

Protocol Title: Near-infrared fluorescence lymphatic imaging to assess improved lymphatic drainage in head and neck cancer survivors after a single- use and two weeks use of the Flexitouch Head and Neck System

Protocol Number and Version HSC-MS-16-0465; Version 1.10

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Study Coordinator: John R. Morrow

Sponsor: Tactile™ Medical

Population: A total of ten (10) subjects who complete both, over the age of 18, from the patient population at UT Physician's Otorhinolaryngology Outpatient Clinic who have undergone surgery and/or radiation therapy for treatment of cancer of the head and/or neck

Number of Sites: Single site: UT Physician's Otorhinolaryngology Outpatient Clinic

Study Duration: Three (3) months

Subject Duration: Twenty-four (24) hours over Two (2) weeks

1.0 General Information

There were nearly 62,000 new head and neck cancer (HNC) cases last year accounting for 3% of all cancers in the US (1) with an increasing incidence among younger adults due to the human papillomavirus (HPV) infection. Treatment is typically surgical resection of primary lesions and extensive lymph node (LN) dissection, followed by fractionated radiation therapy (RT). Because the neck and cervical region contains 1/3 of the body's LNs (2) surgical disruption of the lymphatic vasculature and LNs together with subsequent RT of the head and neck region results in the debilitating condition of lymphedema and extensive fibrosis in an estimated 75% of all HNC survivors (3, 4). Although the cure rate of these patients is high with extensive LN dissection and RT, the debilitating effects of this treatment significantly reduces the quality of survivorship. HNC lymphedema can have a profound effect on the range of motion, swallowing, and evening breathing.

Unlike breast cancer where a 10% increase in arm volume is used for diagnosis of lymphedema, there is no accepted objective measurement to base the diagnosis of HNC lymphedema. Weight loss and extensive surgery can mask the early signs of edema and lymphedema. As a result, HNC patients/survivors are not screened for lymphedema and early treatment of manual lymphatic drainage to move accumulated tissue fluid and prevent irreversible tissue changes is typically not offered to HNC cancer survivors.

2.0 Background Information

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.0 Objectives

The primary objective of the pilot study is to use NIRF imaging to assess whether pneumatic compression can move lymph in HN cancer patients and survivors. The secondary objectives are to assess whether compliant use over a two week period can reverse or reduce the dermal backflow that is associated with HN lymphedema and to collect patient feedback on the ease of use and perception of symptom alleviation with the Flexitouch System and associated head and neck garments after two weeks of daily home use.

The Flexitouch System and associated garments for extremities and trunk are approved for use by patients who are under medical supervision for the treatment of 1) lymphedema (primary or secondary); 2) edema resulting from mastectomies, trauma, sports injuries or post immobilization; 3) venous insufficiencies; 4) wounds and 5) stasis dermatitis, venous stasis ulcers, arterial leg ulcers and diabetic leg ulcers. The variety of garments and accessories available with the Flexitouch system are designed to provide targeted compression therapy to different areas of the body. Tactile Medical™ secured FDA clearance via the 510(k) program to market their newly designed head and vest garments and Flexitouch Treatment Program H1 (Appendix A, p14). When the head garment and vest garment are used together, the resulting compression directs fluid from the head to the axilla in one continuous motion, presumably moving fluid from the head and neck region into the axilla for uptake into the regional lymphatic.

We will assess whether the Flexitouch System can move lymph from the region by using NIRF imaging before and after treatment with the Flexitouch system, as well as, after 2 weeks of compliant home use. We will assess whether Flexitouch usage is associated with alleviation of lymphedema symptoms.

4.0 Study Design

A non-randomized, non-blinded, single site pilot study designed to assess whether NIRF imaging can report on the efficacy of the Flexitouch System used to move lymph in HNC survivors. Specifically, we will assess whether the Flexitouch System can move lymph from the region by using NIRF imaging before and after treatment with the Flexitouch system, as well as, after 2 weeks of compliant home use. Participation will require approximately 24 hours over 2 weeks. Enrollment is targeted to be completed within 3 months.

Assessment of efficacy and safety

[REDACTED]

[REDACTED]

The Flexitouch System, when used for upper and lower extremity lymphedema is a standard-of-care PCD treatment device used routinely in the clinic and for at-home use. In this study, we seek to deploy NIRF imaging to assess the efficacy of the Flexitouch system for moving lymph in HNC survivors and to assess whether this correlates with symptom alleviation. [REDACTED]

[REDACTED]

5.0 Study Population

5.1 Inclusion Criteria

- 1) Participants must be 18 years of age or older
- 2) Participants must be diagnosed with Lymphedema of the Head and/or Neck
- 3) Participants must be diagnosed with squamous cell carcinoma of the oral cavity, oropharynx or larynx and underwent surgery and/or radiation as part of their standard-of-care treatment plan.
- 4) Participants must be ≥ 4 weeks post-radiation therapy
- 5) Female participants of childbearing potential must have a negative urine pregnancy test ≤ 36 hours prior to study drug administration
- 6) Female participants of childbearing potential must agree to use a medically accepted method of contraception for a period of one month after each imaging session
- 7) Participants must be willing to use the Flexitouch® System at home daily for two (2) weeks

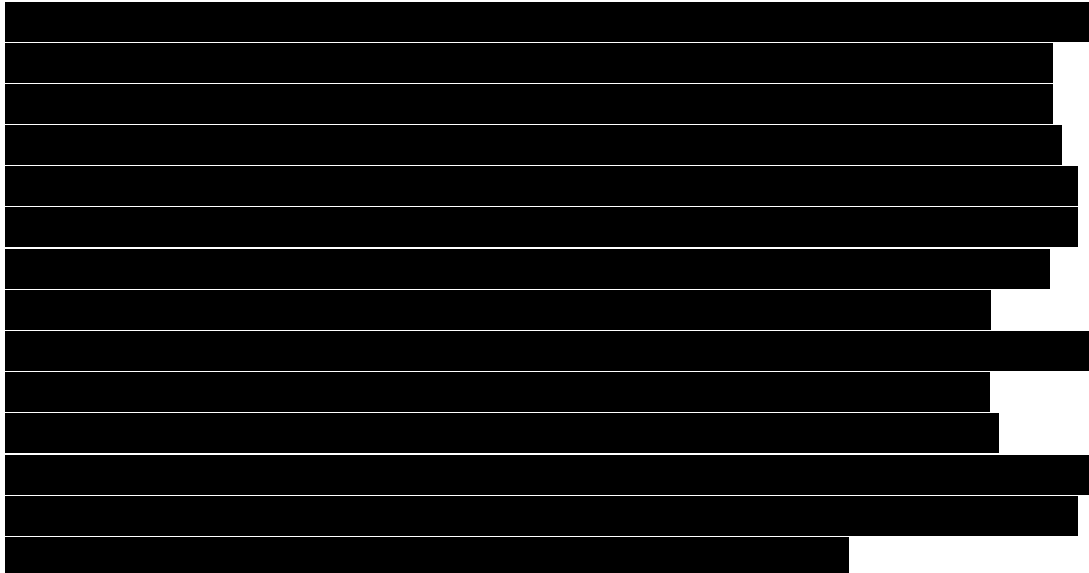
5.2 Exclusion Criteria

- 1) Women who are pregnant or breast-feeding
- 2) Persons who are allergic to iodine
- 3) A female of child-bearing potential, who does not agree to use an approved contraceptive for one month after study participation
- 4) Persons who do not meet inclusion criteria
- 5) Persons with pulmonary edema, thrombophlebitis, congestive heart failure, deep vein thrombosis, episodes of pulmonary embolism, infections and inflammation, or acute cancer
- 6) Persons with uncontrolled hyperthyroidism or parathyroidism (for with an endocrinologist recommends against neck compression)
- 7) Carotid sinus hypersensitivity syndrome

- 8) 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)
- 9) Symptomatic bradycardia in the absence of a pacemaker
- 10) Internal jugular venous thrombosis, acute or within 3 months
- 11) Known intracranial pressure or other contraindication to internal or external jugular venous compression
- 12) Acute radiation dermatitis, unhealed surgical scar, unhealed or open wound(s), surgical flap less than 6-8 weeks post-operative
- 13) Facial or head and neck dermal metastasis
- 14) Acute facial infection (e.g., facial or parotid gland abscess)
- 15) Any condition where increased venous and lymphatic return is undesirable

5.3 Risks/Discomforts

Near-infrared fluorescence lymphatic imaging



Flexitouch® Advance Pneumatic Compression System

Participants enrolled in the sub-study are not expected to be at any higher or additional risk than those who use non-study pneumatic compression devices (PCD), or static compression garments approved for use in head and neck region since pressures do not exceed the pressures of static compression garments. There is risk associated with using any PCD. These risks include, but are not limited to, risk of explosion if the device is used in the presence of flammable gases, risk of electrical shock if the device is immersed in water, or if the housing is broken and subject attempts to service the unit.

5.4 Potential Benefits

While there is no guarantee of a direct benefit to participants, there is a possible benefit of improved lymphatic function and decreased edema with use of the Flexitouch system.

5.5 Cost/Payment

[REDACTED]

[REDACTED]

6.0 Sample Size/Data Analysis/Subject Withdrawal and Replacement

In this pilot sub-study of a total of ten patients who complete both study visits, we will assess whether there are any changes to lymphatic function after a single use of the pneumatic compression device and after a two week period of daily home use. Five patients will undergo daily ICD of approximately 32 minutes while another five patients will undergo daily ICD of approximately 60 minutes in order to assess the effect of duration on response to therapy. If, after the initial consent and imaging session are completed, a subject withdraws, opts not to complete the daily home therapy (<75% of total treatments), OR does not properly use the device as instructed, they may be dropped from the study cohort and a replacement subject may be enrolled to ensure a full cohort of 10 subjects completes the study.

[REDACTED]

Because this is a pilot study, we cannot statistically power the study for conclusions. Instead we will assess results to visualize trends for a subsequent properly powered study to statistically test the hypothesis that the Flexitouch system can restore lymphatic function.

7.0 Study Procedures

The sub-study consists of two NIRF lymphatic imaging sessions (see Section below for NIRF procedure) separated by approximately two (2) weeks. At each session, measurements of the subject's head and neck will be recorded and 3D images and/or digital photographs will be taken before and after treatment. Participants will don the head and neck and vest garments before undergoing Treatment Program H1 with the Flexitouch System. Imaging with NIRFLI system will

occur before, during and after treatment with the Flexitouch System. The first NIRF lymphatic imaging session will establish the presence of lymphatic dysfunction as visualized with the NIRFLI System. The subject will be loaned the Flexitouch® Advanced Pneumatic Compression system along with the Head Garment and Vest for Head & Neck. The subjects will be instructed in the proper fitting of the garments and the use of the Flexitouch system. The subjects will complete the Flexitouch Treatment Program H1 (~30-40 minutes or ~60 minutes) daily for approximately two (2) weeks. Participants will be asked to keep a diary of their daily use on the Flexitouch System. After approximately two (2) weeks of daily use, the subject will return for the second and final NIRF lymphatic imaging session, at which time they will return the Flexitouch System and associated garments to the research team. Subjects will then be asked a series of questions related to the ease of use of the Flexitouch System and their perception of the treatment they received while using the Flexitouch System.

NIRF Lymphatic Imaging

[REDACTED]

8.0 Data and Safety Monitoring

The Principal Investigator will be responsible for the monitoring of study data and subject safety. Due to the small number of research subjects, the most comprehensive and effective method of monitoring will be an individual case review by the PI (Eva M. Sevic-Muraca, PhD) and clinical investigators (Ron J. Karni, MD; Erik A. Maus, MD; and physician designates). As this has always been the policy of the PI, the researchers and study team are under specific instructions to make the PI aware of all adverse events, expected or unexpected; therefore, the responsibility for reporting adverse events is shared with the PI and the research team.

Case Report Forms (CRFs) containing all monitoring information will be completed by the PI, clinical investigator(s) or designee and reviewed by the PI and clinical investigator(s). Case report forms (CRFs) will be kept in a locked office or archive.

[REDACTED]

[REDACTED]

9.0 Statistics

In this pilot sub-study we will assess whether there are any changes to lymphatic function after a single use of the pneumatic compression device and after a two week period of compliant use.

[REDACTED]

[REDACTED] Specifically, we seek to determine the change in the percentage of area that is demarked by dermal backflow in response to the Flexitouch System use after a single session and after two weeks of compliant use.

[REDACTED]

Because this is a pilot study, we cannot statistically power the study for conclusions. Instead we will assess results to visualize trends for a subsequent properly powered study to statistically test the hypothesis that the Flexitouch system can reduce dermal backflow and restore lymphatic function.

10.0 Ethics

This sub-study will be submitted to the local IRB, the Committee for the Protection of Human Subjects (CPHS), for approval to begin research and study oversight.

Informed consent will be conducted by a member of the research team. When possible, a copy of the consent will be provided to the study candidate prior to the clinic visit. At the first clinic visit, a private room will be used to review the consent with the candidate and to answer any questions or concerns they may have regarding participation in the research study.

11.0 Data handling and record keeping

Physical records related to the study are kept in a secure location, with controlled access. Electronic records are maintained on a secure server, behind a firewall, with restricted access by username and password. A study specific identifying will be assigned to each participants in lieu of personal identifiers.

12.0 Quality control and assurance

This study will be conducted in accordance with Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) Guidelines, Code of Federal Regulations (CFR), state and local guidelines and institutional research policies and procedures to ensure subject safety and quality of data.

Raw data will be collected on the appropriate source document worksheets. Data collected in the source will be transcribed by the research staff onto paper Case Report Forms (CRFs).

12.1 Product Release Information

Product release information for ICG will be maintained by the manufacturer.

12.2 Accountability of Test Products

Indocyanine Green (ICG)

A record of lot number and expiration date will be maintained for ICG used in this study.

Near-infrared fluorescence lymphatic imaging (NIRFLI)



Flexitouch® Advanced Pneumatic Compression System

Site personnel must maintain a device accountability log. Completion of this log will ensure that all Flexitouch® Advance Pneumatic Compression pumps and garments are properly tracked and accounted for throughout the study, from the time they are received by the research team to the time they are returned to Tactile Medical. Device location, subject ID assigned, date and final disposition (e.g. return to Tactile Medical, garment discarded, etc.) of all control units and garments will be documented.

12.3 Protocol Modifications / Deviations

Protocol amendments will be submitted to the UTHSC-H CPHS (IRB) for approval prior to implementation. Protocol deviations will be acknowledged according to UTHSC-H CPHS policies, including electronic notification through the iRIS system at UTHSC-H. Exceptions to the protocol will be approved by the UTHSC-H CPHS prior to implementation.

12.4 Subject Compliance

Flexitouch® Advanced Pneumatic Compression System

Subject compliance will be evaluated through a daily diary completed by each subject.

13.0 Publication Plan

All information obtained in this study may be used for publications, presentations and conferences of a medical or scientific nature. All patient identifiers will be removed before data is disseminated in presentations and publications and any image will be de-identified to the greatest extent possible.

14.0 Key Roles

Sponsor Contact:

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Principal Investigator:

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Clinical Investigator(s):

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Study Monitor(s):

[REDACTED]

15.0 References

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16.0 Attachments

Appendix A: Flexitouch User's Guide