Low-Level Laser in Treatment of Head and Neck Chronic Lymphedema: A Pilot Randomized Controlled Trial

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List of Abbreviations

CDT: Complete decongestive therapy

HNC: Head and neck cancer

LLLT: Low-level laser therapy

Study Summary

Title	**Low-Level Laser in Treatment of Head and Neck Chronic Lymphedema: A Pilot Randomized Controlled Trial**
Short Title	Low-level laser therapy in head and neck chronic lymphedema
Study ID Number	UPCC01320
Protocol Number	Version Date: 09-12-2022
Phase	Pilot study
Methodology	Randomized, wait-list controlled trial
Study Duration	24 months
Study Center(s)	Single-center
Objectives	**Primary Aim**: To determine the impact of LLLT, as compared to a wait-list control, on changes in severity of lymphedema. **Secondary Aim**: To determine the impact of LLLT, as compared to a wait-list control, on lymphedema-related symptom burden (e.g., tightness), functional impairments (e.g., range of motion in the jaw and neck) and QOL. **Exploratory Aim**: To explore the relationships among LLLT, the inflammatory biomarkers (e.g., TNF-α, TGF-β, IL-6), and the severity of lymphedema.
Number of Subjects	40 subjects expected to be enrolled
Main Inclusion and Exclusion Criteria	Inclusion criteria: 1) >18 years of age; 2) > 6 months post HNC treatment; 3) no evidence of cancer confirmed with imaging tests within 6 months or clinical examination by an oncologist as documented by progress note; 4) having head and neck lymphedema with or without fibrosis; 5) completion of initial lymphedema therapy; 6) lymphedema duration between 3-36 months; 7) ability to speak and read English; and 8) ability to provide informed consent. *Exclusion criteria*: Patients will be excluded if they have any of the following medical conditions that would prohibit the safe implementation of LLLT: pregnancy; acute infection; photosensitivity; chronic inflammatory diseases; venous thrombosis; carotid artery stenosis; history of severe trauma; medication that affects body fluid and electrolyte balance; use of high doses of non-steroidal anti-inflammatory drugs; or pre-existing skin rash, ulceration, open wound in the treatment area; active lymphedema therapy or physical therapy; and allergic and other systemic skin diseases.
Investigational device **For Device include the planned use**	RianCorp LTU-904 Low-level laser therapy unit
Duration of administration (if applicable)	6 weeks
Reference therapy	Usual care – Wait-list control
Safety Evaluations	Common Terminology Criteria for Adverse Events (CTCAE version 5.0) will be used to document adverse events of the clinical trial.
Data and Safety Monitoring Plan	PI Deng will be responsible for monitoring the data quality and the ongoing safety of subjects. The Medical Monitor, Dr. Sunita Nasta, will monitor and review all AEs and other safety data and activity data observed in the trial.

BACKGROUND AND STUDY RATIONALE

This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including the use of a medical device (i.e., RianCorp LTU-904).

1 Introduction

Current standard of care for head and neck lymphedema treatment provided by therapists is short-term in nature (usually up to 4-8 weeks); however, lymphedema is a chronic condition and often worsens over time. Therefore, alternative treatment modalities need to be investigated for effective and long-term management of lymphedema and associated late fibrosis in the head and neck cancer (HNC) population.

1.1 Background and Relevant Literature

There has been an increase in the incidence of head and neck cancer (HNC) largely related to the epidemic of human papillomavirus (HPV) associated disease.[1,2] HPV- associated HNC occurs in younger and middle-aged patients; cure rates in this population are markedly higher compared to other HNC groups.[3,4] This contributes to more than half a million HNC survivors in the U.S. today.[5] Regardless of the cause, patients with locally advanced HNC are usually treated with aggressive multi-modality regimens.[6] These regimens often lead to numerous long-term toxicities. One common but under-treated late effect of treatment is damage to lymphatic structures and soft tissues resulting in lymphedema.[7,8] Animal studies indicate that lymphedema is associated with chronic inflammation leading to fibrosis.[9,10] Our work was the first to assess lymphedema in HNC patients in a systematic manner.[7,11] We demonstrated a prevalence rate of 75% in HNC survivors.[7] We confirmed that lymphedema occurs both externally (e.g., face and neck) and internally (e.g., pharynx and larynx).[7,12] Subsequent work demonstrated that external lymphedema resulted in a decreased range of motion in the jaw, neck, and shoulders.[13] Internal swelling was found to cause substantial impact on critical functions (e.g., swallowing, speaking, and breathing).[13,14] Psychological effects (e.g., body image disturbance) were also correlated with lymphedema.[13,15-17] Finally, lymphedema has the potential to negatively impact HNC survivors' ability to function in both home and work environments, resulting in both emotional and financial burden for these individuals, their families, and the healthcare system.[11,18]

The current standard of care for treatment of lymphedema is complete decongestive therapy (CDT), which consists of 4 main parts: manual lymphatic drainage, compression (bandaging or garments), exercise, and skin care. [10,19-22] These treatments are expensive, time-consuming, and labor-intensive. Although CDT is routinely used in clinical settings, no level I evidence is available on the use of CDT for the treatment of HNC-related lymphedema.[11] In addition, CDT provided by therapists is short-term in nature (usually up to 4-12 weeks); however, lymphedema is a chronic condition and often worsens over time.[10,19] Therefore, alternative treatment modalities need to be investigated for effective and long-term management of lymphedema and associated late fibrosis in the HNC population.

Among many alternative treatment options, low-level laser therapy (LLLT) is a promising, noninvasive modality for the treatment of lymphedema. LLLT, also named photobiomodulation therapy (PBMT), has had a place in general medicine for more than 40 years.[24] It has been used as a treatment option to stimulate wound healing and reduce inflammation, edema, and pain.[24] The U.S. Food and Drug Administration (FDA) accepted it as a treatment approach for breast cancer-related upper extremity lymphedema (BCRL) in 2006.[24] One recent systematic review evaluating 7 randomized clinical trials (RCT) concluded that available evidence supports LLLT in the management of BCRL, with clinically meaningful reductions in lymphedema-related swelling and symptom burden (e.g., pain).[25] Compared to other treatment modalities, LLLT is a noninvasive modality, repeatable, easily performed in outpatient settings, and without any known long-term side effects. LLLT may be effective in treating chronic lymphedema in the HNC population, as it may reduce the generation of proinflammatory cytokines (e.g., tumor necrosis factor-alpha, TNF-α) and increase anti-inflammatory cytokines (e.g., interleukin-10, IL-10).[31-33] This is particularly important because many HNC survivors develop both lymphedema and late fibrosis.[7,15]

Therefore, LLLT may have the potential to effectively treat and manage HNC-related lymphedema. To our knowledge, the current proposal is the first RCT investigating the use of LLLT in the treatment of head and neck chronic lymphedema. The goal of this study is to evaluate the effect of LLLT on the severity of lymphedema, symptom burden, functional status, and quality of life (QOL) in HNC survivors, through a pilot, randomized, wait-list controlled trial.

1.2 Name and Description of the Investigational Product

We will use a RianCorp LTU-904, FDA-approved, Class I laser device in this study. The device will be used by the study lymphedema therapist, Joy Cohn, who has had more than 20 years of experience treating individuals with lymphedema.

1.2.1 Nonclinical Data

Findings from nonclinical data indicate that LLLT stimulates lymphatic vessels and lymphocytes, as well as increases local fluid circulation.[34,35]

1.2.2 Clinical Data to Date

Currently, only case studies indicate the potential value of the use of LLLT for treating head and neck lymphedema.[36,37] No prospective trials are available to evaluate feasibility, prophylactic and/or therapeutic use of LLLT for lymphedema in HNC patients. However, a large body of evidence is available in supporting the safety and efficacy of LLLT for the management of lymphedema in breast cancer patients. For instance, since 1995, the use of LLLT has been investigated in the treatment of breast cancer-related lymphedema (BCRL).[38] A meta-analysis of 9 studies (7 of them were RCTs) provided evidence that LLLT alone or combined with other treatments was able to reduce the arm swelling and pain in women with BCRL.[38-46] LLLT does not increase the risk of cellulitis, a known side effect in patients with arm lymphedema.[38] A recent systematic review also suggested the use of LLLT for treating the following conditions in the breast cancer population: oral mucositis, radiodermatitis, chemotherapy-induced peripheral neuropathy, and osteonecrosis of the jaw.[24] In another recent systematic review, the authors concluded that LLLT may have potential applications in the management of a broad range of side effects (e.g., lymphedema/fibrosis) of chemo-radiation therapy in patients with HNC.[47,48]

To fill in the gap, we have recently completed a **pilot, single-group, pre-post design clinical trial, the first prospective trial in this area**, that demonstrated it is feasible and acceptable to use LLLT for treating chronic lymphedema in HNC survivors.

1.2.3 Clinical Studies in Children

Not applicable.

1.3 Dose Rationale (if applicable)

We propose that participants will receive LLLT twice a week for 6 weeks (12 sessions). This regimen was developed based on the evidence from the literature as well as the data from our pilot feasibility trial.

2 Study Objectives

The major objective of this proposed research is to determine preliminary efficacy of the use of LLLT for HNC survivors with chronic lymphedema.

2.1 Primary Objective

- To determine the impact of LLLT, as compared to a wait-list control, on changes in severity of lymphedema.

2.2 Secondary Objective

- To determine the impact of LLLT, as compared to a wait-list control, on lymphedema-related symptom burden (e.g., tightness), functional impairments (e.g., range of motion in the jaw and neck) and QOL.

2.3 Exploratory Objective

- To explore the relationships among LLLT, the inflammatory biomarkers (e.g., TNF-α, TGF-β, IL-6), and the severity of lymphedema.

3 Investigational Plan

3.1 General Design

We will conduct a randomized, wait-list controlled trial to compare: Group 1 (laser therapy) and Group 2 (wait-list control). Outcome measures include: 1) changes in severity of lymphedema [Primary aim]; 2) changes in lymphedema-related symptom burden, functional status, and QOL [Secondary aim]; and 3) the relationships among LLLT, the inflammatory biomarkers, and severity of lymphedema [Exploratory aim].

3.1.1 Screening Phase

We will recruit a minimum of 3-4 participants per month. The volume of HNC patients at Penn's Clinic is sufficient to complete this trial without additional sites. The following recruitment procedures will be used: screening at HNC clinics and attendance at Head and Neck tumor boards and case conferences. All direct patient recruitment activities will be conducted at the Penn HNC clinics where private rooms are available to be used for conducting clinical research projects.

3.1.2 Allocation to Interventional Group

After completion of baseline measures, participants will be randomized via a computer-generated, permuted block program, conducted by Co-I Statistician Chittams, to one of 2 arms: Group 1 (laser therapy) and Group 2 (wait-list control). Randomization will be stratified by lymphedema laterality (unilateral vs. bilateral) with a 1:1 allocation, which will allow us to balance potentially important subgroups equally among the two groups.

3.1.3 Study Intervention Phase and Follow Up Phase

Group 1 (laser group): After completion of the baseline measures, Group 1 participants will be scheduled for LLLT. The LLLT includes receiving LLLT twice a week for 6 weeks (12 sessions). After completion of the 12-sessions of LLLT, participants will be given a) contact information and instructions to call for problems and b) a calendar outlining dates for the 4- and 8-week post-LLLT follow-up data collection. Group 1 participants will need to complete 4 study assessment visits.

Group 2 (wait-list control group): After completion of the baseline measures, Group 2 participants will not undergo the LLLT therapy but will complete all the same study assessments as the laser therapy group, including the baseline, 6-week after the baseline, 10-week and 14-week after the baseline assessments. After the 14-week baseline assessment, they will be offered the same LLLT sessions as the laser group. After completion of the 12-sessions of LLLT, participants will undergo the 4- and 8-week post-laser follow-up data collection. Group 2 participants will need to complete 7 study assessment visits.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

The primary endpoint will be the preliminary efficacy of LLLT in HNC survivors, including changes in severity of lymphedema using the Head and Neck Lymphedema and Fibrosis (HN-LEF) Assessment Criteria.

3.2.2 Secondary Study Endpoints

The secondary study endpoint will be the impact of LLLT on lymphedema-related symptom burden (e.g., tightness), functional impairments (e.g., range of motion in the jaw and neck), and QOL.

4 Study Population and Duration of Participation

4.1 Inclusion Criteria

- >18 years of age
- > 6 months post HNC treatment
- No evidence of cancer confirmed with imaging tests within 6 months or clinical examination by an oncologist as documented by progress note
- Having head and neck lymphedema with or without fibrosis
- Completion of initial lymphedema therapy
- Lymphedema duration between 3-36 months
- Ability to speak and read English
- Ability to provide informed consent

4.2 Exclusion Criteria

Patients will be excluded if they have any of the following medical conditions that would prohibit the safe implementation of LLLT: pregnancy; acute infection; photosensitivity; chronic inflammatory diseases; venous thrombosis; carotid artery stenosis; history of severe trauma; medication that affects body fluid and electrolyte balance; use of high doses of non-steroidal anti-inflammatory drugs; or pre-existing skin rash, ulceration, open wound in the treatment area; active lymphedema therapy or physical therapy; and allergic and other systemic skin diseases.

4.3 Subject Recruitment

The following recruitment procedures will be used: screening at HNC clinics and attendance at Head and Neck tumor boards and case conferences. All direct patient recruitment activities will be conducted at the Penn HNC clinics where private rooms are available to be used for conducting clinical research projects.

4.4 Duration of Study Participation

The duration of the study subjects' participation will be 14 weeks (laser group) – 28 weeks (wait-list control group), including screening, study intervention phase (6 weeks) and any follow-up time period.

4.5 Total Number of Subjects and Sites

Total number of subjects: 40
Total number of subjects was determined with consideration for an estimated 20% attrition rate.
Single-site study: Subjects will be enrolled at Penn only.

4.6 Vulnerable Populations

Although not directly targeted, mentally disabled persons, economically or educationally disadvantaged persons, and/or employees or students of the University of Pennsylvania will not be denied enrollment and any special protections and/or additional safeguards will be undertaken in order to protect the rights and welfare of these subjects from coercion or undue influence as appropriate.

5 Study Intervention (Study drug, device, biologic, vaccine, food, etc.)

Group 1 participants will be scheduled for LLLT.
Group 2 participants will be scheduled for the LLLT after they complete the baseline visit and 3 follow-up assessment visits.
The RianCorp LTU-904 laser therapy unit will be used for LLLT.

5.1 Description

The LTU-904 is a Class I laser device, which is a low output laser in the infrared wavelength (904nm) and no safety glasses are required as there is no risk of eye damage as defined by the standards set by the International Electrotechnical Commission.

5.2 Intervention Regimen

The LTU-904 will be used in the study. The following LLLT parameters were successfully tested and finalized through our pilot study will be used in the proposed clinical trial: 904nm wavelength in pulsed mode, 5mW output, spot size of 0.2 cm^2, and dosage (energy density) of 1.5J/cm^2.

Participants in the laser group will undergo the following procedures at each laser therapy visit. First, they will be asked to lie flat on their back on a treatment bed. The study lymphedema therapist will conduct simple manual lymph drainage in the head and neck region. Then, the trained study lymphedema therapist will mark the participant's treatment anatomical sites in the face and neck region, using a skin-safe and washable marker. A total of 12-22 spots on the face and neck will be treated. The spots include: mandible (2 points), pre auricular (1 point), submental (2 points), sternocleidomastoid muscle (3 points), supraclavicular area (2 points), and scalene muscle (2 points). The lymphedema therapist will place the laser device head vertically and lightly touch the treatment spots on the participant's face and neck region. Each spot will be treated for 60 seconds. After the laser therapy, the lymphedema therapist will help clean the patient's marks using a skin-friendly, anti-bacterial wipe. Each laser therapy session will take approximately 20-30 minutes.

Participants in the wait-list control group will undergo the same procedures for the low-level laser therapy after they complete all the study assessment visits.

5.3 Receipt

The LTU-904 will be purchased from RianCorp directly. The device will be shipped to the PI directly.

5.4 Storage

The LTU-904 unit comes with a carrying case that ensures the unit is stored safely. Both the PI Deng and the study lymphedema therapist (Joy Cohn) were trained by an expert from RianCorp directly regarding how to store, dispense, and manage the device appropriately in PI Deng's previous pilot feasibility study. The study lymphedema therapist will be responsible for storing, dispensing, and managing the laser device. The study lymphedema therapist will evaluate and monitor the LTU-904 unit regularly to ensure its normal function and prepare it for administration to subjects. The study lymphedema therapist will make sure the LTU-904 is stored properly after use of the device each time. The study lymphedema therapist will report the failed device to the PI Deng. The PI Deng will return the failed device to the manufacturer. The PI Deng will monitor the storage, delivery, management, and use of the laser device throughout the study.

5.5 Preparation and Packaging

The study lymphedema therapist will properly prepare the LTU-904 unit for administration to subjects. The study lymphedema therapist will make sure the LTU-904 is stored properly after use of the device each time.

5.6 Blinding

Not applicable.

5.7 Subject Compliance Monitoring

The participants are encouraged to be compliant with the scheduled visits. The reasons for non-compliance with the study scheduled visits will be documented and potential underlying barriers will be explored.

5.8 Screening

The screening will be conducted by a trained staff member. Individuals who are interested in this research will be screened for eligibility for being in the study. A Screening Checklist will be used to ensure that eligible participants are enrolled in the study. A Recruitment Log will be used during the recruitment.

5.9 Baseline Assessment – Visit 1

The following procedures and data collection will take place at study visit 1.

- Demographic Form
- Physical Exam for completing HN-LEF Grading Criteria
- Digital photographs of face and neck
- Modified Patterson Scale
- Symptom burden assessments (HN-LEF Symptom Inventory and NDI)
- Functional status (jaw/neck/shoulder range of motion)
- Quality of life status (EORTC QLQ-H&N35)
- Blood sample (10 cytokines)

In addition, the following variables will be abstracted from the medical chart with participants' permission.

- HNC Disease and treatment information (HNC Clinical Form)
- Lymphedema and fibrosis diagnosis and treatment information (LEF Treatment Form)

5.10 Study Intervention Phase – 6- Week Low-Level Laser Therapy

5.11 Follow-Up Assessments

5.11.1 Visit 2: Follow-Up Assessment (either End of Intervention for Group 1 or 6-week after the baseline for Group 2)

The following procedures and data collection will take place at study visit 2.

- Physical Exam for completing HN-LEF Grading Criteria
- Digital photographs of face and neck
- Symptom burden assessments (HN-LEF Symptom Inventory and NDI)
- Functional status (jaw/neck/shoulder range of motion)
- Quality of life status (EORTC QLQ-H&N35)

5.11.2 Visit 3: Follow-Up Visit (either 4 – week post laser therapy for Group 1 or 10-week after the baseline for Group 2)

The following procedures and data collection will take place at study visit 3.

- Physical Exam for completing HN-LEF Grading Criteria
- Digital photographs of face and neck
- Symptom burden assessments (HN-LEF Symptom Inventory and NDI)
- Functional status (jaw/neck/shoulder range of motion)
- Quality of life status (EORTC QLQ-H&N35)

5.11.3 Visit 4: Follow-Up Visit (either 8 – week post laser therapy for Group 1 or 14-week after the baseline for Group 2)

The following procedures and data collection will take place at study visit 4.

- Physical Exam for completing HN-LEF Grading Criteria
- Digital photographs of face and neck
- Modified Patterson Scale
- Symptom burden assessments (HN-LEF Symptom Inventory and NDI)
- Functional status (jaw/neck/shoulder range of motion)
- Quality of life status (EORTC QLQ-H&N35)
- Blood sample (10 cytokines)

5.11.4 Visit 5: Follow-Up Visit (End of Laser Therapy- Group 2 only)

The following procedures and data collection will take place at study visit 5.

- Physical Exam for completing HN-LEF Grading Criteria
- Digital photographs of face and neck
- Symptom burden assessments (HN-LEF Symptom Inventory and NDI)
- Functional status (jaw/neck/shoulder range of motion)
- Quality of life status (EORTC QLQ-H&N35)

5.11.5 Visit 6: Follow-Up Visit (4 – Week post laser therapy – Group 2 only)

The following procedures and data collection will take place at study visit 6.

- Physical Exam for completing HN-LEF Grading Criteria
- Digital photographs of face and neck
- Symptom burden assessments (HN-LEF Symptom Inventory and NDI)
- Functional status (jaw/neck/shoulder range of motion)
- Quality of life status (EORTC QLQ-H&N35)

5.11.6 Visit 7: Follow-Up Visit (8 – Week post laser therapy– Group 2 only)

The following procedures and data collection will take place at study visit 7.

- Physical Exam for completing HN-LEF Grading Criteria
- Digital photographs of face and neck
- Modified Patterson Scale
- Symptom burden assessments (HN-LEF Symptom Inventory and NDI)
- Functional status (jaw/neck/shoulder range of motion)
- Quality of life status (EORTC QLQ-H&N35)
- Blood sample (10 cytokines)

5.12 Subject Withdrawal

Subjects may withdraw from the study at any time without impact on their care. They may be discontinued from the study at the discretion of PI Deng, due to lost follow-up or adverse events. Subjects may also be withdrawn by PI Deng from the study given safety consideration.

6 Statistical Plan and Statistical Analysis

While this study is a preliminary study of efficacy and effect sizes, a maximum alpha level of 0.05 will be used for the statistical tests.

Aim 1 and Aim 2: Preliminary Efficacy of the Intervention. All of the measures used for estimates of efficacy are continuous in scale. Mixed effects and generalized estimating equation (GEE) models, with the generalized linear modeling framework with the appropriate link function for the nature of the specific

outcome variable being analyzed, will be used to generate estimates of the effect of the intervention on the severity of lymphedema, symptom burden, function status, and QOL.

Exploratory Aim: Inflammatory Biomarkers. Inflammatory biomarkers will be analyzed using methods identical to those described for aims 1 and 2.

7 Safety and Adverse Events

8.1 Safety Monitoring

The following strategies will be in place to monitor the safety of participants during the course of the study.

During the course of this study, study staff will monitor any adverse side effects or events when interacting with participants and be trained to report these to the PI's immediately. Common Terminology Criteria for Adverse Events (CTCAE v5.0) will be used to document adverse events of the trial. All of the staff members who are involved in this study will be trained by the PI Deng on how to use CTCAE v5.0.

In addition, participants in this study will be screened against the inclusion and exclusion criteria. Participants will be educated regarding signs and symptoms related to adverse events (e.g., sudden increase in swelling) requiring urgent or emergent medical care.

8.2 Recording of Adverse Events

During each contact with the subject, the trained staff will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document.

All adverse events will be reviewed by PI Deng and Study Physicians Lin/Lukens (Co-Is), and the Medical Monitor, Dr. Sunita Nasta (see 8.6 Medical Monitoring section), any contributing factors will be reviewed, and strategies to prevent further complications will be developed and implemented. Dr. Deng will meet with the study staff monthly to evaluate any other safety concerns. Adverse events will be reported to the Penn IRB within the window required by the IRB. If the study staff identify the following unanticipated problems related to the research (e.g., infection in the treated area, sudden increase in swelling), which occur during the study, Drs. Deng, Lin/Lukens, and study lymphedema therapists, as well as the Medical Monitor, Dr. Nasta, will be notified immediately. Patients will be referred and receive appropriate and timely treatment. Deng and Lin/Lukens will determine if participants with adverse events or any unexpected issues will remain on the study based on safety considerations. Deng and Lin/Lukens as well as the Medical Monitor, Dr. Nasta, will evaluate the relationship of each adverse event to the study procedures. Deng, Lin/Lukens, and the Medical Monitor, Dr. Nasta, will make the determination of the relationship of the adverse event to the study procedures (e.g., definitely related, probably related, possibly related, unlikely or unrelated).

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

8.3 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems to Penn IRB and ACC

PI Deng and the study team will conform to the adverse event reporting timelines and formats, per the Penn IRB reporting requirements and Abramson Cancer Center reporting guidelines.

The following information will be included at the time of the initial report:

- Study identifier
- Study site
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as adverse events
- Investigator assessment of the association between the event and study intervention

Additionally, all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints) will be recorded and reported with respect to Penn policies as described in the Penn Manual.

8.3.1 Investigator reporting: notifying the study sponsor

Not applicable. The study has no external sponsor.

8.4 Unblinding Procedures

Not applicable.

8.5 Stopping Rules

We do not anticipate significant adverse events. Given no safety data available in the population under study, the research may involve risks that are currently unforeseeable. If any one event is identified that may have caused any type of harm to a participant, study recruitment and associated study activities will be immediately halted until the Medical Monitor, Dr. Nasta, and the study team review the event and determine if any study procedures need to be revised. Study recruitment and associated study activities will only resume after review of the study protocol has been completed and any recommended revisions made as advised by both the Medical Monitor, Dr. Nasta, and the Penn IRB.

8.6 Medical Monitoring

Dr. Sunita Nasta has agreed to be the Medical Monitor for the proposed project. This person is not directly involved in the trial and is not collaborating with the investigators in any other trials. In this role, Dr. Nasta will review all AEs including grading, toxicity assignments, and all other safety data and activity data observed in the trial. Dr. Nasta may recommend reporting of adverse events and relevant safety data not previously reported and may recommend suspension or termination of the trial.

8.6.1 Data and Safety Monitoring Plan

The data and safety monitoring plan will adhere to policy guidance and standards set by the Penn IRB. The PI Deng will be responsible for monitoring the entire study. The Medical Monitor, Dr. Nasta, will provide oversight for this trial.

Data Management: 1) Self-reported questionnaires will be completed by participants using a tablet to enter their responses into REDCap. The research assistant will review participants' completeness for each questionnaire. If participants prefer, or if there are technical difficulties, hard copy forms will be used. All hard copy data will be double-entered into REDCap, checked for discrepancies, and reconciled with hard copy forms. All forms will be stored in a secured cabinet. 2) Physical examination data collected by the study staff will be entered by the research assistant into REDCap. These data will also be double-entered, checked for discrepancies, and reconciled with the hard copy form. 3) Imaging data (digital photos) will be deidentified (white-out eyes) and only scoring data will transfer out to REDCap. Data from various sources will be integrated into the study databases by the Data Specialist. All data will be coded without any identifiable information. The PI Deng and the data specialist will monitor and ensure that all data are timely entered into the databases and all protocol specifics are met. PI Deng will monitor all databases monthly and maintain a master table that links participants to ID numbers in a password-protected database on a secure server throughout the study and after the close of the study.

Monitoring by the PI: PI Deng, with assistance from the Co-Is Lin/Lukens, the study lymphedema therapists, and other study staff members, will monitor all of the study activities to ensure safety of participants and integrity of the data collection and management. The research team will meet monthly to discuss recruitment, retention, study progress, and any safety concerns. Any potential issues related to the study activities will be discussed and addressed appropriately and timely. Participants will be educated regarding signs and symptoms related to adverse events requiring urgent or emergent medical care. All adverse events will be documented using CTCAE criteria, reviewed by Deng, Lin/Lukens, and the Medical Monitor, Dr. Nasta. Any contributing factors will be reviewed. Strategies to prevent further complications will be developed and implemented. Although adverse events are highly unlikely, should they develop, they will be reported to the Medical Monitor immediately and to the Penn IRB within the required time window.

8.7 Data Safety Monitoring Board

Not applicable.

8 Study Administration, Data Handling and Record Keeping

8.1 Confidentiality

All of the study data will be stored in a secured network drive managed by University of Pennsylvania School of Nursing IT staff member. All participants will be assigned a study ID number (e.g., 300). Numbers will be assigned by trained study staff. It is important and necessary for the study team to know participants' names in order to communicate with them during the study. This information will be maintained in a participant tracking database that is not stored on the hard drive, accessible only to the study team members through a password protected computer, and linked to a Penn School of Nursing server that is accessible only the study team. The name column will be deleted at the end of the study.

8.2 Data Collection and Management

Data collection will be conducted by a trained staff member in a private room at the Abramson Cancer Center (ACC) HNC clinics (participant recruitment) and at the Penn Nursing Biobehavioral Lab (baseline and follow-up data collection, as well as the low-level laser therapy). The following procedure will be utilized to protect the privacy of the research participant. All data will be coded and filed without any names or other identifiable information. Self-reported questionnaires will be completed by participants using an encrypted and secured tablet to enter their responses into REDCap. The research assistant will review participants' completeness for each questionnaire. If participants prefer, or if there are technical difficulties, hard copy forms will be used. All hard copy data will be double-entered into REDCap, checked for discrepancies, and reconciled with hard copy forms. All hard copies will be placed in a locking file cabinet. Only the study team has access to the file cabinet and electronic database. After the study is concluded, the research data will be stored at Penn School of Nursing.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

Monitoring by the PI: The PI Deng, with assistance from the Co-Is Lin/Lukens, the study lymphedema therapists, and other study staff members, will monitor all ~~the~~ study activities to ensure safety of participants and integrity of the data collection and management. The research team will meet monthly to discuss recruitment, retention, study progress, and any safety concerns. Any potential issues related to ~~the~~ study activities will be discussed and addressed appropriately and timely. Participants will be educated regarding signs and symptoms related to adverse events requiring urgent or emergent medical care. All adverse events will be documented using CTCAE criteria, reviewed by Deng, Lin/Lukens, and the Medical Monitor, Dr. Nasta. Any contributing factors will be reviewed. Strategies to prevent further complications will be developed and implemented. Although adverse events are highly unlikely, should they develop, they will be reported to the Medical Monitor immediately and to the Penn IRB, within the required time window.

9.2 Auditing and Inspecting

PI Deng will permit study-related monitoring, audits, and inspections by the Medical Monitor, the Penn IRB, government regulatory bodies, and University compliance and quality assurance groups of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc.).

10 Ethical Considerations

Although this is an interventional study, foreseeable physical, psychological, financial, legal, or other risks from study participation are believed to be minimal.

10.1 Risks

1) Physical: LLLT will be used in the trial. No physical risks (e.g., worsening lymphedema or fibrosis) from using LLLT in individuals with breast cancer-related lymphedema have been reported in the known current literature review. No physical risks from using LLLT were reported in the case studies conducted in individuals with head and neck lymphedema. Subjects will not have any burning sensation, warmth, or any other uncomfortable sensations on the sites treated with low-level laser. Currently, there is no safety data in the population under study. Thus, we will inform participants of reporting any physical damages they have during the course of the study.

2) Psychological: There are no known psychological risks associated with LLLT.

3) Financial: The LLLT will be provided free of charge. Patients may incur gas expenses when driving to the Penn Clinic.

4) Legal: There are no known legal risks.

5) Other: There may be risks that are unknown at this time.

Our planned protections from the above-noted risks are as follows:

1) Physical: Currently, there are no known potential physical risks for being in this study. Given no safety data available in the population under study, the research may involve risks that are currently unforeseeable. To minimize any potential physical risks, the following will be done: a) Participants will be given the study contact phone numbers and emails to ask any questions or to report any unexpected problems if the problems are directly related to the study activities; b) if study staff identify any unanticipated problems, Deng, Lin/Lukens, and study lymphedema therapists, as well as the Medical Monitor, Dr. Nasta, will be notified immediately. Appropriate evaluation and timely therapy will be provided to the participant. Deng, Lin/Lukens, study lymphedema therapist, and the Medical Monitor will determine if participants with significant unanticipated issues will remain on the study based on safety consideration; and c) if anyone experiences an adverse event directly related to the study activities that are done for research, they can get reasonable, immediate, and necessary medical care for their adverse events at Penn.

2) Psychological: If study staff identifies participants with significant distress during the course of the study, PI Deng, Co-Is Lin/Lukens, and the Medical Monitor, Dr. Nasta, will be notified immediately so that appropriate psychological evaluation and referrals will be made. Deng, Lin/Lukens and the Medical Monitor, Dr. Nasta, will determine if participants with significant psychological issues will remain on study.

3) Financial: The LLLT will be provided free of charge. Patients will incur the expense of gas when driving to the Penn Clinic during study follow-up visits. To offset travel/gas cost, participants will be provided a financial token of appreciation for participation in the study.

4) Legal: There are no known legal risks.

5) Other: Should the team become aware of any additional risks, participants will be notified, and informed consents will be modified to reflect the new information.

10.2 Benefits

Potential benefits to the individual: Although the potential direct benefit to study participants is unknown, individual participants will be exposed to and have increased knowledge about lymphedema and fibrosis. Participants may have positive feelings about participation in a research program that may benefit others.

Potential benefits to humankind: Possible future benefits for HNC survivors are potentially substantial. If we are able to demonstrate that LLLT is safe, feasible, and effective in HNC patients, we will be adding to the armamentarium of an alternative intervention that can diminish the progression of lymphedema and fibrosis, decrease symptom burden, increase function, and improve overall quality of life.

10.3 Risk Benefit Assessment

Currently, there are no known potential risks for being in this study. Given no safety data available in the population under study, the research may involve risks that are currently unforeseeable.
As noted above, potential benefits are reasonable and substantial. Thus, based on the risk benefit assessment, it appears to be acceptable for this research within human subjects.

10.4 Informed Consent Process / HIPAA Authorization

Once the study is approved by the Penn IRB and the ACC, the trained study team members will meet with potential participants who express interest in the study. Potential study participants will be provided one copy of the informed consent to read and review. Study team members will review the study procedures and activities with potential participants. The informed consent document will be written in lay language and cover all study activities participants will engage in during the study, define the length of time the study will be conducted, and provide instructions for participant withdrawal from the study should they choose to do so. Study staff will review and, when necessary, read the informed consent document to potential participants. Participants will be given ample time and opportunity to ask questions, and all questions will be answered by study staff. The consent process will take place in a private location, with a closed door. Once participants have had an opportunity to ask questions, those questions have been answered, and they indicate an interest in participation, they will be asked to sign a written informed consent document as the study staff witnesses. In addition, the participant will be given a copy of informed consent signed by both the participant and study staff. We will not seek waivers of the informed consent process.

11 Study Finances

11.1 Funding Source

Abramson Cancer Center Early Phase Clinical Research Support (ACC EPCRS).

11.2 Conflict of Interest

All of the team members will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

11.3 Subject Payments

All participants will be provided with a financial token of appreciation.

For participants in Group 1, if they complete all the study related activities, they will be paid $135 in total

For participants in Group 2, if they complete all the study related activities, they will be paid $240 in total

12 Benchmarks for Study/Publication Plan

The key benchmark for success of this study is to complete recruitment goals and data collection as scheduled. The information gathered from this study will provide important data for designing a future RCT that tests the efficacy of LLLT on lymphedema in the HNC survivors. Additional benchmarks for success include: 1) dissemination of preliminary findings at professional conferences and 2) submission of articles to peer-reviewed journals.