A Registry to Evaluate the Flexitouch System and Flexitouch Plus for Treatment of Head and Neck Lymphedema

Protocol# 4060

24 January 2019

Protocol Version 4.0

Investigator Signature

Protocol Title: A Registry to Evaluate the Flexitouch System and Flexitouch Plus for Treatment of Head and Neck Lymphedema

Protocol Number: 4060

Version: 4.0; 24 January 2019

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.

_____
Site Principal Investigator Name (Print)

_____ _____
Site Principal Investigator Signature Date

SYNOPSIS

Registry Title	A Registry to Evaluate the Flexitouch System and Flexitouch Plus for Treatment of Head and Neck Lymphedema
Protocol Date	24 January 2019
Protocol Version	4.0
Name of Sponsor	Tactile Medical™
Device	Flexitouch system or Flexitouch Plus with Head and Neck Garments
Registry Objective	To evaluate the long term effectiveness of the Flexitouch system and Flexitouch Plus in those with head and neck lymphedema.
Primary Endpoint	Symptom and function improvement
Secondary Endpoints	Changes in QOL, changes in pain, reduction in head and neck swelling, ease of use, treatment satisfaction
Registry Design	This registry is a multi-center, prospective, observational, registry designed to evaluate patients with head and neck lymphedema who receive the Flexitouch system or Flexitouch Plus.
Treatment	Flexitouch Head and Neck Treatment, as prescribed.

Eligibility	**Inclusion Criteria:**
	• Age ≥ 18 years
	• A diagnosis of head and/or neck lymphedema
	• Must be able and willing to participate in all aspects of the registry and provide informed consent prior to registry participation
	• Head and chest measurements within the following:
	  o Crown of head circumference: ≤ 72 cm
	  o Chest circumference: ≤ 158 cm
	• Prescribed the Flexitouch system or Flexitouch Plus
	
	Exclusion Criteria:
	• Uncontrolled hyperthyroidism or parathyroidism (for which endocrinologist recommends against neck compression)
	• Carotid sinus hypersensitivity syndrome
	• Symptomatic carotid artery disease, as manifested by a recent transient ischemic attack (within 30 days), ischemic stroke, or amaurosis fugax (monocular visual ischemic symptoms or blindness)
	• Symptomatic bradycardia in the absence of a pacemaker
	• Internal jugular venous thrombosis (within 3 months)
	• Increased intracranial pressure or other contraindications to internal or external jugular venous compression
	• Acute radiation dermatitis, unhealed surgical scar, unhealed or open wound(s), or surgical flap less than 6-8 weeks post-operative

	• Facial or head and neck dermal metastasis • Acute facial infection (e.g., facial or parotid gland abscess) • Any condition in which increased venous and lymphatic return is undesirable • Heart failure (acute pulmonary edema, decompensated acute heart failure) • Subject is pregnant or trying to become pregnant • Acute venous disease (acute thrombophlebitis, acute deep venous thrombosis, acute pulmonary embolism)
Subject Participation Duration	Approximately 6 months
Sample Size	Open

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1.0 Contact Information

1.1 Sponsor Contact Information

Tactile Medical™
Jill Christensen, Clinical Research Manager
1331 Tyler Street NE, Suite 200
Minneapolis, MN 55413
612-355-5123
jchristensen@tactilemedical.com

2.0 Abbreviations

AE	Adverse Event
CDT	Complete Decongestive Therapy
CFR	Code of Federal Regulations
CRF	Case Report Form
EDC	Electronic Data Capture
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HNC	Head and Neck Cancer
HNL	Head and Neck Lymphedema
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MLD	Manual Lymph Drainage
QOL	Quality of Life
ROM	Range of Motion
SAE	Serious Adverse Event
VAS	Visual Analog Scale

3.0 Introduction

3.1 Background and Rationale

Secondary head and neck lymphedema (HNL) is a frequent late effect in patients treated for head and neck cancer (HNC) as the primary cancer or factors related to treatment (surgery, radiation, or chemotherapy) either destroy or obstruct lymphatic vessels and damage adjacent soft tissue.[1,4] HNL occurs in over 50% of patients receiving radiation and/or surgery for HNC.[2] HNL may involve external structures (soft tissues of the face, neck, and eyes) or internal structures (oral cavity, mucous membranes, larynx, and pharynx), but most often both are involved simultaneously.[3] The resultant clinical impact is dependent on the anatomic sites involved and the extent of associated lymphatic dysfunction. These symptoms can range from mild to severe. The most common areas of external swelling and fibrosis are in the submental region and the neck.[2,4] In severe cases, HNL may impact critical physical functions (e.g., respiration, mastication, swallowing, communication, and vision). HNL, comparable to lymphedema at other sites, is often associated with psychological distress and degradation to quality of life.[3,4] In a recent study of 1,202 HNC patients, the majority of patients reported cosmetic concerns and discomfort. More than one third reported functional complaints, including difficulty swallowing (68%) and difficulty breathing (39%).[2] The most common functional complaint among patients who underwent total laryngectomy was difficulty breathing, often related to tracheostomal obstruction from submental edema.[2]

Damaged lymphatics result in high-protein fluid collection in the affected tissues. Lymphedema is associated with chronic inflammation, which may lead to a self-perpetuating and progressive course.[5] HNL patients often experience tightness and discomfort in the muscles of the neck and shoulders which may impede range of motion and function of these muscular groups.[3] Damage to the muscles in the affected region may also occur after radiation, resulting in atrophy, weakness, and altered sensation.

The treatment of HNL utilizes modified techniques of in-clinic complete decongestive therapy (CDT), including manual lymph drainage (MLD). Currently, some patients are able to continue simplified versions of these techniques at home, yet, many patients with HNL experience difficulty performing the treatment and/or find the treatment is insufficient in effectively managing their symptoms long-term. Clinicians and patients have therefore identified a need for additional effective options for at home treatment of HNL. In response, Tactile Medical has developed a garment for the treatment of HNL utilizing the Flexitouch system or Flexitouch Plus pneumatic compression device. Tactile Medical seeks to evaluate the long term effectiveness of the Flexitouch system and Flexitouch Plus.

3.2 Device Description

The Flexitouch system and Flexitouch Plus (Tactile Medical™, Minneapolis, MN, USA) are pneumatic compression devices which have been cleared by the Food and Drug Administration (FDA) for market in the US (K153311 and K170216, respectively; US HCPCS code E0652).

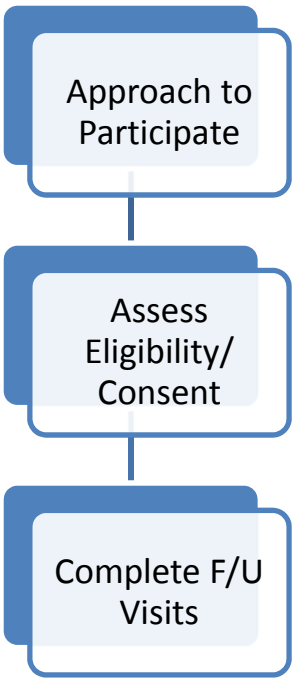
The Flexitouch® Head and Neck Garment is constructed of nylon and has up to 16 pneumatic chambers covering part of the head, neck, and chest. The device applies brief applications of dynamic pressure in a wave-like manner to the treatment area. Used in conjunction with the Flexitouch controller, the Head and Neck Garment is intended to treat lymphedema affecting the head and neck by stimulating the adjacent axillary lymphatic tributary regions and directing fluid from the affected area to healthy, functioning regions.

4.0 Registry Objective

The objective of this registry is to evaluate the long term effectiveness of the Flexitouch system and Flexitouch Plus in those with head and neck lymphedema. This outcome data will include information regarding each subject's medical history, symptoms, quality of life, pain, range of motion (ROM), swelling, ease of use, treatment satisfaction, treatment compliance, and device-related adverse events.

5.0 Registry Design

This multi-center, prospective, observational, registry will follow patients with head and neck lymphedema who are using the Flexitouch system or Flexitouch Plus. Data collection will occur at Baseline and Days 14, 28, 56, 84, and 168.



5.1 Endpoints

5.1.1 Primary Endpoints

To evaluate symptom and function improvement after 168 days (approximately 6 months) of treatment with the Flexitouch system or Flexitouch Plus based upon:

- Symptom survey (EORTC H+N35); and
- Range of motion measures (neck, mouth, and shoulder).

5.1.2 Secondary Endpoints

To evaluate quality of life (QOL), pain, swelling, ease of use, and treatment satisfaction after 168 days (approximately 6 months) of treatment with the Flexitouch system or Flexitouch Plus based upon:

- Change in the QOL (EORTC C30);
- Change in pain (VAS);
- Change in swelling (upper neck, lower neck, and ear to ear measurements); and
- Ease of use and treatment satisfaction (survey).

5.2 Subject Selection

The registry population will be drawn from patients who have head and neck lymphedema and are prescribed the Flexitouch system or Flexitouch Plus for in-home treatment of their head and neck lymphedema. Only patients who meet the criteria listed below and have provided informed consent will be considered for participation. Subjects will be considered enrolled in the study after they have signed the Informed Consent Form, met all inclusion/exclusion criteria, and completed the device training visit. Any subjects who do not meet inclusion/exclusion criteria, or do not ultimately receive the device, will be considered screen failures.

5.2.1 Inclusion Criteria

Patients must meet the following criteria:

- Age ≥ 18 years
- A diagnosis of head and/or neck lymphedema
- Must be able and willing to participate in all aspects of the registry and provide informed consent prior to registry participation
- Head and chest measurements within the following:
  - Crown of head circumference: ≤ 72 cm
  - Chest circumference: ≤ 158 cm
- Prescribed the Flexitouch system or Flexitouch Plus

5.2.2 Exclusion Criteria

Patients must not meet any of the following criteria:

- Uncontrolled hyperthyroidism or parathyroidism (for which endocrinologist recommends against neck compression)
- Carotid sinus hypersensitivity syndrome
- Symptomatic carotid artery disease, as manifested by a recent transient ischemic attack (within 30 days), ischemic stroke, or amaurosis fugax (monocular visual ischemic symptoms or blindness)
- Symptomatic bradycardia in the absence of a pacemaker
- Internal jugular venous thrombosis (within 3 months)
- Increased intracranial pressure or other contraindications to internal or external jugular venous compression
- Acute radiation dermatitis, unhealed surgical scar, unhealed or open wound(s), or surgical flap less than 6-8 weeks post-operative

- Facial or head and neck dermal metastasis
- Acute facial infection (e.g., facial or parotid gland abscess)
- Any condition in which increased venous and lymphatic return is undesirable
- Heart Failure (acute pulmonary edema, decompensated acute heart failure)
- Subject is pregnant or trying to become pregnant
- Acute venous disease (acute thrombophlebitis, acute deep venous thrombosis, acute pulmonary embolism)

5.3 Registry Duration

Enrollment will occur at centers throughout the United States. Subjects will remain active in the registry for a period of 168 days (approximately 6 months), and after that time, no additional information will be collected. The duration of the registry has not been specified; however, enrollment will be open for the duration of the registry. Registry analyses will be completed at various times throughout the lifecycle of the project.

6.0 Registry Visit Summaries

6.1 Screening/Baseline Visit #1

All potential subjects will be screened to ensure compliance to general inclusion and exclusion criteria. If subjects appear eligible to participate based on their medical history, they will be consented to participate in the registry. All consented subjects will undergo the following procedures:

- Obtain Informed Consent;
- Obtain Medical History and Current Medications;
- Administer a pregnancy test for all female subjects of child-bearing potential;
- Complete lymphedema evaluation;
- Complete the Clinical Intake Form (Appendix A);
- Obtain vital signs (if collected as part of standard of care);
- Obtain baseline ROM measurement (Appendix B);
- Obtain baseline swelling measurements (Appendix C);
- Have subject complete the EORTC C30 (Appendix D), EORTC H+N35 (Appendix E), and VAS (Appendix F);
- Instruct the subject on the methods to track compliance;
- Instruct subject on device prescription and training procedures at home or at the clinic; and
- Ensure a clinical research coversheet is submitted with the device order to Tactile Medical when ordering the Flexitouch system or Flexitouch Plus.

6.2 Device Training Visit #2 (Day 0)

All subjects will be instructed to conduct head and neck lymphedema treatment as prescribed by their treating clinician. Prior to using the Flexitouch system or Flexitouch Plus in-home, Tactile personnel will perform device training either in-home or at the clinic, per standard practice. The date of training (Day 0), which will

take place approximately 1-3 weeks after the device order is placed, will be used to determine the timing of the follow-up schedule.

6.3 Week 2 Phone Call Visit #3 (Day 14±3)

Approximately 14 days after the subject receives training and begins using the prescribed treatment, clinic personnel will call the subject to assess the following at Visit 3:

- Changes to medical history;
- Device-related adverse events (NOTE: Compare events to pre-existing conditions documented in Medical History to determine if the event is a new event, a worsening of a pre-existing event, or just a reoccurrence of a pre-existing event); and
- Any questions/concerns the subject has regarding device use and/or compliance.

6.4 Month 1 Clinic Visit #4 (Day 28±5)

Approximately 28 days after the subject begins using the prescribed treatment, he or she will return to the clinic and undergo the following procedures at Visit 4:

- Changes to medical history;
- Obtain vital signs (if collected as part of standard of care);
- Obtain ROM measurement (Appendix B);
- Obtain swelling measurements (Appendix C);
- Have subject complete the EORTC C30 (Appendix D), EORTC H+N35 (Appendix E), and VAS (Appendix F);
- Record device-related adverse events (NOTE: Compare events to pre-existing conditions documented in Medical History to determine if the event is a new event, a worsening of a pre-existing event, or just a reoccurrence of a pre-existing event); and
- Review treatment compliance with subject.

6.5 Month 2 Phone Call Visit #5 (Day 56±5)

Approximately 56 days after the subject begins using the prescribed treatment, clinic personnel will call the subject to assess the following at Visit 5:

- Changes to medical history;
- Device-related adverse events (NOTE: Compare events to pre-existing conditions documented in Medical History to determine if the event is a new event, a worsening of a pre-existing event, or just a reoccurrence of a pre-existing event); and
- Any questions/concerns the subject has regarding device use and/or compliance.

6.6 Month 3 Clinic Visit #6 (Day 84±5)

Approximately 84 days after the subject begins using the prescribed treatment, he or she will return to the clinic and undergo the following procedures at Visit 6:

- Changes to medical history;

- Obtain vital signs (if collected as part of standard of care);
- Obtain ROM measurement (Appendix B);
- Obtain swelling measurements (Appendix C);
- Have subject complete the EORTC C30 (Appendix D), EORTC H+N35 (Appendix E), and VAS (Appendix F);
- Record device-related adverse events (NOTE: Compare events to pre-existing conditions documented in Medical History to determine if the event is a new event, a worsening of a pre-existing event, or just a reoccurrence of a pre-existing event); and
- Review treatment compliance with subject.

6.7 Month 6 Clinic Visit #7 (Day 168±14)

Approximately 168 days after the subject begins using the prescribed treatment, or upon early termination of a subject (if possible), he or she will return to the clinic and undergo the following procedures at Visit 7:

- Changes to medical history;
- Obtain vital signs (if collected as part of standard of care);
- Complete lymphedema evaluation;
- Obtain ROM measurement (Appendix B);
- Obtain swelling measurements (Appendix C);
- Have subject complete the EORTC C30 (Appendix D), EORTC H+N35 (Appendix E), VAS (Appendix F), and Ease of Use and Treatment Satisfaction Survey (Appendix G);
- Record device-related adverse events (NOTE: Compare events to pre-existing conditions documented in Medical History to determine if the event is a new event, a worsening of a pre-existing event, or just a reoccurrence of a pre-existing event); and
- Review treatment compliance with subject.

6.8 Registry Exit

Once a subject completes all required visits, or chooses to withdraw from participation prior to Clinic Visit #7, ensure the following has been recorded:

- Date and reason for registry exit;
- Changes to medical history;
- Device-related adverse events (NOTE: Compare events to pre-existing conditions documented in Medical History to determine if the event is a new event, a worsening, of a pre-existing event or just a reoccurrence of a pre-existing event); and
- Treatment compliance.

7.0 Registry Schedule of Activities

Procedures	*Visit 1 (in clinic)*	*Visit 2 (in home or clinic)*	*Visit 3 (phone call)*	*Visit 4 (in clinic)*	*Visit 5 (phone call)*	*Visit 6 (in clinic)*	*Visit 7 (in clinic)*
	Screen/ Baseline	**Day 0**	**Week 2 (Day 14 ± 3 Days)**	**Month 1 (Day 28 ± 5 Days)**	**Month 2 (Day 56 ± 5 Days)**	**Month 3 (Day 84 ± 5 Days)**	**Month 6 (Day 168 ± 14 Days)**
Informed Consent	X						
Device Training		X					
Pregnancy Test (if applicable)	X						
Medical History	X		X*	X*	X*	X*	X*
Vital Signs (if applicable)	X			X		X	X
Lymphedema Evaluation	X						X
Range of Motion (Neck, mouth, shoulders)	X			X		X	X
Assess Swelling	X			X		X	X
QOL (EORTC C30)	X			X		X	X
Symptoms (EORTC H+N35)	X			X		X	X
Assess Pain (VAS)	X			X		X	X
Ease of Use and Satisfaction Survey							X
Complications/ AEs/SAEs			X	X	X	X	X
Device Use Evaluation			X		X		
Compliance			X	X	X	X	X

* Change in medical history.

8.0 Registry Procedures

8.1 Laboratory Testing Procedures

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

If the subject becomes pregnant at any time during the registry, the subject will be withdrawn from registry participation and followed at the Investigator's discretion.

8.2 Vital Signs & Lymphedema Evaluation

Research personnel will assess vital signs at each clinic visit (if collected as part of standard of care).

The clinical stage of lymphedema will be evaluated by a clinician at Baseline and Visit 7 using the following definitions:

- Stage 0: No visible edema but patient reports heaviness
- Stage 1a: Soft visible edema; no pitting, reversible
- Stage 1b: Soft pitting edema; reversible
- Stage 2: Firm pitting edema; not reversible; no tissue changes
- Stage 3: Irreversible; tissue changes

The evaluation will also document the presence or absence of issues with speech, edema, wounds, facial asymmetry, and skin changes.

8.3 Function Assessment

Cervical, mouth, and shoulder range of motion measurements will be taken at each in-clinic visit (Appendix B). The measurements will be completed by research personnel with documented training showing the individual was able to independently and accurately conduct the measurements on 2 occasions.

8.4 Swelling Assessment

Swelling measurements will be taken at each in-clinic visit (Appendix C). The measurements will be completed by research personnel with documented training showing the individual was able to independently and accurately conduct the measurements on 2 occasions.

8.5 Symptom Assessment

Symptoms will be assessed at each in-clinic visit using the EORTC H+N35 (Appendix E). The survey will be completed by the subject.

8.6 Quality of Life & Pain Assessment

Quality of Life will be assessed at each in-clinic visit using the EORTC C30 (Appendix D). The survey will be completed by the subject.

Pain will be assessed at each in-clinic visit using the VAS (Appendix F). The assessment will be completed by the subject.

8.7 Device Use Evaluation

During the phone follow-up at Visit 3 and 5, site research personnel will ask the subject questions about device use to evaluate if additional device training by Tactile personnel is warranted.

8.8 Ease of Use and Treatment Satisfaction

Ease of use and treatment satisfaction will be assessed by survey (Appendix G). The survey will be completed by the subject.

8.9 Compliance Assessment

Compliance with device treatment may be assessed at each in-clinic and phone follow-up visit. The subject may be asked to record compliance in a diary (Appendix H), or device use data may be downloaded periodically for subjects using the Flexitouch Plus.

8.10 Adverse Event Reporting & Device Observations

Reportable events, as defined below, will be recorded in the subject's medical record and on the Adverse Event (AE) Log.

8.10.1 Device-Related Adverse Event (AE)

This registry will only collect device-related adverse events. A device-related adverse event is defined as any untoward medical occurrence in the subject that is associated with the use of the Flexitouch system or Flexitouch Plus.

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

8.10.2 Serious Adverse Event (SAE)

A serious adverse event is an untoward medical occurrence where the outcome is:

- Death;
- Life-threatening event (places the subject at immediate risk of death from the experience as it occurred);
- Hospitalization (initial or prolonged) if admission to hospital was warranted as a result of an adverse event;
- Disability or permanent damage (substantial disruption of one's ability to carry out normal life functions);
- Congenital anomaly or birth defect;
- Required intervention to prevent permanent impairment or damage; or
- Important medical event that required medical or interventional treatment to prevent one of the previous outcomes.

Investigators must report all device-related, Serious Adverse Events (SAEs) to Tactile Medical within 10 work days of becoming aware of the event. Device-related SAEs will be summarized in writing and reported to the IRB in accordance with IRB policy.

8.10.3 Device Observations

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

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

9.0 Subject Withdrawal or Early Termination

Subject participation may be terminated prior to completing the registry for any of the following reasons:

- Withdrawal of Consent
  Subjects may withdraw their consent to participate at any time. If a subject withdraws consent, previous information that has already been obtained will be available for analysis.
- Lost to Follow-up
  A certified, return-receipt letter must be sent to the subject after 2 attempts to reach the subject by telephone have failed. The subject will be considered lost to follow-up if this communication is unsuccessful.
- Adverse Event
  Subject experiences an adverse event that in the investigator's clinical judgement necessitates discontinuation of their participation in this registry.
- Discretion of the Principal Investigator
  Subjects may be withdrawn at the investigator's discretion in the event of subject noncompliance, changes in the subject's health, or other reasons based on the investigator's clinical judgment.

When a subject withdraws prior to completing the registry, all effort should be made to complete Visit 7 prior to documenting the reason for withdrawal in the subject's medical record.

10.0 Device Accountability

To participate in the registry, the Flexitouch system or Flexitouch Plus must be prescribed by a clinician and paid for by the subject or their payer. The Flexitouch system or Flexitouch Plus will be provided to the subject and tracked according to normal business practices at Tactile Medical.

11.0 Risk Analysis and Adverse Events

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

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

Likely:

- Pain or discomfort
- Increased swelling

Less Likely:

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

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

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

This research represents a registry documenting head and neck lymphedema. 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. The Information Security Plan, per the requirements of VHA Handbook 1200.05 include, but are not limited to, the following provisions:

a. Individually identifiable information will be collected and used in accordance with ICH GCP
b. Data are to be collected via clinical research forms

c. Data will be stored at the Investigation Site and at the Company in accordance with ICH GCP and retained in accordance with the Company's Policy 30 (Record Retention Policy)
d. Data will be transported or transmitted from one location to another via Federal Express or secure email in accordance with the Company's internal Policy 45 (Confidentiality and Privacy of Patient Information) and Policy 91 (Data Transmission)
e. The PI, Company clinical research team, and authorized Site personnel will have access to the data and thus are responsible for its security
f. Company will abide by all HIPAA regulations when considering Business Associates or downstream entities that may have access to data
g. The Coordinating Center, Investigation Site, PI, and Company clinical research team will have access to and be responsible for the security of the information. Company will abide by its internal Policy 45 (Confidentiality and Privacy of Patient Information)
h. Medical records, verbal reports, and clinical research forms will account for the information
i. Company will follow guidelines established by the Company (Policy 45), ICH GCP, and HIPAA to ensure security measures are in place to protect individually identifiable information
j. If VA information is suspected or confirmed lost, a report will be filed with the Department of Veterans Affairs, Office of the Inspector General at https://www.va.gov/oig/hotline/

13.0 Deviation from Registry Plan

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

14.0 Quality Assurance Procedures

This registry will be conducted in accordance to all applicable regulations. Good Clinical Practice (GCP) (GCP E6 R2) will be used as a guidance for the preparation and conduct of the clinical registry.

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 registry completion.

14.2 Site Initiation

Tactile Medical personnel will conduct a Site Initiation Visit onsite or by telephone to ensure all required regulatory documents are accurate and complete, and site personnel has been adequately trained on the registry protocol. An activation letter will be sent to the Principal Investigator once the site is approved to enroll subjects.

14.3 Data Collection Procedures

Raw data will be collected on appropriate source document worksheets and CRFs will be submitted to Tactile Medical for data entry. Alternatively, at some point

during the registry, source document data may be entered directly into a validated and secure electronic data capture (EDC) system by trained site personnel.

14.4 Onsite Monitoring

Clinical sites will be monitored for compliance with the clinical protocol, investigator agreement, and applicable regulations throughout the registry. Prior to each visit, the investigator will receive a confirmation letter outlining the scheduled dates and activities.

Regular site contact will be maintained to ensure:

- Subject safety;
- Clinical site staff are well informed of regulations and sponsor requirements;
- The clinical protocol is followed;
- Data are gathered in a complete and timely manner;
- Problems with data or data collection are addressed appropriately and in a timely manner;
- Adverse events are properly reported in a timely manner; and
- Each onsite visit is recorded on the Site Visit Log.

After each visit, the investigator will receive a follow-up letter summarizing site progress as well as any outstanding items that need to be addressed.

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

The Principal Investigator and Institution agree to permit trial related monitoring, audits, IRB review, and regulatory inspection(s); providing direct access to source data and documents, as appropriate. Monitoring and source verification will be performed by a Tactile Medical CRA and/or designee. Source verification includes reviewing subject source documentation and Case Report Forms (CRFs) for accuracy, completeness, and compliance with GCP.

14.5 Data Safety Monitoring

A periodic review may be completed by a designated member of the Scientific Advisory Board or the Chief Medical Officer at Tactile Medical. The frequency of the review will be determined based on a number of parameters including, but not limited to: the rate of enrollment, number of AEs and/or SAEs, and number of significant deviations from the protocol. At the conclusion of the review, the reviewer may provide recommendations pertaining to registry continuation, modification, or termination of the trial or investigational site.

14.6 Reports and Records

Records to be maintained by the investigator in a designated registry 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 registry between the site and sponsor, IRB, and registry monitor;
- Curriculum Vitae and professional license for all registry personnel, if applicable;
- Site personnel signature and documentation regarding the investigator's delegation of responsibility;
- Site visit log;
- Protocol/device related training records for all applicable registry personnel;
- Screening log; and
- Reports (shown below).

The Principal Investigator is required to prepare and submit to Tactile Medical, or its designees, complete, accurate, and timely reports on this investigation as required by regulations. These reports include:

Reports	**Submit To**	**Timeframe**
Device-Related AE	Sponsor and Reviewing IRB	Sponsor: Within 15 working days of becoming aware of the event; IRB: In accordance with IRB procedure.
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
Progress	Sponsor and Reviewing IRB	Annually, at a minimum
Final	Sponsor and Reviewing IRB	Within 3 months following the completion or termination of the Investigator's part

The following records must be maintained for each subject enrolled:

- Original, signed and dated informed consent form, as well as documentation of the process of consent;
- Completed CRFs, queries, and source document worksheets, as applicable; and

- Complete medical records including procedure reports, lab reports, etc., as applicable.

Subject registry records, correspondence files, all supporting registry documentation, and reports must remain on file at the site for a minimum of ten years after the conclusion of this registry. All investigators must contact Tactile Medical personnel prior to destroying or archiving off-site any records and reports pertaining to this registry to ensure that they no longer need to be retained on-site. Additionally, Tactile Medical personnel must be contacted if the investigator plans to leave the investigational site to ensure that arrangements for a new investigator or records transfer are made prior to the investigator's departure.

15.0 Statistical Methods

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, inter-quartile range, minimum, and maximum, based upon subjects with reported data for the variable being analyzed.

Frequencies (numerator and denominator), percentages, and 95% confidence intervals will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing (unreported) data for the specific variable being analyzed and the count of the patients for each individual level of the categorical variable (the level specific numerators). Percentages will add up to 100%, unless otherwise indicated.

There are no plans to impute missing data and there are no plans to explicitly report missing data (counts and/or percentages) in the tables for all variables as part of the planned study report content. Variations in the reported sample sizes within and/or between relevant tables can be used to ascertain insights into unreported data. In some cases, unreported data may be due to it not being clinically relevant to a particular patient or may represent expected data that was not collected. Selected analyses pertaining to unreported and/or missing data may be discussed and considered as future findings warrant.

The observational nature of the study suggests that the statistical focus will be on estimation and hypothesis generation and not hypothesis testing. Though p-values will be reported as apropos, point estimates, and 95% confidence intervals will be used to guide exploratory analyses for potentially clinically meaningful differences or changes to be discussed and evaluated.

Inter-group (e.g., bivariate) comparisons, when performed, will utilize chi-square, ANOVA, t-test, and appropriate non-parametric tests, unless otherwise specified.

Multivariable models (e.g., linear regression or logistic regression) may be used to assess the predictive relationships and control for possible confounding imbalances of selected multiple variables to specific outcome measures of interest.

Any formal null hypothesis-based statistical comparisons will be made using two sided tests at the α=0.05 significance level unless specifically stated otherwise. All null hypotheses will be of no inter-group difference, all alternative hypotheses will be two-sided, unless specifically stated otherwise.

All data processing, summarization, and analyses will be performed using R Version 3.4.0 or higher.

16.0 Compensation

Registry subjects may be compensated for their time and travel for participating in this registry.

17.0 Publication Plan

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

18.0 References

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19.0 Appendices

Appendix A – Clinical Intake Form (Rev B)
Appendix B – Range of Motion Booklet (2010)
Appendix C – Swelling Measurements (ALOHA Protocol) (April 2018)
Appendix D – EORTC C30 (Version 3)
Appendix E – EORTC H+N35 (Version 1)
Appendix F – VAS (2001)
Appendix G – Ease of Use and Treatment Satisfaction Survey (April 2018)
Appendix H – Compliance Diary (April 2018)