF

Use of APCDs to treat head and neck LEF began in 2017.[41] Three preliminary studies and 1 pilot randomized controlled trial (RCT) have been published that address the use of the FT in head and neck LEF.[34,41,42]

The initial study, (n=44), demonstrated potential efficacy and feasibility in a single observed session of 32-45 minutes. Reduction in swelling ascertained by composite surface tape measurements (p=<0.001) was noted, 63% reporting feeling better after treatment, and 93% stated they would likely use the device at home if available.[41] No adverse events were noted. A second study, (N=10) examined response to both a single observed treatment and once (n=5) or twice (n=5) daily 30-minute sessions at home for two weeks.[42] Near-infrared fluorescence lymphatic imaging (NIRFLI) conducted immediately after each observed treatment revealed improved lymphatic uptake and drainage as compared to pre-treatment in all patients, indicative of effective treatment. Using a 20% change as indication of reduction of dermal backflow, NIRFLI conducted after two weeks of home treatment showed disappearance or reduction of backflow in 75% of patients whose initial images revealed backflow. Composite tape measurements of the head and neck were made prior to each NIRFLI measurement. Slight reductions in composite scores,

according to the authors, “tracked with reductions in backflow”. Improvement occurred in patients who had once or twice daily treatment, suggesting that once a day treatment is possibly adequate. A subsequent retrospective study, (n=205), addressed patients using the device at home for a minimum of 30 minutes per day as part of Phase 2 self-care. Average use of the device was about 4 weeks.[34] *Adherence to and satisfaction with the therapy were striking as 71% of patients reported daily use and 87% were satisfied*. This study provided the first firm indication of potential symptom relief when using the device. Responses to a standard 5 item survey administered by Tactile Medical to all patients using a FT, established that 90% reported feeling generally better after using the device and all symptom and function items improved (p=<0.00001).

A pilot RCT (N=49), was conducted at Vanderbilt University School of Nursing and Southern Illinois University with Dr. Sheila Ridner as PI, and Drs. Barbara Murphy and Sandra Ettema as Co-I’s.[43] Eligible patients were cancer-free after completed HNC therapy and had persistent LEF after Phase 1 CDT. Patients who were unable to access CDT were considered eligible for the study. Patients were randomized to wait-list LEF self-management (usual care) or LEF self-management plus the use of the APCD twice per day. Safety (CTCAE V4.0) and feasibility were primary endpoints; secondary endpoints included efficacy measured by objective examination and patient reported outcomes (PRO’s) (symptoms, QOL, function), adherence barriers and satisfaction. Anatomic measures included: a clinician-report measure of external lymphedema, inspection of the UADT for evaluation of the soft tissues and spaces in the pharynx and larynx, a cervical range of motion device, measurement of interincisal distance, and blood specimens. Assessments were conducted at baseline and weeks 4 and 8. Forty-nine patients were enrolled (wait-list n=25; intervention n=24). Forty-three completed the study. No device related SAEs were reported. Most used the APCD once per day, instead of the prescribed twice per day, citing time related factors as barriers to use. APCD use was associated with significant improvement in perceived ability to control lymphedema (p=.003) and reduction in visible external swelling (front view p<.001, right view p=.004, left p=.005) as evidenced by scored digital photography. Use of the APCD was associated with reduced soft tissue symptoms (e.g. heaviness, tightness, p=0.0008), and neurological symptoms (tingling, pins and needles, p=0.047) as captured by the LSIDS-H&N v.2 and improved swallowing solids and improved mucous control as captured using the Vanderbilt Head and Neck Symptom Survey. All wait-list controls opted to

use the device and, without prompting, patients stated they perceived the device to be more effective than the Phase 1 CDT.

3.2.2.3 Strengths of Current APCD Research

Physiologic measurement of lymphatic flow provides documentation of the mechanism of action and effectiveness. [34,41-43] Reduction of external swelling was noted in two of the studies using composite tape measurements and in one study documented reduction of dermal backflow and external swelling occurred simultaneously.[34,41,42] There is support that patients are satisfied with the device, will use it at home, and perceive treatment with the device improves symptom and function.[34,43] No Serious Adverse Events have been reported. Data supports a "dose" of daily one-time use of the device as effective.[43]

3.2.2.4 Weaknesses of Current APCD Research

Research regarding APCD use in the treatment LEF in this population is limited (N=4). The total number of patients studied is 308, and data from 205 (60%) of those came from a retrospective chart review.[34] No RCTs have compared APCDs to usual care, thus it is unknown whether or not this home-self-care method is a viable option for initial therapy of HN LEF. Outcome measures varied across studies making it difficult to compare results.

3.2.3 Summary of Usual Care and APCD

There are few studies addressing Usual Care or APCD therapy in the HNC population. Treatment algorithms for HNC associated lymphedema are based on clinical experience and data from treatment of other anatomical sites of lymphedema. Additional research regarding potential first-line therapies for this patient population is indicated.

4.0 Study Objectives

Our *long-term goal* is to improve outcomes for individuals suffering from LEF. The *overall objective* for this study is to conduct a randomized clinical trial comparing the effectiveness of APCD and Usual Care for the management of LEF.

5.0 Study Design

This study is an open label, multi-site two-group stratified, prospective, randomized clinical trial that will compare Usual Care which entails CDT administered by a lymphedema therapist to decongestive therapy using an APCD. All patients will be consented and then screened to confirm the presence of either internal or external LEF **and** at least one of the core lymphedema associated symptoms identified in our preliminary research.[43] Patients must meet all eligibility criteria to be considered for study. Once eligibility is confirmed, patients will be randomized. Patients randomized to Usual Care will be referred to a local lymphedema therapist per institution standard practice.

If patients are randomized to APCD therapy, the site will arrange an appointment for the patient with a Tactile Representative to initiate therapy. Patients in both arms will undergo

all baseline measures within 7 days prior to the first therapy appointment (exception: CT scan and internal exam may be done up to 28 days prior to initiation of therapy). Measures will be repeated at 2, 4, and 6 months. Study staff will contact patients every 2 weeks to document ongoing lymphedema therapy related activities, barriers to care, and adverse events. After the subject has completed their 6-month visit, they will be exited from the study. Subjects who received Usual Care will be offered a referral to receive an APCD through normal commercial means. Subjects who received an APCD will return their controller and will be offered a referral to receive an APCD through normal commercial means.

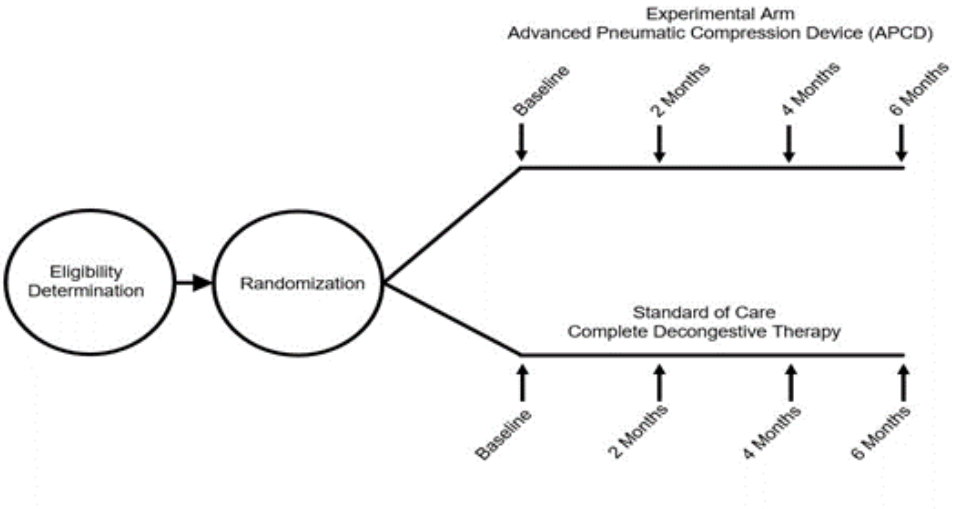


Figure 2. Study Design

5.1 Primary Aims

1) To compare the short-term and long-term effectiveness of self-administered APCD therapy versus Usual Care in HNC survivors with treatment naive LEF on anatomical measures of internal and external LEF. Baseline measures will be obtained at the start of therapy. Short-term effectiveness will be evaluated at 2 months, and long-term effectiveness will be evaluated at 4 and 6 months. Hypothesis: the APCD therapy will be associated with greater short-term and long-term reduction in anatomical measures of LEF.
2) To compare the short-term and long-term effectiveness of self-administered APCD therapy versus Usual Care in HNC survivors with treatment naive LEF on patient reported biopsychosocial outcome measures impacted by LEF. Outcome measures will include: 1) symptom burden, 2) symptom burden and functional impairment, 3) QOL, 4) work and activity, 5) perceived self-management capacity, 6) body image, and 7) diet modifications. Baseline measures will be obtained at the start of therapy. Short-term effectiveness will be evaluated at 2 months and long-term effectiveness will be evaluated at 4 and 6 months. Hypothesis: the APCD therapy will be associated with greater short-term and long-term improvement in patient reported outcomes.

5.2 Primary Endpoints

To compare the short and long-term effectiveness of self-administered APCD therapy to Usual Care in HNC survivors with treatment naïve LEF.

5.2.1 Anatomical Measures

1. Internal lymphedema
   - Assessment of UADT via endoscopy with direct or indirect visualization (Modified Patterson Scale)
   - CT Imaging (CT-LEFAT)
2. External lymphedema
   - Assessment using the HN-LEFG criteria
   - Digital Photographs (30 section grid)

5.2.2 Patient Reported Biopsychosocial Measures

1. Symptom Burden: LSIDS-H&N v2.0
2. Physical Function: VHNSS plus GSS
3. QOL: 5-item Linear Analog Self-Assessment
4. Work and Activity: WPAIQ
5. Perceived self-management compacity: PMCSMS
6. Body image: BIQLI
7. Diet modifications: ASA24

5.3 Outcome Measures

Endpoints will be based on outcome measures as described in Tables 1 and 2.

Table 1. Anatomical Outcome Measures

Endpoint	Outcome Measure
Internal Lymphedema	• Compare Modified Patterson Scale measurements between APCD and Usual Care subjects at baseline, 2, 4, and 6 months • Compare CT-LEFAT Imaging measurements between APCD and Usual Care subjects at baseline, 2, and 6 months
External Lymphedema	• Compare HN-LEFG measurements between APCD and Usual Care subjects at baseline, 2, 4, and 6 months • Compare Digital Photograph measurements (30 section grid) between APCD and Usual Care subjects at baseline, 2, 4, and 6 months

Table 2. Patient Reported Biopsychosocial Outcome Measures

Endpoint	Outcome Measure
Symptom Burden	• Compare LSIDS-H&N scores between APCD and Usual Care subjects at baseline, 2, 4, and 6 months
Symptom Burden and Functional Impairment	• Compare VHNSS plus GSS scores between APCD and Usual Care subjects at baseline, 2, 4, and 6 months
QOL	• Compare QOL scores between APCD and Usual Care subjects at baseline, 2, 4, and 6 months
Work and Activity	• Compare WPAIQ scores between APCD and Usual Care subjects at baseline, 2, 4, and 6 months
Perceived self-management compacity	• Compare PMCSMS scores between APCD and Usual Care subjects at baseline, 2, 4, and 6 months
Body image	• Compare BIQLI scores between APCD and Usual Care subjects at baseline, 2, 4, and 6 months
Diet modifications	• Compare ASA24 data between APCD and Usual Care subjects at baseline, 2, 4, and 6 months

5.4 Subject Selection

The target population includes HNC survivors with treatment naïve LEF who meet the criteria listed below and have provided informed consent.

5.4.1 Inclusion Criteria

1. Age ≥ 18 years
2. Pathologically confirmed cancer of the head and neck (larynx, pharynx, oral cavity, paranasal sinuses, major salivary glands, and HNC of unknown primary)
3. Completed curative intent cancer therapy with no evidence of active cancer at time of study enrollment
4. A diagnosis of either internal or external head and neck lymphedema
5. At least one core lymphedema associated symptom of ≥ 4 out of 10 at the time of study screening
6. Must be able and willing to participate in all aspects of the study and provide informed consent prior to study participation
7. Must be able to speak and understand English

5.4.2 Exclusion Criteria

1. Previous APCD or Usual Care treatment for HNC LEF
2. Acute facial infection (e.g., facial or parotid gland abscess)
3. Known carotid sinus hypersensitivity syndrome
4. Symptomatic carotid artery disease, as manifested by a recent (within 30 days of informed consent) transient ischemic attack, ischemic stroke, or amaurosis fugax (monocular visual ischemic symptoms or blindness)
5. Internal jugular venous thrombosis (within 3 months of informed consent)
6. Patient is pregnant or trying to become pregnant

5.5 Point of Enrollment and Randomization

Randomization codes will be generated by the study statistician in a permuted block design. The block size will be balanced within each block and will maintain a 1:1 ratio between treatment groups. Randomization within each site will proceed in 10-unit blocks with a randomly generated sequence defined a priori.

Subjects will be considered enrolled in the study once the informed consent form (ICF) is signed, all inclusion/exclusion criteria are met, and the Randomization electronic case report form (eCRF) is completed in iMedNet, the study database. Once the Randomization eCRF is saved, the randomization assignment will populate on the eCRF.

Any patient who is approached for participation in the study (including those that decline participation) should be recorded in the iMedNet database.

Consented subjects that do not meet inclusion/exclusion criteria will be considered screen failures and all collected data will be entered into the study database. If consented subjects are found to not meet eligibility criteria, all data up to that point should be entered into the study database and a Study Exit form shall be completed.

If a subject does not meet all the eligibility criteria and is randomized in error, or incorrectly started on treatment, the Investigator should inform Tactile Medical immediately.

6.0 Study Visits

Electronic case report forms (eCRFs) and database queries will be used for data collection and query resolution. 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).

6.1 Screening Visit

If a patient appears eligible to participate based on medical history, he or she will be contacted or approached to assess interest. If the patient is interested in learning more, an ICF will be provided to them (in person, electronically, or via mail) and the subject will be given adequate time to review and ask questions. If the subject

decides to participate and provides documented informed consent, the following screening assessments will be performed and may occur on different days.

- Administer the lymphedema core symptom survey
  - *Note – subject must have a score of ≥4 on at least one question to be eligible for the study*
- Collection of demographic data
- Review of medical history to ensure the subject is an appropriate candidate for APCD or Usual Care treatment
- Height and weight
- Administer a urine pregnancy test for all female subjects of child-bearing potential
- Assess for external or internal LEF – subjects must have positive exam findings for external ***or*** internal lymphedema
  - External assessment
    - Examination of the face, neck, and shoulders using the HN-LEFG Criteria– *if subject has at least mild external lymphedema involving at least one anatomical site, they are considered positive for lymphedema and it is not necessary to perform the internal assessment at the screening visit*
  - Internal assessment
    - Examination of the UADT via endoscopy using the Modified Patterson Scale – *if subject has at least mild internal lymphedema involving at least one anatomical site or space, they are considered positive for lymphedema*
    - CT of the neck – *if subject is not positive for lymphedema via external or internal exam via endoscopy, a standard of care CT that is within the previous 28 days may be reviewed by the Study Investigators for evidence of internal lymphedema. If CT is positive for lymphedema, they may be included in the trial.*
- Collect head and neck measurements
- Confirmation of eligibility & randomization

If the subject continues to meet criteria, the site investigator will confirm the subject is clinically appropriate for APCD or Usual Care treatment and they will be randomized via entry of the randomization eCRF in iMedNet. If the subject is assigned to Usual Care, the site investigator will sign an order for referral to a lymphedema therapist. If the subject is assigned to APCD therapy, the site investigator will initiate an order for a FT through a Tactile Medical Product Specialist.

Study personnel will monitor the scheduling process and arrange for the Baseline Visit procedures to occur within *7 days prior* to the initiation of Usual Care or APCD treatment (exception for CT and UADT evaluation, which may occur up to 28 days prior).

6.2 Baseline Visit

The following baseline assessments will be performed and may occur on different days but within either 7 days prior to therapy initiation **or** 6 weeks (±5 days) from the date of the Screening Visit (whichever occurs first) unless otherwise noted:

- Examination of the head, neck, and shoulders using the HN-LEFG Criteria
- Digital photographs
- Patient reported biopsychosocial measures.
- Examination of the UADT via endoscopy using the Modified Patterson Scale
  - *Note – if this screening examination was performed within 28 days of therapy initiation, it does not need to be repeated at baseline*
- CT of the neck
  - *Note – scans performed as part of standard surveillance that are within the previous 28 days of therapy initiation may be used in lieu of obtaining a separate scan*

If the visit is conducted at 6 weeks in place of therapy initiation, this date will be considered "day 0" for the purposes of calculating the follow-up schedule.

6.3 Therapy Initiation

6.3.1 Usual Care

Patients randomized to Usual Care will be referred for lymphedema therapy per standard procedures at their site and the Site Principal Investigator (PI) or Sub-Investigator (Sub-I) will sign the order for the referral. Patients will be encouraged not to share with the lymphedema therapist that they are participating in a research study.

It is anticipated that there will be variability in Usual Care. This includes variability in the accessibility to lymphedema care, assessment tools and techniques, treatment recommendations, implementation, patient adherence, enactment, and follow-up.

No attempt will be made to influence or modify the treatment plan generated by the lymphedema therapist unless:

- there is a concern about the patient's health or safety or;
- the lymphedema therapist refers a Usual Care subject for a Flexitouch. If a Flexitouch referral is made, the prescription should not be signed/processed until the subject has completed the study.

6.3.2 APCD

Patients randomized to the APCD will be referred to a Tactile Medical Product Specialist and the Site PI or Sub-I will sign the order for the APCD.

A Tactile Medical Product Specialist will schedule a visit with the subject to fit the device and provide training. At this visit, measurements of the subject's head, neck, and chest may be collected to confirm garment size selection, including ensuring fit does not interfere for those patients with

tracheostomies. Should the Product Specialist not be able find a garment that will fit the patient, the patient will continue study participation with a referral to Usual Care.

Patients will be trained on donning and doffing the head and neck garments and operating the controller and will demonstrate proficiency at doing this independently. The APCD prescription will be a daily H1 treatment at normal pressure. If the subject is having difficulty tolerating the device pressure, they may work with Tactile Medical to modify settings as needed. These modifications will be documented.

6.4 2, 4, & 6 Week Contacts

Subjects will be contacted at 2, 4, and 6 weeks post therapy initiation (±5 days) and the following assessments will be performed in person, via telephone, or video conference:

- Adherence assessment
- Adverse event assessment

6.5 2 Month Visit

The following assessments will be performed 2 months (±7 days) from therapy initiation unless otherwise noted:

- Examination of the head, neck, and shoulders using the HN-LEFG Criteria
- Examination of the UADT via endoscopy using the Modified Patterson Scale (±14 days)
- Digital photographs
- CT of the neck (±14 days)
- Patient reported biopsychosocial measures
- Adherence assessment
- Adverse event assessment

6.6 10, 12, & 14 Week Contacts

Subjects will be contacted at 10, 12, and 14 weeks post therapy initiation (±5 days) and the following assessments will be performed in person, via telephone, or video conference:

- Adherence assessment
- Adverse event assessment

6.7 4 Month Visit

The following assessments will be performed 4 months (±7 days) from therapy initiation unless otherwise noted:

- Examination of the head, neck, and shoulders using the HN-LEFG Criteria
- Examination of the UADT via endoscopy using the Modified Patterson Scale (±14 days)
- Digital photographs
- Patient reported biopsychosocial measures

- Adherence assessment
- Adverse event assessment

6.8 18, 20, & 22 Week Contacts

Subjects will be contacted at 18, 20, and 22 weeks post therapy initiation (±5 days) and the following assessments will be performed in person, via telephone, or video conference:

- Adherence assessment
- Adverse event assessment

6.9 6 Month Visit

The following assessments will be performed 6 months (±7 days) from therapy initiation unless otherwise noted:

- Examination of the head, neck, and shoulders using the HN-LEFG Criteria
- Examination of the UADT via endoscopy using the Modified Patterson Scale (±14 days)
- Digital photographs
- CT of the neck (±14 days)
- Patient reported biopsychosocial measures
- Adherence assessment
- Adverse event assessment
- Study exit interview *(optional)*

After the subject has completed their 6-month visit, they will be exited from the study. Subjects who received Usual Care will be offered a referral to receive an APCD through normal commercial means. Subjects who received an APCD will return their controller and will be offered a referral to receive an APCD through normal commercial means.

7.0 Study Schedule of Activities

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

Table 3. Schedule of Activities

Assessments	**Screening**	**Baseline**	**Therapy Initiation**	**2, 4 & 6 Week Contact**	**2 Month Visit**	**10, 12, & 14 Week Contact**	**4 Month Visit**	**18, 20 & 22 Week Contact**	**6 Month Visit**
	NA	*-7 to 0 Days*[◊◊]	*Day 0*	*±5 Days*	*±7 Days*	*±5 Days*	*±7 Days*	*±5 Days*	*±7 Days*
Informed Consent	X								
Lymphedema Core Symptom Survey	X								
Demographics & Medical History	X								
Height[*] & Weight	X								
Pregnancy Test	X								
Exam using HN-LEFG	X	X			X		X		X
Exam of UADT via endoscopy using Modified Patterson Scale	X[†]	X[‡]			X[§]		X		X[§]
Randomization	X								
Digital Photographs		X			X		X		X
CT of the Neck		X[‡]			X[§]				X[§]
LSIDS – H&N		X			X		X		X
VHNSS plus GSS		X			X		X		X
5-item Linear Analog Self-Assessment		X			X		X		X
WPAIQ		X			X		X		X
PMCSMS		X			X		X		X
BIQLI		X			X		X		X
ASA24		X			X		X		X
Usual Care/APCD Initiation			X						
Adherence Assessment				X	X	X	X	X	X
Adverse Event Assessment				X	X	X	X	X	X
Study Exit Interview *(optional)*									X

*Height collected at Screening visit only; historical records may be used for height

[†]If exam using HN-LEFG shows at least mild external lymphedema involving at least one anatomical site, they are considered positive for lymphedema, and it is not necessary to perform the Exam of UADT via endoscopy

[‡]Visit window is within 28 days prior to therapy initiation

[§]Visit window is ±14 days

[◊◊]*Or 6 weeks (±5 days) post Screening Date whichever comes first. If the visit is conducted at 6 weeks in place of therapy initiation, this date will be considered "day 0" for the purposes of calculating the follow-up schedule.*

8.0 Study Assessments

8.1 Informed Consent

A sponsor and IRB-approved ICF must be signed by each subject before study participation.

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 medical record.

8.2 Lymphedema Core Symptom Survey

The Lymphedema Core Symptom Survey is a brief screening questionnaire which includes core symptoms associated with lymphedema that are deemed clinically meaningful. Subjects must rank at least one core symptom ≥4 to be eligible for this study.

8.3 Demographics & Medical History

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

Significant medical history and treatment data will be obtained through chart review and patient interview.

8.4 Height and Weight

Height and weight will be collected at the screening visit. If the clinic does not have access to a stadiometer to measure height, a historical value from the subject's medical record may be used.

8.5 Pregnancy Test

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

8.6 Examination of the head, neck, and shoulders using the HN-LEFG Criteria

Trained study staff will perform an examination of face, neck, and shoulders and grading will be performed based on the HN-LEFG criteria.[47] This tool assesses the type and grade of soft tissue abnormalities at different anatomical sites. The anatomical sites include:

- Left/right peri-orbital region
- Left/right cheek
- Submental
- Left/right neck
- Left/right supraclavicular fossa
- Additional sites noted, as specified by the examiner

Each anatomical site is assessed and if soft tissue abnormality is noted, it is assigned a type and grade using the following criteria:

Type	Description & Grades
A	No visible tissue swelling; Palpable thickening and/or tightness of dermis
B	Visible soft tissue swelling; involved tissues are soft to touch; tissue swelling is reducible and fluctuates in severity **Grade:** • **Mild** – visible soft tissue swelling on close inspection • **Moderate** – easily visible swelling that significantly alters normal tissue contours • **Severe** – extreme or massive swelling
C	Visible soft tissue swelling; involved tissues are firm to touch; tissue swelling is non-reducible and persistent **Grade:** • **Mild** – visible soft tissue swelling on close inspection • **Moderate** – easily visible swelling that significantly alters normal tissue contours • **Severe** – extreme or massive swelling
D	Firm skin with increased density and decreased compliance in the absence of swelling **Grade:** • **Mild** – palpable firmness of soft tissues • **Moderate** – soft tissues are extremely hard and have a woody texture • **Severe** – fibrosis associated with contracture

8.7 Examination of the UADT via endoscopy using the Modified Patterson Scale

The original Patterson Scale was developed to assess edema/swelling in the pharynx and larynx for patients treated with radiation. The scale included 11 structures and 2 spaces and had good intrarater reliability (weighted kappa, 0.84) and moderate interrater reliability (weighted kappa, 0.54).[44] Four grades are used to evaluate the internal edema level, in the pharynx and larynx, from normal (no edema) to severe edema.[13] Previously reported findings have been reported showing internal lymphedema captured by the Patterson Scale correlated with patient reported swallowing difficulty as well as objective findings of swallowing dysfunction on modified barium swallow.[45]

A Modified Patterson Scale will be used in this trial. This modified scale now includes 16 structures and 2 spaces. An examination of the UADT via endoscopy will performed by a trained clinician and the following anatomical sites will be assessed for lymphedema/edema using this Modified Patterson Scale:

- Lip
- Oral tongue (Anterior 2/3)
- Uvula
- Buccal Mucosa
- Floor of the Mouth
- Soft Palate
- Base of Tongue
- Posterior Pharyngeal Wall
- Epiglottis
- Pharyngoepiglottic Folds
- Aryepiglottic Folds
- Interaryenoid Space
- Arytenoids
- False Vocal Folds
- True Vocal Folds
- Anterior Commissure
- Valleculae Space
- Pyriform Sinus Space

If lymphedema/edema is present, severity will be graded as mild, moderate, or severe.

8.8 Digital Photographs

Using well-established procedures that have been successful in both single and multi-site studies, research team members will photograph patient's right and left profiles and front from the shoulders to top of head.[43] Patients will be seated against a plain background and have clear visibility to their head, neck, and shoulders (see Appendix A for additional detail).

Digital photos will be uploaded to iMedNet and centrally scored by a blinded assessor. Each photo will be divided into 30 quadrants and the presence or absence of swelling will be assessed.

8.9 CT of the Neck

CT of the neck, with and without contrast, will be collected at Baseline and the 2 and 6-month follow-up visits. A baseline standard of care scan may be used if it is within 28 days prior to the initiation of therapy. Standard of care scans may be used for the 2 and 6-month follow-up visits if they are within 14 days of the target visit date. All scans will be submitted to the CT Core Lab for analysis per the instructions found in the CRF Completion Guidelines.

CT images are used as part of standard of care to evaluate response to oral cavity and oropharyngeal cancer treatment in the study sites. The scans collected for this trial will be reviewed and scored centrally by a blinded radiologist, using the CT-LEFAT[46]. This CT scoring system was developed to score LEF status post HNC. This tool grades fat stranding at the level of the superior thyroid cartilage in the following five locations:

- Midline anterior subcutaneous fat, anterior to platysma
- Anterior cervical space fat, anterior to SCM – right
- Anterior cervical space fat, anterior to SCM – left
- Posterior cervical space fat, anterior to SCM – right
- Posterior cervical space fat, anterior to SCM – left

In addition, this tool measures midline prevertebral soft tissue (PVST) thickness (mm) at the mid C3 level, epiglottis thickness (mm), and grades submental fat stranding.

8.10 Patient reported biopsychosocial measures

Subjects will complete the biopsychosocial measures at their baseline, 2, 4, and 6-month follow-up visits. When the subject's visit-window opens, they will receive an email with a link to the following questionnaires that will allow them to enter their responses directly into the iMedNet electronic database via the electronic Patient Reported Outcomes (ePRO) function:

- LSIDS – H&N v2.0
- VHNSS plus GSS
- 5-item Linear Analog Self-Assessment
- WPAIQ
- PMCSMS
- BIQLI

Subjects may also complete these questionnaires at the clinic using the ePRO function. If requested by the subject, study staff may read the questionnaires aloud and document the subject's response and/or clarify the meaning of questions. Input from study staff, friends, or family on how to answer questions is strongly discouraged.

Study personnel are responsible for reviewing the questionnaires to ensure they are completed within the study visit window and complete.

Subjects will also complete the ASA24 by logging into a secure web-based system with their own user account and entering their food and liquid consumption for the previous 24 hours. The first time this is administered at the Baseline Visit, study staff should facilitate entry. The subject may request assistance in completed this at subsequent visits.

8.10.1 LSIDS – H&N

This 31 item tool captures LEF-related symptom burden in HNC patients. It includes 7 symptom clusters. Internal consistency values of scores generated from the HNC symptom clusters range from 0.83 to 0.95 confirming the cluster compositions. The LSIDS-H&N v2.0 (manuscript in-press) takes 5-7 minutes to complete.[43,48]

8.10.2 VHNSS plus GSS

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.[43,49] Items are scored on a numeric scale rating the severity of the symptom from 0 (none) to 10 (severe). VHNSS v2.0 plus GSS includes 12 additional items directed at the systemic effects of therapy. Studies have reported good internal consistency for the total scale (alpha=0.94) and five subscales (i.e., swallow, nutrition, mucous/dry mouth, pain, voice) (alphas=0.77-0.93), and adequate convergent and divergent validity. The VHNSS v2.0 plus GSS takes approximately 10 minutes to complete.

8.10.3 5-item Linear Analog Self-Assessment

The scale assesses physical, emotional, spiritual, intellectual, and over-all well-being, on a 0-10 scale. It has been used successfully in cancer populations.[50] It takes approximately less than 1 minute to complete.

8.10.4 WPAIQ

This commonly used, valid and reliable, 9-item questionnaire evaluates lost hours of productivity seven days prior to administration and can be targeted to evaluate lost productivity due a specific medical condition (e.g., lymphedema). When compared to the SF-36, it has been found to correlate with general health scores (r=0.52), and physical role (r=0.52).[51,52] The WPAIQ takes less than 5 minutes to complete.

8.10.5 PMCSMS

The PMCSMS is a generic (template) instrument that can be specific to any medical condition. The scale was initially used in individuals with diabetes (N=398) and Cronbach's alpha was .84 and has since been validated against a shorter version of the instrument that did not perform as well.[53,54] The PMCSMS takes less than 5 minutes to complete.

8.10.6 BIQLI

This validated, self-report measure captures body image (19 items, Cronbach's α =.95).[55] The BIQLI takes 10 minutes to complete.

8.10.7 ASA24

Detailed information about dietary intake and nutritional values can be obtained using this NCI tool. 56 It can be completed using smart phones, tablets, laptops, and desktops. Patients will enter their information and the program will calculate nutrition results. LEF has been associated with dysphagia and dietary adaptations. This will allow us to determine whether improvement in swallow function can result in improvement in dietary intake. The ASA24 takes approximately 30 minutes to complete.

8.11 Adherence assessment.

Study staff will assess subject adherence and barriers to their lymphedema treatment by asking the questions below. If the subject does report issues or barriers to APCD use or Usual Care, study personnel should not attempt to provide

additional support or guidance on how to address these issues. Instead, the subject should be encouraged to contact their Tactile Medical Product Specialist (APCD Group) or Lymphedema Therapist (Usual Care Group) or.

If study personnel have questions or concerns about a subject's ongoing lymphedema care, they will be directed to contact their Site PI or a Study PI. Study personnel should avoid influencing physician or patient behavior.

APCD Group

1) In the past week, how many days did you use your Flexitouch?
2) In the past week, did you experience any barriers that prevented you from using your Flexitouch? *If yes, ask subject to specify barriers impacting their use of the Flexitouch (select all that apply).*
   - Did not know how to perform
   - Does not feel treatment works
   - Does not have the motivation to perform
   - Does not have the time
   - Treatment is uncomfortable
3) Since your last visit, did you have any other treatment for your Lymphedema? *If yes, ask subject to specify type of treatment and number of days within the past week the treatment has been used / administered (select all that apply).*
   - MLD
     a) Self-only massage
     b) Healthcare professional – If so, how many tx since last visit?
   - Compression
   - Myofascial release
   - Other, specify (attach field notes, etc.)

Usual Care Group

1) Have you been instructed to perform self-administered massage or manual lymph drainage to manage your lymphedema? *If yes, continue below.*
   a) How many days did you perform self-administered massage or manual lymph drainage in the past week?
   b) In the past week, did you experience any barriers that prevented you from performing self-administered massage? *If yes, ask subject to specify and select all that apply.*
      - Did not know how to perform
      - Does not feel treatment works
      - Does not have the motivation to perform
      - Does not have the time
      - Treatment is uncomfortable
2) Have you been instructed to wear a compression garment to manage your lymphedema? *If yes, continue below.*
   a) How many days did you wear a compression garment the past week?

b) In the past week, did you experience any barriers that prevented you from wearing your compression garment? *If yes, ask subject to specify and select all that apply.*
- Did not know how to perform
- Does not feel treatment works
- Does not have the motivation to perform
- Does not have the time
- Treatment is uncomfortable

3) Have you been instructed to wear bandaging to manage your lymphedema? *If yes, continue below.*
   a) How many days did you wear bandaging in the past week?
   b) In the past week, did you experience any barriers that prevented you from wearing bandages? *If yes, ask subject to specify and select all that apply.*
   - Did not know how to perform
   - Does not feel treatment works
   - Does not have the motivation to perform
   - Does not have the time
   - Treatment is uncomfortable

4) Have you been instructed to use skin care techniques to manage your lymphedema? *If yes, continue below.*
   a) How many days did you use skin care techniques in the past week?
   b) In the past week, did you experience any barriers that prevented you from using skin care techniques? *If yes, ask subject to specify and select all that apply.*
   - Did not know how to perform
   - Does not feel treatment works
   - Does not have the motivation to perform
   - Does not have the time
   - Treatment is uncomfortable

5) Have you been instructed to perform exercises to manage your lymphedema? *If yes, continue below.*
      a) How many days did you perform these exercises in the past week?
      b) In the past week, did you experience any barriers that prevented you from performing these exercises? *If yes, ask subject to specify and select all that apply.*
   - Did not know how to perform
   - Does not feel treatment works
   - Does not have the motivation to perform
   - Does not have the time
   - Treatment is uncomfortable

6) Have you been instructed to perform breathing exercises to manage your lymphedema? *If yes, continue below.*
   a) How many days did you perform these breathing exercises in the past week?

b) In the past week, did you experience any barriers that prevented you from performing these breathing exercises? *If yes, ask subject to specify and select all that apply.*
   - Did not know how to perform
   - Does not feel treatment works
   - Does not have the motivation to perform
   - Does not have the time
   - Treatment is uncomfortable

7) Have you been instructed to perform any other treatments/activities to manage your lymphedema? *If yes, continue below.*
   a) Please describe this treatment/activity.
   b) How many days did you perform this treatment/activity in the past week?
   c) In the past week, did you experience any barriers that prevented you from performing this treatment/activity? *If yes, ask subject to specify and select all that apply.*
      - Did not know how to perform
      - Does not feel treatment works
      - Does not have the motivation to perform
      - Does not have the time
      - Treatment is uncomfortable

Information collected will not be shared with the treating physician unless such information is deemed important for patient care and safety.

In addition, the APCD records device usage, including number of sessions and minutes of therapy delivered.

Clinic records of Phase 1 CDT will be collected and reviewed, and the details of the treatment(s) will be captured in the study database.

8.12 Adverse event assessment

Adverse event assessment will occur after randomization and continue throughout the study. Reportable events, as defined below, will be recorded on an Adverse Event eCRF and classified and graded using Common Terminology Criteria for Adverse Events (CTCAE) v5.0. *This study will collect severe (Grade 3-5) adverse events that are possibly, probably, or definitely related to participation in the trial and the administration of the intervention (APCD or Usual Care).*

An adverse event is defined as 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 intervention (APCD or Usual Care).

An adverse event will be classified as serious if the outcome:

1) Results in death;
2) is life-threatening (places subject at immediate risk of death from the experience as it occurred);
3) hospitalization (initial or prolonged) if admission to hospital was warranted as a result of the adverse event);

4) results in disability or permanent damage (substantial disruption of one's ability to carry out normal life functions);
5) results in congenital anomaly or birth defect; or
6) required intervention to prevent permanent impairment or damage.

Investigators must report all serious adverse events to Tactile Medical within 10 working days of becoming aware of the event. Serious events will be reported in writing to the appropriate IRB in accordance with IRB policy.

8.13 Subject Exit Interview *(optional)*

Subjects will be invited (via the informed consent process) to participate in an optional exit interview. Participation in this interview is optional and subjects must provide additional consent to be contacted. If the subject declines participation in the exit interview they will not be excluded from the trial and will not be contacted.

Subjects agreeing to participate will be contacted by Vanderbilt University Medical Center (VUMC) staff and will be asked to share their lymphedema care experience. This interview will be done remotely (by telephone or video conference) and will last 10-15 minutes.

Participation in this interview is optional; if subject wishes to participate, they must provide consent for the release of their contact information to VUMC.

9.0 Subject Discontinuation or Withdrawal

Subjects may choose to discontinue the use of the APCD or Usual Care therapy. Discontinuation of the APCD or Usual Care therapy will not constitute a reason for the subject to be withdrawn from the study. The subject will be encouraged to continue in the study and complete all planned and future assessments. Should the subject choose to terminate their participation in the study, they will be treated according to the standard of care that applies at the point of withdrawal.

The Site PI may choose to withdraw a subject from the study if:

- It is deemed medically necessary
- Subject non-adherence with study procedures as defined by failure to participate in study related outcome measures
- Subject is no longer able to provide informed consent (i.e., subject voluntarily withdraws)
- Recurrence of HNC

10.0 Accountability

The FT will be provided at no cost to the site and subject. For subjects randomized to the APCD group, the FT system (controller & garments) will be provided to the subject by the Tactile Medical Product Specialist/Trainer at their Treatment Initiation Visit. When the subject completes the study, they will return the controller to the study site, where the study site will arrange for the return to Tactile Medical. The study subjects may keep their FT garments and are not to return them to the site.

11.0 Risk Analysis

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.

11.1 Anticipated Side Effects of Pneumatic Compression

Pneumatic compression is a minimal risk therapy with minimal known complications or side effects. The expected side effects that are experienced are often due to the natural history of the primary disease or failure to achieve adequate response to the treatment. Side effects may include a local skin reaction to the device materials, increased swelling at other sites, or pain and discomfort. The subject will be made aware of known complications and adverse events at time of consent and monitored closely throughout the study.

11.2 Anticipated Side Effects of Usual Care

Risks of Usual Care are not well understood. As with APCD, the expected side effects that are experienced are often due to the natural history of the primary disease or failure to achieve an adequate response to CDT.

Standard Compression Garments: It is possible, though unlikely, that some patients could experience skin irritation due to an allergic response to garment material, increased swelling at other sites, or pain and discomfort. It is also likely that an ill-fitting garment could lead to itching, redness, pain, increased swelling, or numbness. Other expected likely risks are often a failure to respond to the standard compression intervention and not related to the compression itself.

11.3 Reportable Events

Reportable events are defined as any unanticipated or severe complications that are possibly or probably related to Usual Care or APCD. Adverse events will be graded using CTCAE v5.0. and a severe event will be defined as Grades 3-5.

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 from the protocol will be documented on a Protocol Deviation eCRF and reported to the IRB as required by IRB policies and / or the terms of the IRB approval.

14.0 Quality Assurance Procedures

This study will be conducted in accordance with GCPs, 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 ICF will be reviewed and approved, according to 21 CFR §50 and §56, by each center's IRB.

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

A Site Initiation Visit will be conducted 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 Site PI once the site is approved to enroll subjects.

14.3 Fidelity Monitoring

Annual visits, from the time of site initiation, conducted in person or via videoconference, will be made by Dr. Ridner or a trained designated alternate to observe all measurements, data collection, and site-specific intervention, and communication methods/techniques with the device manufacturer. This will include direct observation of subjects during all data collection procedures except CT and UADT scoping procedures. Just-in-time training for any deficits noted during the visit will be provided and documented.

14.4 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;
- 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

The Site PI and Institution agree to permit all trial related monitoring, audits, IRB review, and regulatory inspection(s); providing direct access to source data and documents, as appropriate. Monitoring and source verification will be performed by Tactile Medical personnel and/or designee. Source verification includes

reviewing subject source documentation and eCRFs for accuracy, completeness, and compliance with GCP.

14.5 Data Collection Procedures

Data will be collected using iMedNet, a CFR Title 21 Part 11 compliant electronic data capture (EDC) tool. Sites will be expected to enter data directly into iMedNet instead of using hard copy source documents. However, in the rare incidence when hard copy source documents are used, the site will upload a scanned image of the source document to the applicable eCRF and it will be 100% source document verified by the sponsor.

14.6 Data Safety Monitoring

The Site PI will be responsible for subject safety. Additionally, a periodic review of safety data may be completed by an independent monitoring committee (IMC), whose members will not be associated with the research project.

14.7 Reports and Records

Records to be maintained by the Site PI 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 (if applicable) for all investigators;
- Site personnel signature and documentation regarding the investigator's delegation of responsibility;
- Site visit log;
- Protocol related training records for all applicable study personnel;
- Device accountability log;
- Screening log; and
- Reports (shown below).

The Site PI 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	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 Report	Reviewing IRB	Annually, at a minimum
Final Clinical Study Report	Sponsor and Reviewing IRB	Within 3 months following the completion or termination of the Investigator's part

The following records must be maintained for each subject enrolled:

- Original, signed and dated ICF (electronic or hard copy), as well as documentation of the process of consent;
- Completed eCRFs, database queries, 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 site 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 site 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.

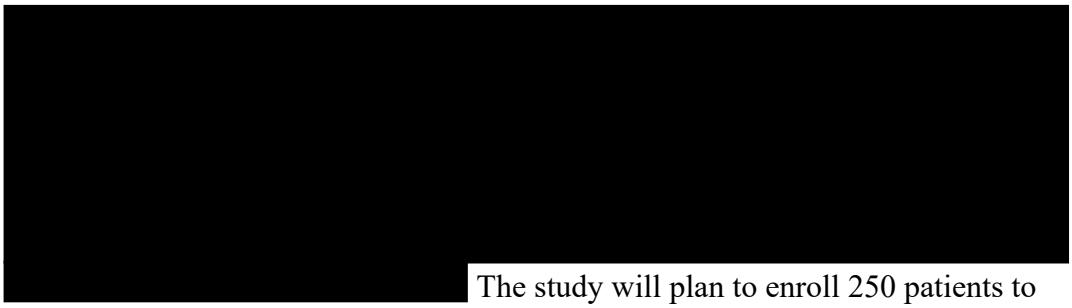
15.0 Change to Investigational Plan

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 and the Study PIs, and IRB approval will be obtained before any changes are implemented.

16.0 Statistical Methods

16.1 Sample Size Determination

Preliminary data from a previous study, which was administered in patients whose LEF was refractory to usual care, was used to perform the power calculations for this study. Because the previous study selected for patients who had already failed usual care, at least for a time, it was expected that the effect sizes in that population were somewhat attenuated compared to what we will see in this study's treatment naïve population. Thus, we expect that the power calculated here is slightly conservative.



The study will plan to enroll 250 patients to ensure sufficient power with a dropout rate of up to 20%. In the previous trial 12.2% of the patients withdrew from the study.

16.2 Randomization

This is a multicenter study with up to 10 sites. Each site will have a target enrollment of 50 patients. Randomization within each site will proceed in 10-unit blocks with a randomly generated sequence defined a priori. If a site is unable to meet its recruitment target, a block will be removed from that site and assigned to one of the remaining four sites or an additional site that may be added at a later date.

16.3 Statistical Analysis

This study has a classical design with no early looks at aggregate data. At the conclusion of the study, data will be exported, checked for errors, and appropriately cleaned. Graphical and numeric summaries of relevant patient demographics and baseline characteristics will be generated by site and in aggregate. Subscale scores will be calculated for each, or the responses designated as outcomes at each timepoint (baseline, 4 Month, 6 Month). The 4- and 6-Month measures will be analyzed separately with the 4 Month data being used to determine effectiveness of the intervention and the 6 Month data representing the durability of the effect. The data will be analyzed using a mixed effects generalized linear model with a random intercept for study site. Each model will be adjusted for relevant covariates including the baseline subscale score. Results will be deemed statistically significant if they attain a p-value<0.05 and will be reported as an effect size with its associated 95% confidence interval.

All analyses will be conducted as both complete case analysis. Whenever missing data exceeds 10% of the data, the analysis will be repeated under multiple

imputation with an assumption that the data is missing at random. In the case that these analyses disagree, both results will be reported.

17.0 Publication Plan

The sponsor and the investigators are committed to the publication and widespread dissemination of the results of the study. This study represents a joint effort between sponsors and investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or text shall be taken into consideration in the preparation of final scientific documents for publication or presentation.

All information concerning this study that has not been previously published is considered the confidential property solely of Tactile Medical. This information includes, but is not limited to, the protocol, workbooks, technical methodology, and resulting data. Investigators will maintain the intellectual property rights of assessment tools and methodologies developed prior to and outside of this protocol. All proposed publications and presentations by the sponsor and investigators or their personnel and associates resulting from or relating to the study must be submitted to Tactile Medical for review and written consent prior to submission for publication or presentation. To allow for the use of the information derived from this study and to ensure compliance with current USA Federal Regulations, the Investigator is obliged to provide Tactile Medical with complete test results and all data developed from this study. Regulatory audits and inspections of the information obtained during this study may be made available to others (including but not limited to government, institutional, corporate, regulatory, news media, or other organizations) at the sole discretion of Tactile Medical.

If any such proposed publication or presentation contains patentable subject matter, which in the sponsor's opinion warrants intellectual property protection, the sponsor may delay any publication or presentation for the purpose of pursing such protection. The first author will be the coordinating investigators, followed by the other investigators in order of patient recruitment (taking into account the number of analyzable follow-up patients and occurrence of protocol violations/deviations). The number of authors will be determined according to the rules of the addressed scientific journal. Sites may not publish or present their own single-center experience or multi-center results until the main study results have been published, or at least 1 year following study closure.

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19.0 Appendices

Appendix A: Standard Digital Photography Procedure

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Standard Digital Photography Procedure

1.0 PURPOSE

To ensure that the imaging for all photos taken for study assessments meet necessary quality requirements.

2.0 DEFINITIONS

Photo Background: Should be an even, neutral, non-reflecting, monochromatic surface. The preferred background colors are white, grey and blue. Having a fixed place in the clinic for photography will allow for standardization.

Subject Position: The subject will be asked to wear garments that expose their full head, neck and shoulders. If necessary, a gown can be provided. The subject should sit normally on a chair or stool and positioned at least one foot in front of the background. The seating should not have any recline and the subject should have both feet on the floor and their hands placed on their knees.

Frontal View: This includes the upper limit of the subject's head to just below their collar bone with the subject looking at the camera.

Lateral View: From the frontal view body positioning, with the subject's whole body rotated 90° and align the nasal tip and chin. Have the subject keep their head in its anatomical position with no lateral inclination, flexion, or extension.

3.0 PROCEDURE

3.1 Set-up:

- Use the same cameral, lens, settings, magnifications, illumination, and positions at each visit.
- The camera should be in the same position and distance at each visit (floor markings can be used to keep this uniform).
- A tripod is recommended to fix the camera in position
- Ensure proper background set-up prior to taking photos. Ensure the chair or stool is placed at least one foot from the background.
- Have the subject in a chair or stool and assume the proper position in the frontal view position to start.
- Preferably the same photographer should take the pictures at each visit after reviewing the photos taken at the previous visit.

3.2 Image Capturing:

- Ensure the subject is in the proper frontal view position and instruct the subject to look straight ahead and assume a neutral facial expression, holding their head in a natural head position and relaxed.
- Take the frontal view photo and review the photo against the previous visit's photos to ensure even placement of the head and neck.
- Have the subject move into the lateral view position on the right side and

again instruct the subject to look straight ahead and assume a neutral face expression, holding their head in a natural head position and relaxed.

- Take the right lateral view photo and review against the previous visits photos to ensure even placement of the head and neck.
- Repeat again on the left side lateral view.

3.3 Uploading Images:

- Save images for subject and visit and upload to iMedNet (refer to Case Report Form Completion Instructions for more detail on how to upload images).