INTERVENTIONAL
RESEARCH PROTOCOL

STUDY INFORMATION

- **Title of Project:** *Healthy ME*: Advancing **Health** Equit**y** in Lymphatic Pain and Lymphedema in Black and Hispanic Wo**me**n with Breast Cancer
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ABSTRACT

PURPOSE/SPECIFIC AIMS The purpose of this project is to adapt The-Optimal-Lymph-Flow (TOLF) behavioral intervention to be culturally appropriate, and subsequently test the intervention in Black and Hispanic patients. Our team has developed and tested behavioral intervention program TOLF that builds patients' self-management skills to promote lymph flow and results in complete pain reduction, reduced lymph fluid level, reversed mild lymphedema, and improved quality of life (QOL). Of concern, this promising intervention has not been adapted to reduce patient barriers (e.g., relevance, cost, time, travel, competing demands) and system barriers (e.g., intervention availability, staffing, therapist) to timely interventions faced by Black and Hispanic women. Specific aims are to:

Aim 1: Engage Black and Hispanic women (N=24) in adapting TOLF to be highly culturally appropriate. We will conduct focus groups to refine TOLF focusing on barriers faced by and preferences of Black and Hispanic women.

Aim 2: Conduct a pilot randomized controlled trial (RCT) (N=60) equally allocating women to either 1) TOLF or 2) lymphedema education (e-Lymph) to examine feasibility, acceptability, and examine primary outcomes (lymphatic pain, pain severity and interference, and lymph fluid level) and secondary outcomes (daily living function, psychological distress, QOL, self-efficacy for pain management) of the culturally appropriate behavioral interventions.

RATIONALE/SIGNIFICANCE OF THE STUDY. Lymphatic pain refers to pain, aching or soreness in the ipsilateral body or upper limb following breast cancer treatment. More than half of the 3.8 million women with breast cancer suffer lymphatic pain which leads to impaired daily living function, psychological distress, and compromised QOL. Most importantly, lymphatic pain is significantly associated with lymphedema, a chronic and incurable condition caused by an abnormal accumulation of lymph fluid. Black and Hispanic women are three times as likely to suffer from lymphedema compared to White women. Timely intervention for lymphatic pain can decrease the risk and severity of lymphedema. However, there are persistent barriers to timely interventions faced by Black and Hispanic women with breast cancer – a group at high risk for developing lymphedema, pain, and other negative breast cancer related outcomes.

THEORETICAL FRAMEWORK. Self-efficacy theory guides the project. Behavioral pain interventions focus on training patients on self-management skills to be implemented in their daily lives.

MAIN RESEARCH VARIABLES. Behavioral pain intervention (IV), Outcomes (DVs): lymphatic pain, pain severity and interference, lymph fluid level, daily living function, psychological distress, QOL, self-efficacy for pain management.

DESIGN. Qualitative and randomized clinical trial (RCT)

SETTING. All participants will be recruited from UMKC University Health and surrounding communities.

SAMPLES. Black and Hispanic women with lymphatic pain

METHODS. Focus groups will be conducted with Black and Hispanic women to gather data that will lead to culturally appropriate adaptation of TOLF. Then, a pilot RCT will be used to examine feasibility, acceptability, and evidence of future efficacy of this culturally adapted intervention.

IMPLICATIONS FOR PRACTICE. The successful completion of the project will advance health equity in pain and lymphedema by making this culturally appropriate, highly accessible, and effective behavioral intervention available to Black and Hispanic women.

1.0 Research Design

1.1 Purpose/Specific Aims

Lymphatic pain affects more than half of 3.8 million women treated for breast cancer in the United States.[1-4] Lymphatic pain significantly compromises patients' daily living function,[2] increases psychological distress,[5] and decreases quality of life (QOL).[6-7] Lymphatic pain refers to various pain (e.g., aching or soreness) in the ipsilateral body or upper limb due to a compromised lymphatic system from breast cancer treatment.[2-4] Lymphatic pain is significantly associated with lymphedema,[2-5] a chronic and incurable condition caused by an abnormal accumulation of lymph fluid in the ipsilateral body or upper limb.[8] **Black and Hispanic women are three times more as likely to suffer from lymphedema compared to White women following breast cancer treatment.**[9-10] High rates of lymphedema and lymphatic pain in Black and Hispanic women are partially due to health inequities as these groups are more likely to be diagnosed with advanced stages of cancer leading to more aggressive treatments.[11-12] Effective management of lymphatic pain can decrease the risk of developing lymphedema and lessen lymphedema severity.[13-18] However, there are persistent barriers to timely interventions faced by Black and Hispanic patients – a group at high risk for developing lymphedema, pain, and other negative cancer related outcomes.[9-12] Ethnic disparities in offering interventions after pain complaints and financial hardship are identified barriers.[2,9-12] The proposed work aims to decrease health inequities in lymphatic pain intervention in Black and Hispanic women with breast cancer and ultimately decrease the development of and lessen the severity of lymphedema, a chronic and debilitating illness for these women.

We have developed and tested in largely White patients a non-pharmacological, behavioral intervention, The-Optimal-Lymph-Flow (TOLF) that builds patients' self-management skills to promote lymph flow and results in complete pain reduction, reduced lymph fluid level, reversed mild lymphedema, and improved QOL.[13-21] Of concern, this promising intervention has not been adapted to reduce patient barriers (e.g., relevance, cost, time, travel, competing demands) and system barriers (e.g., intervention availability, staffing, therapist) to timely interventions faced by Black and Hispanic women. The purpose of this two-phase project is to adapt The-Optimal-Lymph-Flow (TOLF) a non-pharmacological, behavioral intervention to be culturally appropriate, and subsequently test the intervention in Black and Hispanic patients. We will recruit study participants from UMKC University Health. Women of minority are more likely to have comorbid health problems (e.g., obesity/high body mass index [BMI]) and financial hardship;[2,11-12;25-28] which are risk factors for lymphatic pain and lymphedema.[2-3;30-32] Based on prior research and our preliminary studies,[3-18] our **central hypothesis** is that lymphatic pain increases the risk of lymphedema and behavioral intervention can reduce pain and lymph fluid level to prevent lymphedema. Our group is **uniquely qualified** to lead this project due to our expertise in lymphedema, lymphatic pain, health disparity, breast cancer, pain and cancer-related symptoms, and the clinical volume of Black and Hispanic patients with breast cancer at our center. Guided by self-efficacy theory,[33-34] the specific aims of this two-phase project are to:

Aim 1: Engage Black and Hispanic women (N=24) in adapting TOLF to be highly culturally appropriate. We will conduct focus groups to refine TOLF focusing on barriers faced by and preferences of Black and Hispanic women.

Aim 2: Conduct a pilot randomized controlled trial (RCT) (N=60) equally allocating women to either 1) TOLF or 2) lymphedema education (e-Lymph) to examine feasibility, acceptability, and examine primary outcomes (lymphatic pain, pain severity and interference, and lymph fluid level) and secondary outcomes (daily living function, psychological distress, QOL, self-efficacy for pain management) of the culturally appropriate behavioral interventions.

Impact. Our project has the potential to have a major impact on reducing cancer-related disparities (lymphedema, pain, QOL) among Black and Hispanic women. The project will also build clinical capacity to provide quality care for lymphatic pain and lymphedema prevention for women living in environmental justice communities. By focusing ethnic disparities in offering behavioral interventions to Black and Hispanic

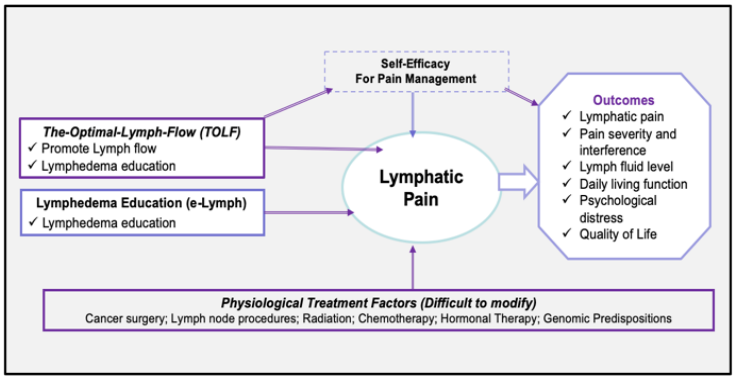
women, adapting and testing interventions for culturally sensitive care, this project addresses ONS Research Agenda Priority of Cancer Health Disparities and Promote Equity in Oncology Healthcare Access.

1.2 Research Significance

Lymphatic pain is a cardinal sign for an early stage of lymphedema.[35-37] Patients who report lymphatic pain are nearly twice as likely to develop lymphedema.[4] Without timely intervention in this early stage, lymphedema can progress into a chronic condition that no surgical or medical interventions can cure.[8] In addition, lymphatic pain and lymphedema significantly impact patients' daily living function,[2,38-39] psychological distress,[5] and QOL.[40-41] *The burden from lymphatic pain and lymphedema and can be even higher for Black and Hispanic women.* Studies show that women of racial minority background experience delays in breast cancer treatment and/or inadequate treatment.[10-12;42-45] Later stage diagnosis and delayed treatment lead to high risk of lymphedema and pain due to the needs to have more aggressive surgical treatment, more lymph nodes removed, and radiation.[9-12] Further, women of minority are more likely to have comorbid health problems (e.g., obesity), [2,11-12;25-28] the risk factor for lymphatic pain and lymphedema.[3;31-34] Women with financial hardship are 4.64 times more likely to report lymphatic pain.[2] Our recently published study detailed that patients with lymphatic pain reported impairments in 45% of ADLs and had a significantly increased risk of having difficulty in performing all the 13 ADLs (i.e., cooking, using a knife, writing/typing, cleaning, vacuuming, laundry, carrying objects, yard work, dressing self, bathing self, driving, making bed, and taking care of children).[2] Patients' psychological distress was further compounded when they felt that clinicians did nothing but "pity me."[5] Disparities among women with breast cancer in environmental justice communities are maintained by a lack of cost-effective, accessible, and appropriately adapted supportive care opportunities found at more resourced medical centers.[43-44] This results in a large symptom burden (i.e., lymphatic pain,) for patients, providers, and healthcare systems.

1.3. Theoretical Framework

Self-efficacy theory guides the proposed project.[33-34] Behavioral interventions for managing lymphatic pain and lymphedema prevention focus on building patients' self-management skills to be implemented in their daily lives outside clinical settings without professionally administered therapy (e.g., by therapists or nurses).[14-17] To achieve the therapeutic effects, patients have to execute self-management skills outside of clinical settings. Self-efficacy is defined as a person's belief in his/her ability to perform specific skills to reduce lymphatic pain and to prevent lymphedema. (See Adjacent **Figure**).



1.4. Review of Literature

State-of-the-Art for Lymphatic Pain and Lymphedema Prevention. Behavioral strategies are commonly used for pain control in cancer patients.[50-53] Pharmacologic interventions, such as NSAIDS, opioids, antiepileptics, ketamine and lidocaine, have very limited effects on pain;[8,46-49] Very limited RCTs were designed to build patients' self-management skills to manage lymphatic pain, a major predictor for lymphedema, impaired daily living function, psychological distress, and poor QOL.[2-5] Majority of RCTs were devoted to lymphedema treatment administered by professional therapists, such as Complete Decongestive Therapy (CDT), compression garments and bandaging, pneumatic pumps, or supervised physical therapy.[50-52] The cost and time to attend therapist-administered treatments, the potential harm by the poor fit of compression sleeve, and patients' unwillingness to wear and cost for compression sleeve remain wide-spread challenges for patients. These challenges can be even more impactful for Black and Hispanic patients who face personal barriers (e.g., time, travel, competing demands, cost) and system barriers (e.g., treatment availability, staffing, therapist).

***Behavioral Interventions Are Efficacious in Treating Lymphatic Pain*.** Lymphatic pain is associated with increased lymph fluid accumulation,[2-4] and inflammatory responses.[39-41] Limited research tested integrative behavioral interventions based on physiological (lymph fluid accumulation and inflammation) and cognitive principles (low self-efficacy). We have developed and extensively tested a non-pharmacological, behavioral *The-Optimal-Lymph-Flow* (TOLF) intervention that includes strategies to promote lymph flow: therapeutic lymphatic exercises, healthy diet (i.e., nutrition-balanced, portion-appropriate diet, adequate hydration), and proper sleep.[13-21] The core TOLF intervention is 8-minute TOLF lymphatic exercises to promote lymph flow (i.e., muscle-tightening deep breathing, muscle-tightening pumping, and limb mobility exercises).[13] TOLF includes a website that provides patients with TOLF intervention materials, information, and daily assessments used to personalize sessions.[13-21] One dose of TOLF lymphatic exercises can produce immediate significant effects on reductions in pain, swelling, and reduction in lymph fluid levels.[13] Our recent publish RCT demonstrated that 50% of patients who received TOLF intervention achieved a complete pain reduction (50% vs 22%; OR=3.56, *CI* = [1.39, 9.76], p=0.005) compared to control of 22%.[14] Given TOLF is efficacious, focusing on self-management skills, having immediate therapeutic effects, and welcomed by patients (only 6% attrition), TOLF may provide particular benefits for Black and Hispanic patients who face personal challenges of time, travel, competing demands, cost for therapist-administered treatment. In addition, technologically-driven delivery model makes it easy for community-level implementation to address system barriers of intervention availability, staffing, therapist.

1.5. Innovation

This project is innovative for multiple reasons. **1)** This will be the first study to address ethnic disparities and system barriers (e.g., intervention availability, staffing, therapist) in offering behavioral interventions to Black and Hispanic women with lymphatic pain to prevent lymphedema by adapting efficacious, non-pharmacological, behavioral interventions to be culturally appropriate, and subsequently test the interventions in Black and Hispanic patients. **2)** The project is innovative in disrupting place-based health disparity and social determinants of health on lymphatic pain and lymphedema prevention. There is an increased urgency for completing the proposed project in the population of interest rather than hoping to recruit "enough" Black and Hispanic participants to examine disparities. Our ongoing community engagement, our geographic location, and our current and prior successful experiences[25-26] with patients in environmental justice communities enable us to engage Black and Hispanic patients in these hard-to-reach settings. **3**) The use of technologically-driven intervention delivery not only enhances the fidelity and transparency of the interventions but also the reproducibility of the interventions, which may enhance the generalizability and dissemination of the interventions. **4)** This project is innovative in addressing major personal barriers (e.g., cost, time, travel, competing demands) faced by Black and Hispanic patients. For example**,** the adaption of the daily 8-minute TOLF lymphatic exercises, which is effective even with one dose[13] and easy for patients to implement it;[13-18] in turn, it addresses barriers of limited time and competing demands faced by Black and Hispanic women. **5)** Because previous research found that traditional measures of ADLs (i.e. toileting, ambulation, continence, and feeding) are less relevant to women with breast cancer,[2,5,38-41] the breast cancer specific measures of ADLs is another innovation.[2,38] **6**). The proposed intervention is cost-effective and sustainable (e.g., by intervening in the health system and reducing the reliance on pain medication and medical intervention). Thus, our project provides a unique opportunity to provide empirical evidence and generate knowledge to advance health equity in lymphatic pain and lymphedema prevention.

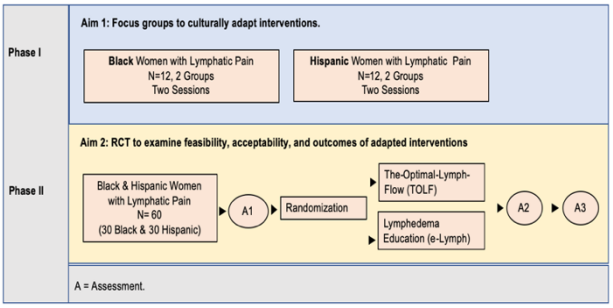
1.6. Preliminary Work and Research Team

Dr. Mei Rosemary Fu (The Dorothy and Dale Thompson Missouri Endowed Professor in Nursing and Associate Dean for Research) is a well-established nurse scientist who is well-positioned to lead the project as the PI. Dr. Fu is one of very few researchers who has had funded work on lymphedema, pain and symptoms related to lymph fluid accumulation, and developing non-pharmacological behavioral interventions to prevent lymphedema and pain following breast cancer treatment (F31 NR07851, 1R21NR012288-01A1, P60 MD000538-03 [Pilot PI], 1R01CA214085-01 [Multiple PI], Oncology Nursing Foundation, 13371953 The-Optimal Lymph-Flow Pfizer Independent Grants for Learning & Change, Avon

Breast Cancer Research Grant 02-2008-077). She has led multiple projects on lymphedema and pain and from which this proposed study is built upon.[2-5,13-21,35-36;38] Dr. Fu also has extensive and published experience working with minority patients and residents in environmental justice communities;[25-26,53-54] such experience will ensure the success of the project. Dr. Fu has established a strong collaboration within the University Missouri communities and nursing team with whom Dr. Fu has worked closely on the proposed project (co-investigators: Drs. Cynthia L. Russell Lippincott, Sue Lasiter, Elizabth Ann Anderson, and Steven Chesnut). We have a strong research team with rich research experience in developing and testing behavioral interventions in women with breast cancer and health disparities.

1.7. Research Design and Methods

Design. This two-phase project uses qualitative (i.e., focus group) and pilot randomized clinical trial (RCT) design to adapt TOLF to be culturally appropriate, and subsequently test the intervention in Black and Hispanic patients. (See Adjacent Figure for study design.)



Sample. The participants are Black and Hispanic women (over age 18) with lymphatic pain following breast cancer treatment. These women will be recruited for the **Phase I focus groups** (N=24), and **the Phase II** RCT (N=60). Participants will include women who **1)** have received surgical treatment for breast cancer at least 3 months prior to the study enrollment, **2)** report persistent or intermittent pain/aching/soreness in the ipsilateral body or upper limb; **3)** self-identify as either Black or Hispanic; and **4)** are able to understand the study protocols presented in English. Exclusion criteria include: **1)** presence of a serious psychiatric condition (e.g., schizophrenia, suicidal intent) indicated by medical chart, treating oncologist or other staff, or study staff interactions that would contraindicate safe study participation; **2)** known metastatic disease (Stage IV), recurrence of cancer, or lymphedema due to cancer recurrence, or other bulk disease in the thoracic or cervical regions; **3)** were diagnosed or treated for lymphedema.

Setting. All participants in the proposed work will be recruited from UMKC (University of Missouri-Kansas City) Health System and Kansas City Metropolitan eastside communities, which is recognized as the fifth most economically and racially segregated city in the U.S. Black and Latino individuals in Kansas City, Missouri (KCMO) die up to 18 years earlier than White individuals. Majority of breast cancer patients are Black and Hispanic and rely on Medicaid and Medicare for health insurance. Drs. Lippincott, Lasiter have strong collaboration with University Health and will be responsible for the recruitment.

Recruitment. Our team consists of experienced clinical trials investigators with extensive histories of successful recruitment. We will use electronic medical records (EMR), tumor registry information, and clinic staff to identify potential trial participants. The clinical research coordinator will send an email to the treating oncologist to alert them of potential participants. Participating oncologists will alert the study team if there is a known psychotic disorder, suicidal intent, or other conditions that would contraindicate safe study. Potential participants will be mailed a letter or an email or a phone call from their provider or the research study team with study information. The communication will let the patient know that a member of the study team will call them to follow-up; an opt-out phone number will also be provided. Following recruitment communication, study staff will contact potential participants to assess interest in the study and to conduct pre-screening. If patients meet eligibility criteria, they will be invited to schedule informed consent in-person or via telephone. <u>All participants will continue to receive routine standard medical care from their medical team.</u> The study team will closely track participant recruitment; additional clinics will be quickly implemented if recruitment has not been met at 90% in any 3-month period.

Phase I Focus Groups. The TOLF intervention will be adapted to be culturally-appropriate using input from Black and Hispanic women with lymphatic pain (N=24; 2 groups: Black [n=12] and Hispanic [n=12]). To our

knowledge, this is the first study to systematically adapt efficacious behavioral interventions for Black and Hispanic women with lymphatic pain. To adapt the interventions, we will use qualitative data gathered during focus groups held separately with Black and Hispanic patients. Semi-structured interview guides will be used to facilitate focus groups; we have drafted a focus group discussion guide. The group leaders (Drs. Lippincott, Anderson, and Lasiter, co-investigators) will guide the discussion. The interview guides will be reiterated following each group to attend to themes of previous groups. The aim of the focus groups is to better understand the needs and preferences of the Black and Hispanic women with lymphatic pain. Each Black and Hispanic woman will participate in two sessions of focus group. In Session I, Black and Hispanic women will be systematically presented with the content of TOLF and be asked to provide their opinions on the content, the current patient handouts, and how to modify the handouts, the intervention format (e.g., in-person, web-based, telehealth conferencing, timing of interventions, length of the intervention). Participants will be asked to practice TOLF self-management skills for a week before Session II. Session II will focus on barriers in implementing TOLF self-management skill to further refine the interventions. All focus groups will be 60 minutes long and audio recorded. Our team has extensive experience conducting qualitative interviews and focus groups, as well as a using focus groups to inform intervention adaptation and development.[5,25-26,53,58]

Intervention/Independent Variables. ***Phase II RCT Randomization and Conditions.*** In Phase II RCT, a total of 60 participants will be recruited consisting of 30 Black and 30 Hispanic patient participants, respectively. Following baseline assessment, 30 Black and 30 Hispanic patient participants will be randomly assigned with equal allocation to one of two conditions: 1) TOLF (Intervention), or 2) e-Lymph (Control). e-Lymph includes training sessions on the lymphatic system, lymphedema, lymphedema diagnosis and measurement, risk of lymphedema. The major goals of skill training sessions for TOLF and e-Lymph are described in **Table 1**. Randomization will be blocked by ethnicity to ensure reasonable balance in each treatment condition. The data manager on this study who is not involved with recruitment will randomly draw a number of 1, or 2 to be given the participant's study number (not name) to randomize the participant. Our research evaluator will not be involved in recruitment or have other contact with participants; she/he will be blinded to participant randomization and conduct all study procedures where blinding is indicated (e.g., assessments). All efforts will be made for study staff and oncologists to be blinded to participant condition.

Table 1. Overview of Session Skills for TOLF and e-Lymph

Patient Sessions	The-Optimal-Lymph-Flow (TOLF)	Lymphedema Education (e-Lymph)
1 In-person (40 minutes)	▪ In-person learning the Importance of promoting lymph flow ▪ In-person training and practicing lymphatic exercises using Kinect-TOLF ▪ Learning on lymphatic system, lymphedema, lymphedema diagnosis and measurements ▪ Home practice planning	▪ In-person learning on lymphatic system, lymphedema, lymphedema diagnosis and measurements
2 Virtual (20 minutes)	▪ Home practice review ▪ Learning the importance of large muscle exercises to promote lymph flow ▪ Home practice planning for large muscle exercises (e.g., walking, running, dancing, yoga) 3 times per week for 30 minutes ▪ Home practice planning	▪ Home review ▪ Questions and Answers
3 Virtual (20 minutes)	▪ Home practice review ▪ Learning the importance of weight for lymph flow ▪ Planning for healthy diet and sleep hygiene ▪ Home practice planning	▪ Home review ▪ Questions and Answers
4 Virtual (20 minutes)	▪ Home practice review ▪ Planning for maintenance of all learned skills	▪ Home review ▪ Questions and Answers
Program Materials	TOLF materials include information about the lymphatic system, lymphedema, lymphedema diagnosis and measurement, risk of lymphedema, healthy diet, sleep hygiene, and daily therapeutic lymphatic exercises training and videos; participants will be granted access to all of the materials in TOLF website. A workbook with worksheets and pencil will be given to participants for recording.	e-Lymph materials include information about the lymphatic system, lymphedema, lymphedema diagnosis and measurement, risk of lymphedema; participants will be granted access to the e-Lymph materials on TOLF website.

The-Optimal-Lymph-Flow (TOLF). TOLF includes training sessions on the lymphatic system, lymphedema, lymphedema diagnosis and measurement, risk of lymphedema, healthy diet, sleep hygiene, and daily lymphatic exercises. It has 8 avatar videos with step-by-step instructions for TOLF lymphatic exercises to promote lymph flow. In Phase I, Aim 1 will adapt the intervention to be culturally sensitive, some changes are expected in the final intervention protocol. It is expected that participants will complete initial in-person or telehealth virtual 40-minute session, and 3 virtual telehealth sessions with each session for 20-minute over the course of 8 weeks. In initial in-person session, the participant will be trained to

practice lymphatic exercises using Kinect-Enhanced TOLF training system, which is a smart AI (artificial intelligent) training system to ensure patients practice lymphatic exercise correctly.[13] For the telehealth sessions, the participant and interventionist will complete a session once the telehealth session has been connected. For 8-week study duration, participants in TOLF will be asked to practice lymphatic exercises twice a day. They will also be directed to use the strategies presented in the program and review the strategies periodically on the website. A workbook will be provided to record practice of the daily lymphatic exercises and large muscle exercises. The sessions will be scheduled bi-weekly with some flexibility (8 weeks to complete sessions) provided for scheduling conflicts (e.g., sickness, holidays). The content of the TOLF protocol was carefully designed choosing skills shown to be efficacious in reducing lymphatic pain and lymph fluid level.[13-16]

Intervention Training Protocol. Intervention training for TOLF is designed to provide training that will result in a high level of intervention fidelity. Interventionists on this trial will be licensed nurses or nurse practitioners; this model increases patient access to interventions as clinical sites often do not have staff to conduct such interventions. Training will be organized into four sessions expected to take a total of four weeks to complete. Study interventionists will undergo training and be certified through conducting practice role-play sessions that are recorded and rated by Drs. Fu. Treatment Adherence and Credibility, Therapist Competence. Treatment adherence refers to the extent to which interventions are delivered as prescribed.[59] TOLF protocol adherence and competence ratings will be made by Drs. Fu, which is defined ≥ 90% of the maximum score; and 10% of the trial sessions will be randomly evaluated.
Referral Plan. Patient participants who report no pain reduction at the end of the study will be referred to their oncologists for further medical intervention through an existing physician-nurse referral system.

1.8. Variables and Instruments

Feasibility. Feasibility will be assessed by examining (a) study accrual of Black and Hispanic breast cancer patients (N=60 over 9 months), (b) protocol adherence (>80% adherence to the protocol [defined in this study as the degree to which participants are willing and able to complete the intervention exposure], e.g., TOLF, e-Lymph, and (c) participant retention (>80% data collected at the study appointment, including pre-randomization (A1-Week 0) and post-assessments (A2- Week 9 and A3- Week 13). **Acceptability.** Acceptability will be assessed post-intervention using the validated scale of patient satisfaction and acceptability and exit interview.[60]

Primary and Secondary Outcomes. *Lymphatic Pain*: The Breast Cancer and Lymphedema Symptom Experience Index (BCLE-SEI) Part I, a reliable and valid self-report instrument,[54,61-63] is used to assess self-reported lymphatic pain.[2-3,13,64] The items are rated on a Likert scale from 0 (no lymphatic pain/swelling) to 4 (greatest severity of lymphatic pain/swelling). *Pain Severity and Interference*: are measured using the Brief Pain Inventory-Short Form (BPI-SF) with demonstrated reliability and validity.[65] The BPI-SF consists of four items assessing pain severity (worst, least, average, and current pain) and seven items assessing pain interference in the past week. *Lymph Fluid Level by Bioimpedance*: The Imp XCA® (Impedimed, Brisbane, Australia), a bioelectrical impedance analysis (BIA) device is used to assess lymph fluid level. The device measures the resistance of the extracellular fluid (i.e. the impedance) in terms of the L-Dex ratio, taking into consideration the ratio between the dominant and non-dominant arms.[66-67] *Daily Living Function*: Daily living function is operationalized as Activities of Daily Living (ADLs) that reflect the real-world daily living of breast cancer patients. The 13-item subscale of ADLs in BCLE-SEI Part II is used to assess self-reported difficulty in performing thirteen ADLs.[2,38] Cronbach's alpha for the ADLs subscale is 0.94.[2,38] *Psychological Distress.* The 12-item subscale of psychological/emotional distress subscale from the BCLE-SEI Part II is used to assess the distress of being frustrated, sad, guilt/self-blame, worried, irritable, fearful, angry, lonely, helpless, hopeless, anxious, and depressed. Cronbach's alpha for the psychological/emotional distress subscale was 0.91.[62,64] *Quality of Life.* The 10-item V1.2 Patient Reported Outcome Measure Information System Global Health Scale (PROMIS GHS), (α= 0.80-0.86)[68] that captures self-perception of QOL on a scale from 1 (poor), 2 (fair), 3 (good), 4 (very good) to 5 (excellent). *Self-efficacy for Pain Management.* The 5-item Chronic Pain Self-Efficacy Scale[81] with good reliability[69-70] is used

to assess patients' certainty about their degree of pain control, pain during daily activities, controlling pain during sleep, and making pain reductions without extra medication.

Potential Covariate Variables. *Socioeconomic Determinants of Health*. Items to screen for social needs and financial strains in The Accountable Health Communities (AHC) model[71-76] are used to assess socioeconomic determinants: (1) 2-item for living situation, (2) 2-item for food, (3) 1-item for transportation, (4) 1-item for utilities, (5) 4-item for safety, and (6) 1-item for financial strain. *Medical and Demographic Information*. Demographic data includes age, race, marital status, education, income. Patients will provide information on ethnicity, marital status, and education. Participants' electronic medical record will provide initial and/or recurrent diagnosis date, disease stage, cancer treatments (i.e., chemotherapy, radiation, surgery history/type), medical comorbidities, height and weight, and use of antidepressant, anxiolytics, and pain medications.

1.9.a. Data Collection Schedule and Procedures.

Data Collection. Participants in Phase II/Aim 2 RCT will have three in-person research visits to complete study assessment measures pre-randomization (A1-Week 0), post-intervention assessment measure (A2-Week 9 and A3-Week 13). Data collection during each in-person visit will take approximately 30 minutes. ***Data Recording.*** All participants will be assigned a unique study identification number to ensure confidentiality. Demographic and cancer treatment related data, will be recorded directly into the computer database. Bioimpedance data are recorded directly into the computer database. Field notes at each data collection point will be digitally-recorded and transcribed for data coding and summary. ***Data Storage***. Data will be stored in locked files accessible only to the research team. Electronic data will be stored in a password protected computer accessible only to the PI, Co-Investigators, and the research team members.

1.9.b. Data Analysis and Interpretations

Qualitative Data Analysis (Phase I/Aim 1). Qualitative data obtained from focus groups will be transcribed verbatim. We will use NVivo software to manage data and assist in data analysis. We will use a modified iterative descriptive data analysis method [5,25-26,53,58] to ensure the credibility of data analysis. This iterative process will be used to examine data, compare codes, challenge interpretations, and develop themes inductively. Essential themes and descriptive summary will be produced and used to inform the intervention.

Statistical Analysis for Phase II/Aim 2. Sixty patients (N=60) will be randomized into two equal sized groups with 1:1 ratio, either to TOLF or e-Lymph group. *Feasibility* will be assessed by examining (a) study accrual of breast cancer patients (N=60 over 9 months), (b) protocol adherence (>80% adherence to the protocol [defined in this study as the degree to which participants are willing and able to complete the intervention exposure], e.g., TOLF or e-Lymph), and (c) participant retention (>80% data collected at the study appointments). *Acceptability* will be assessed post-intervention using the validated scale of patient satisfaction and acceptability and exit interview.[77] *Evidence of Promising Outcomes*. Assuming a minimum protocol adherence of 80%, there will be at least 48 participants who will rate whether treatment is acceptable. Assuming acceptability is 50% which has the most conservative precision interval, the acceptability will be estimated within 8%.

Primary Endpoint. The primary endpoint is the complete reduction of lymphatic pain and reduced pain severity and interference reported by participants, and reduced lymph fluid level at week 13 post intervention.

Statistical Analysis for Outcomes. We hypothesize that participants who receive the TOLF will have better primary and secondary outcomes than participants who receive the control e-Lymph over time. Since outcomes will be measured at week 0 (baseline), 9 weeks and 13 weeks post intervention, generalized estimating equation (GEE) model will be used for analyzing each outcome to accommodate the correlation among the repeated measurements within a same subject.[78] Different working correlation matrices will be tested to select the most propriate one for the GEE models. Identity link and logit link will be used for continuous outcomes (lymphatic pain severity, pain severity and interference, lymph fluid level, daily living

function, psychological distress, QOL, and self-efficacy for pain management) and binary outcome (complete pain reduction), respectively. The predictors include two indicators of intervention and control groups respectively. Covariates found to be significantly different between the groups at baseline, will be included in the GEE model.[79] If the primary outcomes of the intervention group are significant at alpha 0.05, we will conclude the intervention works better than the control. Proper methods will be used to address any missing data to maximize the statistical power of our analyses and reduces the likelihood of systematic bias in estimates.

2.0 PROTECTION OF HUMAN SUBJECTS

We will obtain human subject approval and necessary HIPAA waivers from the Internal Review Board (IRB). We will obtain written informed consent from all participants. We will fully disclose all risks and benefits to the participants and give them ample opportunity to decline participation. Documentation is provided here and for each of the Human Subjects' points.

2.1. Human Subjects Involvement and Characteristics

This two-phase project uses qualitative (i.e., focus group) and pilot randomized clinical trial (RCT) design to adapt behavioral interventions (The-Optimal-Lymph-Flow [TOLF]) to be culturally appropriate, and subsequently test the interventions in Black and Hispanic patients. Thus, participants in this work are Black and Hispanic women (over age 18) with lymphatic pain following breast cancer treatment. These women will be recruited for the **Phase I focus groups** (N=24), and **the Phase II** RCT (N=60).

2.2. Recruitment and Informed Consent

All recruitment procedures will comply with HIPAA guidelines. The recruitment procedure will be as follows. For potential participants from University Health, potential participants will be identified through electronic medical record review, or their medical team or potential participants will call the researchers if they see the study flyer and are interested in the study. Once a potential participant has been identified, their primary oncologists will be contacted for permission to attempt to recruit the participant for this study if the potential participants are from University Health. If the oncologist agrees, potential participants will be told about the study by a member of the medical staff and asked if they would be willing to talk with a member of the study team. Potential participants will also be sent an email or a letter through postal mail letting them know that someone will call about the study or meet them at their clinic visit or give them a number to call to completely opt out of any further study activities. If interested in participating in the study, an appointment will be scheduled at which time the study will be explained in detail and signed consent will be obtained.

For potential participants from communities, potential participants will call or email the researchers to express their interest in the study and the researchers will contact the potential participants to confirm their interest in the study and eligibility.

Once a potential subject confirmed their interest in the study either from University Health or communities, a member of the study team will meet the potential participants either in person or virtual as they prefer, the researcher will describe the study in detail, provide the patient with consent forms either in paper or electric form, and offer to answer any questions about the study. Potential participants will then be given sufficient time to read over the consent form, at which time the PI or a member of the study team will ask if they have any further questions. The final component of the consent process will involve reviewing a brief checklist that outlines the major aspects of the study to confirm that the subject fully understands the protocol.

Research subjects will also be asked to carefully review the section in the consent form, entitled, PERMISSION (AUTHORIZATION) TO USE OR SHARE HEALTH INFORMATION THAT IDENTIFIES

YOU FOR A RESEARCH STUDY, at the time they sign the general study consent form. This document, written to ensure compliance with HIPAA Privacy Rule guidelines, provides detailed information about what information is being collected, the participant's privacy rights, and to whom the information may be disclosed. The participant will then sign the consent either in-person or through the electronic signature and be given a signed copy of the consent forms for their records.

Each participant in the focus group will be assigned a pseudonym (i.e., a fake name) to safeguard her identity and protect privacy. The focus group session will be audio recorded using a digital recorder. The audio-recording(s) will be used to transcribe only using pseudonym and ensure the accuracy of each woman's experience from the focus group discussions. Only the research team will have access to the audio recording. For focus group conducted in zoom and in person, pseudonyms will be used throughout the whole session.

For pilot RCT, each participant will be assigned a unique study ID (e.g., TOLF_001 to TOLF_060).

2.3. Protection Against Risk.
The primary risks of this study are those associated with confidentiality. There is some risk attendant to confidentiality of self-report data. Two password protected databases will be used for this study to ensure confidentiality. First, a tracking database will be used for recruitment and follow-up. This data will house information related to tracking the participants in the study, such as phone numbers and addresses. No medically sensitive or outcome data will be stored in this database. This database will also track nonparticipants (i.e., those who have declined participation) only to the barest minimum to ensure that they are not contacted again about participation. At the end of the study, all identifiable data of non-participants such as their names will be deleted. Tracking data on participants will be retained for the usual required period. Second, all study data will be stored in a separate password protected database without any personal identifiers. Data in this database will be derived from patients' direct input into the electronic patient reported outcomes system which is an online survey system; data entered into this system is stored on a secure server housed behind the UMKC firewall. Only a unique study identification number will link the electronic data to the study data file. The tracking data and study data will be stored in a file on a secure study computer which can only be accessed by necessary members of the research team. Access to the computer requires a password protected.

2.4. WOMEN AND MINORITY INCLUSION IN CLINICAL RESEARCH

Inclusion of Women: **Sex as a Variable:** Breast cancer occurs predominantly in women (13%; 1-in-8 women lifetime risk) than men (0.1%).[1] Each year, an estimated 268,600 women in the US are diagnosed with invasive breast cancer but only about 2,670 men.[1] As such, 100% of patient participants will be women.

Inclusion of Minorities: This proposed project aims to develop culturally appropriate, highly accessible, and effective behavioral interventions to reduce lymphatic pain and prevent lymphedema that will address barriers related to social determinants of health faced by Black and Hispanic women. Thus, the project includes only Black and Hispanic women with lymphatic pain following breast cancer treatment.

Inclusion of Individuals Across the Lifespan: Breast cancer does not occur in prepubescent children.[1] Breast cancer rarely occurs in individuals under age 18, individual under age 18 who are diagnosed with invasive breast cancer will be excluded. The project includes only adult women over age 18 with pain and swelling following breast cancer treatment.

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