A. Cover Page:

1. ***Title***: Please include the project title, Grant ID number and main collaborators.

PROJECT TITLE:

***The-Optimal-Lymph-Flow ™*: An e-Health Approach to Enhancing Management of Chronic Pain and Symptoms Related to Lymphedema among Women Treated for Breast Cancer**

Grant ID 13371953 The-Optimal Lymph-Flow ™

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2. ***Abstract***: 248 words.

Despite current advances in cancer treatment, many breast cancer survivors still face long-term post-operative challenges as a result of suffering from daily pain and other distressing symptoms related to lymphedema, i.e. abnormal accumulation of lymph fluid in the ipsilateral upper limb or body. The goal of the proposed project is to improve clinical practice by implementing The-Optimal-Lymph-Flow ™, a patient-centered educational and behavorial symptom management program, to a cost-effective web-based platform that will be accessible via multiple communication devices, including tablets and smartphones. The proposed project will implement the automated touch screen tablet using an evidence-based and reliable assessment tool as part of electronic medical record and part of clinical practice to evaluate pain and symptoms related to lymphedema. Such implementation not only improves patient-provider interaction by encouraging patients to actively report their pain and symptom experience, but also enables cost-effective and accurate identification of patients with pain and symptoms related to lymphedema. Low-cost and pragmatic self-care strategies for symptom management hold great promise for improving patients' quality of life. The effectiveness of the web-based The-Optimal-Lymph-Flow ™ self-care strategies to manage pain and symptoms related to lymphedema will be evaluated by conducting a randomized clinical trial with 120 patients. Successful completion of the project will provide an innovative, low-cost, and pragmatic approach for empowering patients with effective strategies to manage pain and symptoms. The nearly universal access of the Internet means that The-Optimal-Lymph-Flow ™ program has the potential to greatly benefit almost all women treated for breast cancer.

C. Main Section of the proposal (not to exceed 15 pages):

3. Overall Goal & Objectives:

Many breast cancer survivors still face long-term post-operative challenges as a result of suffering from daily pain and other distressing symptoms related to lymphedema, i.e. abnormal accumulation of lymph fluid in the ipsilateral upper limb or body [1-5]. The goal of the proposed project is to improve clinical practice by implementing The-Optimal-Lymph-Flow ™, a patient-centered educational and behavorial symptom management program, to a cost-effective web-based platform that will be accessible via multiple communication devices, including tablets and smartphones. With seed money from Judges and Lawyers for Breast Cancer Alert and the NYU Research Challenge Fund, we have successfully developed and completed usability testing of the web-based The-Optimal-Lymph-Flow ™ system. The-Optimal-Lymph-Flow ™ program includes evidence-based symptom assessment tool using an automated touch screen tablet for collecting patient-generated data to evaluate pain and symptoms related to lymphedema, i.e. abnormal accumulation of lymph fluid in the ipsilateral upper limb or body [1] and the web-based The-Optimal-Lymph-Flow ™ self-care strategies incorporating video avatars and web-based technology to empower patients to gain knowledge and strategies to manage pain and symptoms following breast cancer treatment. The successful implementation of the web-based version of The-Optimal-Lymph-Flow ™ is consistent with the mission of Pfizer Independent Grants for Learning & Change (IGL&C), that is, it empowers patients, encourages patient-generated data, and improves patient outcomes.

The-Optimal-Lymph-Flow ™ is part of the continuum of an eight-year ongoing collaboration to advance the science on symptom assessment and management of breast cancer-related lymphedema and serves as a focal platform to garner the talents from across disciplines at New York University (NYU). This collaboration involves the NYU College of Nursing, NYU School of Medicine (surgery, pathology, and biostatistics), NYU Rusk rehabilitation, NYU Cancer Center, NYU Polytechnic School of Engineering, and NYU Asian Center. This collaboration has led to a successful trajectory of securing external funding from the National Institute of Health, Oncology Nursing Society, Hartford Institute of Geriatric Nursing, Avon Foundation, Vital Fund, Judges and Lawyers for Breast Cancer Alert, as well as productive success in completing the funded projects (a, b, c) essential in informing the project we now propose (d): (a) Validate a symptom assessment tool for evaluating pain and symptoms related to lymphedema [1,3]; (b) Incorporate the infra-red perometer as an objective assessment for limb volume into clinical practice [6]; and (c) Demonstrate the effectiveness of the nurse-delivered The-Optimal-Lymph-Flow ™ program through a prospective**,** repeated measure study [6-7]; and (d) Build a web-based The-Optimal-Lymph-Flow ™intervention using avatar technology. The success of this collaboration has made NYU Cancer Center and College of Nursing renowned for symptom management and breast cancer care. Completion of our proposed project will provide the final data needed for a multi-institutional larger clinical trial.

Exhaustive scientific literature review demonstrates no comparable program to our proposed project. The-Optimal-Lymph-Flow ™ is the first to implement the automated touch screen tablet using an evidence-based and reliable assessment tool as part of electronic medical record and part of clinical practice to evaluate pain and symptoms related to lymphedema.

Such implementation not only improves patient-provider interaction by encouraging patients to actively report their pain and symptom experience, but also enables cost-effective and accurate identification of patients with pain and symptoms related to lymphedema. Low cost and pragmatic self-care strategies for symptom management may hold great promise for improving patients' quality of life. The effectiveness of the web-based The-Optimal-Lymph-Flow ™ self-care strategies to manage pain and symptoms related to lymphedema will be evaluated by conducting a randomized clinical trial with 120 patients. Successful completion of the project will provide an innovative, low-cost, and pragmatic approach for empowering patients with effective strategies to manage pain and symptoms. The nearly universal access of the Internet means that The-Optimal-Lymph-Flow ™ program has the potential to greatly benefit almost all women treated for breast cancer.

4. *Technical Approach:*

a. *Current Assessment of need in target area*

i. *Please include quantitative baseline data summary, initial metrics, or project starting point in **your** target area.*

Annually, more than 230,000 women are diagnosed with breast cancer, and currently there are more than 2.9 million breast cancer survivors in the United States [8]. More than 40% of women treated for breast cancer suffer daily from chronic pain and more than 80% of women report multiple distressing symptoms related to lymphedema (i.e. the abnormal accumulation of lymph fluid in the ipsilateral upper limb or body) even years after cancer treatment [1-5]. The abnormal accumulation of lymph fluid or lymphedema after breast cancer treatment is a result of obstruction or disruption of the lymphatic system associated with cancer treatment (e.g., removal of lymph nodes and/or radiotherapy), influenced by patient personal factors (e.g., obesity or higher body mass index [BMI]), and triggered by factors such as infections or trauma [9-11].

Even breast cancer survivors without a diagnosis of lymphedema suffer from pain (40%), tenderness (47.3%), aching (30%), or soreness (32.7%) while significantly more breast cancer survivors with lymphedema experience pain (45.2%), tenderness (52.4%), aching (61.9%), or soreness (31%) in the ipsilateral upper limb or body [1]. In addition to pain, on average, breast cancer survivors without lymphedema experience about 5 distressing symptoms while breast cancer survivors with lymphedema 10 distressing symptoms related to the accumulation of lymph fluid [1,12]. <u>It is clear that many breast cancer survivors still face long-term post-operative challenges as a result of suffering from daily pain and other distressing symptoms related to lymphedema despite current advance in cancer treatment.</u>

Pain and symptoms related to the accumulation of lymph fluid following breast cancer treatment remain main debilitating late complications that impact the breast cancer survivors' quality of life [2,3,5,13]. Persistent pain related to cancer treatment is considered a stressful complication since it is perceived as a constant reminder of cancer [2,14] and exert tremendous limitations on breast cancer survivors' daily living [2,5]. Pain and other distressing symptoms related to lymphedema following cancer treatment can instigate fears and induce feelings of loss of control [2,3,5]. Specifically, the experience of pain, including tenderness, aching, or soreness, causes significant and unrelenting distress among breast cancer survivors [3]. Such

distress is usually heightened when breast cancer survivors expect pain and symptoms related to lymphedema to disappear but instead stay as a "perpetual discomfort"[3; p853]. The negative impact of pain and symptoms related to lymphedema can be a source of considerable disability and psychological distress that negatively influences the patient's daily living [2,3,13-14]and creates a tremendous burden on the health care system [15]. ***Nonetheless, in clinical practice pain and symptoms related to lymphedema are still under-recognized and undertreated***. To address this critical clinical need, we propose to implement an automated touch screen tablet using an evidence-based and reliable symptom assessment tool to collect patient-generated data to evaluate pain and symptoms related to lymphedema among women treated for breast cancer as part of routine clinical practice and part of electronic medical record.

While more research is needed to explore the exact etiology of persistent pain and other symptoms after breast cancer treatment,(e.g. arm swelling, breast swelling, chest wall swelling, heaviness, firmness, tightness, stiffness, numbness, burning, stabbing, tingling, and limited limb movement), physiologically, the accumulation of lymph fluid in the affected limb may create undue pressure on nerves, producing feelings of pain, aching, tenderness, soreness, burning, tingling, stabbing, and numbness as well as inducing sensations of swelling, heaviness, tightness, and firmness [7, 16]. Accumulated lymph fluid in the affected limb also leads to stiffness and limited limb movement of arm, shoulder, fingers, and elbow [12,16]. Significant associations are found between pain (including aching and tenderness) and accumulation of lymph fluid in the ipsilateral upper limb [12,16]. Research has also shown that with increased number of symptoms reported, breast cancer survivors' limb volume increased [12,16]. Limb volume as detected by the infra-red perometer have significantly increased as breast cancer survivors' reports of pain, tenderness, aching , swelling, heaviness, firmness, and tightness have increased [12]. On average, breast cancer survivors reported 4 symptoms for those with <5.0% limb volume increase; 5 symptoms for 5.0-9.9% limb volume increase, 7 symptoms for 10.0-14.9% limb volume increase, and 13 symptoms for $\geq$ 15% limb volume increase, respectively ($p<0.001$) [12].

Breast cancer survivors are known to have a compromised lymphatic system due to breast surgery, dissection of lymph nodes and vessels, and radiation, which leads to ineffective lymphatic drainage, thus accumulated lymph fluid in the affected limb [12,16-17]. In addition to the risk factor of compromised lymphatic drainage from cancer treatment, higher body mass index (BMI) is also an established risk factor for the accumulation of lymph fluid [9-11]. Physiologically, a larger body mass creates a disproportion in lymph transport and capacity, resulting in excess extracellular fluid [6,18]. Women are 1.11 times more at risk for developing lymphedema with every increase of $1kg/m^2$ in their BMI [9,11,17]. Although the known risk factors for symptoms related to accumulation of lymph fluid directly from cancer treatment cannot be avoided, (such as removal of lymph nodes, surgery, radiation, chemotherapy, and hormonal therapy), some risk factors, (such as compromised lymphatic drainage and higher BMI), can be modified through education and self-care strategies [6-7,19].

Patient education focusing on self-care strategies holds great promise for reducing the risk of lymph fluid accumulation [6-7,19]. Research evidence demonstrates that patient education on self-care remains an important predictor of lymphedema outcome after controlling for

confounding cancer treatment-related risk factors [6-7,19]. Risk factors, such as compromised lymphatic drainage and higher BMI, may be modified through self-care strategies [6-7]. Current patient education emphasizes precautionary lifestyle behaviors, such as avoidance of repetitive limb movement, lifting weighted objects, needle punctures, blood draw, and the use of compression garments for air travel in the affected limb [20-21]. To date, there is a paucity of high quality evidence to support these precautionary practices that reduce the risk of lymphedema and relieve pain or symptoms related to lymphedema [20-21]. Research is lacking to provide evidence to reduce pain and symptoms related to lymph fluid accumulation through self-care strategies targeting compromised lymphatic drainage and higher BMI. To address this important clinical need, we plan to conduct a pilot clinical trial to preliminarily evaluate a web-based The-Optimal-Lymph-Flow*™*, a patient-centered educational and behavorial symptom management program focusing on promoting lymph flow and optimizing BMI.

Low cost and pragmatic self-care strategies for symptom management may hold great promise for improving patients' quality of life [6,19]. To date, no research has been designed to help breast cancer survivors to manage their daily distressful symptoms, including pain. Grounded in research-driven self-care behavioral strategies, The-Optimal-Lymph-Flow *™* is a patient-centered educational and behavioral program focusing on self-care strategies to lessen the symptom burden by promoting lymph flow and maintaining optimal BMI, which targets compromised lymphatic system and BMI, that is, risk factors for pain and symtpoms related to lymph fluid accumulations. Its underlying premise is to empower, rather than inhibit, how breast cancer survivors live their lives by emphasizing "what to do," rather than "what to avoid." It features a safe, feasible and easily-integrated-into-daily-routine self-care strategies that include shoulder mobility exercises to promote shoulder function, muscle-tightening-breathing, muscle-tightening-pumping exercises, and large muscle exercises to promote lymph flow and drainage, as well as general instructions to encourage nutrition-balanced (more vegetables and fruits) and portion-appropriate diet (feeling 75% full for each meal) to strive for maintaining optimal BMI. The efficacy of The Optimal Lymph-Flow ™ has been demonstrated in our recently published study of 140 patients who received the face-to-face nurse-delivered program [6]. Findings of the study demonstrated that over 90% of patients improved their limb volume at 12-month follow-up. To date, The-Optimal Lymph-Flow™ is the only evidence-based self-care program designed to effectively help women treated for breast cancer to prevent lymph fluid accumulation [6-7]. As a first step in recognizing the need for The-Optimal Lymph-Flow ™ in limited English Language Proficient commuities, we are currently piloting a multi-site randomized clinical trial in New York City for Chinese language nurse-patient delivery that is supported by the National Institute of Health. The preliminary trial outcomes are promising.

ii. *Describe the primary audience(s) targeted for this project.*

Successful completion of the proposed project will directly benefit all women treated for breast cancer who suffer from or at risk for pain and symptoms related to lymph fluid accumulation by providing a low-cost, technologically-driven delivery model to universally expand the accessibility of The-Optimal Lymph-Flow *™*. With health care reform under way, using web-based technology to develop low cost and pragmatic patient-centered intervention is the key to lessening the health care cost and advancing the science of symptom management.

b. ***Project Design and Methods***:

The specific objectives of the proposed project are designed to address current practice gaps, that is, (1) pain and symptoms related to lymphedema are under-recognized and undertreated and (2) no research has been designed to help breast cancer survivors to manage their pain and symptoms related to lymphedema. For this project, *chronic pain, including aching, tenderness, soreness, is defined as persistent or intermittent pain in the ipsilateral upper limb or body for more than 3 months after surgical treatment for breast cancer, that is, beyond the expected period of healing* [23-24]. We have designed an *Evaluating Protocol* and *Intervention Protocol* targeting the Specific Objectives to achieve the goal of our proposed project, that is, to improve clinical practice by implementing The-Optimal-Lymph-Flow ™, a patient-centered educational and behavorial symptom management program, to a cost-effective web-based platform.

The specific objectives of the project are:

Specific Objective #1: Implement an automated touch screen tablet using an evidence-based and reliable symptom assessment tool to collect patient-generated data to evaluate pain and symptoms related to lymph fluid accumulation among women treated for breast cancer as part of routine clinical practice and part of electronic medical record.

Specific Objective #2: Conduct a randomized clinical trial to evaluate the efficacy of the web-based The-Optimal-Lymph-Flow ™ system for managing chronic pain and symptoms related to lymphedema focusing on primary outcomes of pain reduction, secondary outcomes of symptom relief, limb volume difference by infra-red perometer, body mass index (BMI), quality of life related to pain.

Evaluating Protocol. Specific Objective #1 is designed to achieve the goal of *Evaluating Protocol*, that is, to implement an automated touch screen tablet using an evidence-based and reliable symptom assessment tool to collect patient-generated data to evaluate pain and symptoms related to lymphedema among women treated for breast cancer as part of routine clinical practice and part of electronic medical record. We will engage women who come for follow-up care after breast cancer surgery to the NYU Langone Laura and Isaac Perlmutter Cancer Center (NYU Cancer Center), a National Cancer Institute-designated cancer center, and provide them with automated touch screen tablet to report their pain and symptom experience as part of routine care. If a patient reports pain or symptoms related to lymphedema, an electronic note will be generated to notify her healthcare providers (e.g. physicians and nurses). There is no standard care for the management of pain and symptoms related to lymphedema in the current clinical practice at NYU Cancer Center. Therefore, any patients who report pain and symptoms related to lymphedema will be offered the opportunity by their physicians and nurses to enroll into *Intervention Protocol*, that is, the randomized clinical trial to evaluate the efficacy of the web-based The-Optimal-Lymph-Flow ™ self-care strategies for managing chronic pain and symptoms related to lymphedema. A trained research coordinator then will explain the study and obtain the study consent for *Intervention Protocol*.

At NYU Cancer Center, each year more than 1,000 women who are newly diagnosed with breast cancer are treated for the disease, which provides a large evaluation population for our proposed project. Since more than 40% of women treated for breast cancer report persistent pain and more than 80% of women report multiple symptoms related to lymphedema, we plan

to evaluate at least 1000 patients to ensure the recruitment of 120 patients to achieve Specific Objective #2 of *Intervention Protocol*.

Intervention Protocol. Specific Objective #2 is designed to achieve the goal of *Intervention Protocol,* that is, to conduct a randomized clinical trial to evaluate the efficacy of the web-based The-Optimal-Lymph-Flow *™* self-care strategies for managing chronic pain and symptoms related to lymphedema over 12-week period. We will employ repeated measures to evaluate the primary outcomes of pain and secondary outcomes of symptoms related to lymphedema, limb volume differences by infra-red perometer, BMI, and quality of life.

We have designed a control-intervention-group randomized clinical trial to compare the outcome of The-Optimal-Lymph-Flow *™*group versus control Arm Precaution group. We have previously developed a web-based platform for The-Optimal-Lymph-Flow *™* system that has been used successfully for its usability testing. The preliminary usability tested was done with 10 breast cancer survivors who evaluated the easiness, difficulties, and feasibility of using the system on computer, iPhone, iPad, or other smartphones. Findings of the usability and feasibility test has demonstrated that patients love the web-based program, especially the avatar technology that demonstrates the complicated lymphatic system and illustrates the physiological functions of each exercise and detailed step-by-step instructions for each exercise. **Here is the link for the website and login information** (http://test-lymphedema.gotpantheon.com/). (To see the site as an intervention group user: username: Interventionuser; password: Nursing1!) (To see the site as a control group user: username: controluser; password: Nursing1!)

We will further develop an interactive and instructional application or App that a patient can download to their smartphones or tablets to conduct self-monitoring and exercise with video instruction anywhere without necessity for Internet access. Patients in The-Optimal-Lymph-Flow *™* group will have choice on which platform they would like to use.

***The Web-Based The-Optimal-Lymph-Flow* ™ platform.** The web-based platform includes information about lymphedema, diagnosis and measurement of lymphedema, lymphatic system, risk of lymphedema, risk reduction for Optimal Lymph Flow, self-monitoring, and tips for an optimal life. Patients will also have the access to the 8 Avatar videos that provide step-by-step instructions for The-Optimal-Lymph-Flow *™*exercises to promote shoulder and limb mobility and optimize lymph flow. The webpage also has a section entitled “Risk Reduction-Arm Precautions,” representing current patient education that emphasizes precautionary lifestyle behaviors, such as avoidance of repetitive limb movement, lifting weighted objects, needle punctures, blood draw, and the use of compression garments for air travel in the affected limb [20-21. Only the patient in the control Arm Precaution group will be given access to this section.

Development of The-Optimal-Lymph-Flow App Design: The web-based platform requires a patient to have an Internet access while doing exercise. Also, currently the patient can only do self-assessment when they visit the clinical center using an iPad with a special program. To enable patients to perform exercise and self-assessment anywhere, we will develop a Mobile App that patients can download to their own smartphones or tablets. Briefly, the App will provide the following functions: 1) Upon initial download, the patient will be prompted to set up an exercise schedule (e.g. daily), symptom assessment schedule (e.g. monthly), as well as

conducting an initial symptom assessment. 2) The App will remind the patient to do exercises and symptom assessment and will generate motivating messages when the patient completes an exercise/assessment. 3) The App will guide the patient through the exercise with video instructions (based on the Avatar video originally developed for our web-based platform) and record the actual exercise duration. 4) The App will provide a friendly user interface for the patient to conduct symptom assessment. 5) The App will send the recorded exercise frequency and duration as well as self-assessment data to a server in our research lab for data analysis when the device has Internet access. 6) The App will enable the patient to view their own exercise record and assessment record, to empower the patient to be self-motivated. We plan to have an initial version developed for iPhone and iPad as well as for Android devices in the first 3 months of the project. This version will be used by the participants in the The-Optimal-Lymph-Flow ™ group. A final revised version will be produced in Year 3 based on feedback from the patients, practitioners, and researchers. The final version will be made publically available for free if feasible or at a very low cost (e.g., $2.99) on Apple App stores and Google App store for Android devices.

The endpoints for *Intervention Protocol* are presence of pain from baseline (prior to intervention) and then again at week 8 and 12 post intervention. Evaluation of these intermediate endpoints will provide important evidence needed to establish guidelines for long-term treatment and management of chronic pain and symptoms related to lymphedema. The design of repeated measures enables phase-specific monitoring of the effectiveness of the intervention: If the web-based and App-based intervention provides a meaningful decrease in pain and symptom reduction at 12 weeks, we plan to move forward with a multi-site larger trial that follow patients for a longer period of time with the additional objective of demonstrating that the reduction in pain and symptoms is sustained over time and leads to an improved pain and symptom profile, limb volume difference, BMI, and quality of life for breast cancer survivors.

c. Evaluation Design

i. In terms of the metrics used for the needs assessment, describe how you will determine if the practice gap was addressed for the target group.

To address the practice gap that no research has been designed to help breast cancer survivors to manage their daily experience of pain and distressful symptoms related to lymphedema, we will conduct a pilot 12-week randomized clinical trial to evaluate the efficacy of the web-based The-Optimal Lymph-Flow ™ self-care strategies versus control Arm Precaution group for managing chronic pain and symptoms related to lymphedema. This pilot clinical trial focuses on primary outcomes of pain reduction and secondary outcomes of relief of symptoms related to lymphedema, limb volume difference by infra-red perometer, BMI, quality of life to refine procedures and estimate effect size for the future efficacy of multi-center randomized clinical trial (RCT) of a web-based intervention for breast cancer survivors suffering pain and symptoms related to lymphedema. **We hypothesize that participants in the intervention group will have improved pain and symptom experiences, limb volume difference, BMI, and quality of life.**

STUDY PARTICIPANTS FOR THE PILOT RANDOMIZED CLINICAL TRIAL: We will enroll a total of 120 participants: 60 participants in The-Optimal-Lymph-Flow™ intervention and 60 participants

in the control Arm Precaution group to account for a potential attrition of 20%, which has been observed in the prior studies in breast cancer survivors [9,26]. *Chronic pain, including aching, tenderness, soreness, is defined as persistent or intermittent pain in the ipsilateral upper limb or body for more than 3 months after surgical treatment for breast cancer, that is, beyond the expected period of healing* [23-24]. Since more than 40% of women treated for breast cancer report persistent pain and more than 80% of women report multiple symptoms related to lymphedema even years after cancer treatment [1-3,5], our study participants will be women who have been surgically treated for breast cancer and who have reported the experience of pain and symptoms related to lymphedema for more than 3 months at the time of the study.

Inclusion Criteria: (1) Patients who have been surgically treated for breast cancer more than 3 months; healing usually occurs within 3 months of surgical treatment for cancer (2) Patients who report pain, including aching, tenderness, soreness for more than 3 months; (3) Patients may or may not report any of symptoms related to lymphedema (i.e. swelling, heaviness, tightness, firmness, numbness, tingling, stiffness, limb fatigue, limb weakness, and impaired limb mobility of shoulder, arm, elbow, wrist, and fingers) [1,5]; (4) Patients may or may not have a history of lymphedema or have been treated for lymphedema.

Exclusion Criteria: (1) Patients who do not report any pain, including aching, tenderness, and soreness; (2) Patients who have known metastatic disease or other bulk disease in the thoracic or cervical regions; (3) Patients who have lymphedema due to cancer recurrence. (4) Patients with documented advanced cardiac or renal disease.

PROCEDURES

Evaluation Protocol Procedure: Using an automated touch screen tablet, if a patient reports pain, including aching, soreness, tenderness, the patient will be invited to *Intervention Protocol*, a pilot randomized trial. After consenting to the study, the patient will undergo a perometer measurement to compare if the limb volume of the affected limb is greater than the non-affected limb, then the patient will be assigned to either The-Optimal-Lymph-Flow ™ intervention or the control Arm Precaution group.

Intervention Protocol Procedures:

Consent Procedures. If a patient report pain using the touch screening tablet, the patient will be presented a flyer which explains the proposed clinical trial by their physicians or nurses. After reading the flyer, if a woman is interested in participating in the study, she would schedule a meeting with the research coordinator or the PI at that time or at other convenient time for them. During the meeting, the research coordinator or the PI will confirm her interest, determine if the woman is eligible for the study and the research coordinator or the PI will again explain the study in detail and provide enough time for the woman to ask questions. If the woman agrees to participate, she will sign the consent form.

Likelihood and Seriousness of Potential Risks to Study Participants. There are no anticipated risks to the women of participating in this study. The perometer and symptom measurement is a noninvasive procedure. No immediate or long-range risks are foreseen from the use of the perometer for limb volume assessment. Participant may skip or not answer any questions in the questionnaires that she would prefer not to answer. Participants have the option to withdraw

from the study at any time. Withdrawing from the study will not affect the care or treatment that a participant receives.

Anticipated benefits. Individual participants may benefit from the trial by the effects of the intervention for managing pain and symptom related to lymphedema. Findings of the proposed study may help healthcare providers to identify the effective interventions to help patients to effectively manage pain and symptoms related to lymphedema Benefits for breast cancer survivors who experience pain and symptoms related to lymphedema are considerable. As minimal foreseeable risks exist, potential benefits are identifiable, and this research requires human participation, the risk/benefit ratio is acceptable for this research with human subjects.

Randomization: The randomization assignment will be generated by Dr. Jason Fletcher, the senior statistician at NYU College of Nursing and provided to the PI or the program coordinator via emails or phone calls. The assignments will be maintained by Dr. Fletcher on a secure server and will be linked to study data as required for safety monitoring and final analysis. Patients will be randomized based on their report of pain, including aching, soreness, or tenderness. The research nurse, who is blinded throughout the study to the patient's assigned arm, will perform pre and post intervention measurements.

The primary outcome variable is pain, including aching, soreness, tenderness, over 12 weeks. The secondary outcome is symptoms related to lymphedema, the difference between limb volume differences by perometer, BMI, quality of life over 12 weeks. Assessments for pain, symptoms related to lymphedema, and perometer arm measurements will occur at the following time points: at baseline prior to intervention, at week 8 and 12 post intervention. This study can be classified as a randomized phase II design since the endpoints assessed are intermediate (pain status at 12 weeks) rather than long-term (pain status at 1 or 2 years). Evaluation of long-term endpoints for pain would require substantially more patients and follow-up time than is feasible within this funding.

- *Identify the sources of data that you anticipate using to make the determination.*

MEASURES

The following measures will be used to collect data regarding the clinical trial variables for *Interventional Protocol*. **Study variables** are listed in Table 1.

Table. 1. Study variables

Intervention Variables	Outcome Variables	Covariates
✓The-Optimal-Lymph-Flow ™ self-care program ✓Arm Precaution Program	Primary outcome variable ✓Presence of pain or pain severity reduction, including aching, tenderness, soreness Secondary outcome variables ✓Symptoms related to lymphedema ✓Limb volume Difference by the perometer ✓Body Mass Index [BMI] ✓Quality of Life related to pain	✓Age ✓Types of surgeries (lumpectomy or mastectomy) ✓Status of lymph nodes (number of nodes removed, number of nodes positive for cancer, presence of extracapsular extension) ✓Radiation (type, dose, and location) ✓Hormonal Therapy ✓Chemotherapy ✓Self-care Behaviors ✓Pain medications ✓Frequency of participants' accessing to the website and the App

Within 1 week of enrollment for the pilot clinical trial, patients will have baseline assessment of pain, limb volume difference, BMI, and quality of life and follow-up assessment will occur at week 8 and 12 post intervention.

Demographic and Medical Information. A structured interview tool will be used to gather demographic and medical information and verified through reviewing participants' medical records [9,11,14]. The demographic and medical information will be considered as covariates, including pain medications, age, surgeries, lymph nodes procedure, radiation, chemotherapy, and hormonal therapy.

Pain and Symptoms Related to Lymphedema. The Lymphedema and Breast Cancer Symptom Experience Index is a valid and reliable self-report tool to assess pain, including aching, soreness, tenderness, as well as symptoms related to lymphedema (i.e. , arm swelling, breast swelling, chest wall swelling, heaviness, firmness, tightness, stiffness, burning, stabbing numbness, tenderness, stiffness, redness, blistering, and tingling (pins and needles [9,11,14]. Each symptom can be treated as categorical variable by choosing a "Yes" or "No" to indicate the presence or absence of a given symptom. Each item can also be rated on a Likert-type scale from 0 (no presence of a given symptom) to 4 (greatest severity of a given symptom). Higher scores indicate more severe symptom presence. A response frame of last three months will be used for all participants to ensure the chronicity of symptom presence.

Limb Volume Difference by Infra-red Perometer. Perometry 350S will be performed on each arm as it is held horizontally. The perometer maps a 3-dimensional graph of the affected and non-affected extremities using numerous rectilinear light beams, and interfaces with a computer for data analysis and storage. A 3-dimensional limb image will be generated and limb volume will be calculated. This optoelectronic method has a standard deviation of 8.9 ml (arm), less than 0.5% of LV with repeated measuring [6,12]

Quality of life Related to Pain. The Pain Impact Questionnaire™ (PIQ-6™), a reliable and valid six question health survey, will be used to measure pain severity and the impact of pain on an individual's functional health and well-being. The PIQ-6 measures the severity of pain and its impact on work and leisure activities, as well as on emotional well-being within a variety of diseases and general populations. High PIQ-6™ *T* scores indicate greater pain impact/worse health [24-25].

Body Weight and Body Mass Index [BMI]. An electrical bioimpedance device (InBody 520, Biospace Co., Ltd) will be used to measure the participants' body weight, BMI is calculated using the formula: weight (kg) / height (m^2).

Practice of Self-Care Behaviors. Risk Reduction Behavior Checklist is a structured self-report checklist that will be used to quantitatively and qualitatively assess patients' practice of self-care behaviors at the study endpoint of 12-week after intervention [6-7]. The checklist include a list of self-care behaviors that promote lymph flow, e.g. muscle-tightening deep breathing, muscle-tightening pumping, shoulder exercises, large muscle exercises, and having nutrition-balance and portion-appropriate diet, as well as compression therapy for lymphedema.

- *Describe how you expect to collect and analyze the data.*

DATA COLLECTION AND MANAGEMENT

Data Collected from Evaluation Protocol*.* Data collected from screening for pain, including aching, soreness, tenderness, using an automated touch screen tablet will be directed store into NYU Cancer Center patient electronic medical record.

Data Collection from Intervention Protocol. A research coordinator and a research nurse will be hired and supervised closely by the PI for data collection and management.

*Data Collection****.*** The data collected for *Intervention Protocol*, including patient demographic data, treatment variables, and measurements. Once the participant has provided informed consent, the research coordinator or the PI will arrange a time for data collection by the research nurse who is blinded from the participant assigned arm. Data will be collected at baseline prior to intervention, and at week 8 and 12 post intervention. Data collection at each time point will take approximately 30 minutes. For the first 8 cases, all data will be verified. Subsequently, random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

*Data Recording****.*** All participants will be assigned a unique study identification number to ensure confidentiality. Pain and symptoms will be assessed using the touch-screen tablet and data are directly recorded into the computer database. Perometer data are recorded directly into the computer database. Demographic and cancer treatment related data will be collected using paper and pencil method and entered into the computer database. Field notes at each data collection point will be tape-recorded and transcribed for data coding and summary.

Data Storage. Confidentiality will be maintained. Data will be stored in locked files accessible only to the research coordinator, research nurse, or the PI. Electronic data will be stored in a password protected computer accessible only to the PI, the research nurse, and the research coordinator. Data analysis will be carried out and reported in the aggregate data so that individual identities are not revealed. Careful training and supervision of research coordinator and research nurse will insure procedures are carried out in accordance with established protocols. A data and safety-monitoring plan for this project will be used that follows guidelines set forth by the NYU Medical Center Institutional Review Board.

STATISTICAL ANALYSIS

Data Analysis for *Evaluation Protocol* (Specific Aim #1): We will conduct descriptive analysis regarding the screening data in terms of pain occurrence among the pool of patients screened for pain.

Data Analysis for *Intervention Protocol* (Specific Aim #2):

Sample Size Considerations for Intervention Protocol. We will enroll total of 120 participants: 60 participants in The-Optimal-Lymph-Flow ™ intervention and 60 participants in the Arm Precaution control group to account for a potential attrition of 20%, which has been observed in the prior studies in breast cancer survivors [12]. This will yield an adequate analytic sample size even with 20% attrition based on a 2 sample 2-sided t-test with alpha =0.05 and power of 90%, we can detect a difference of 0.7 standard deviations in the difference between the presence of pain in the intervention group compared to the control group at 8 weeks or at 12 weeks. The projected sample size will also provide sufficient statistical power for mixed

regression models. For linear mixed models of continuous outcomes (e.g. pain ratings), statistical power will exceed 80% to detect a medium effect, assuming a constant group effect, correlations of r = .5 between observations, alpha =.05, and compound symmetry of the covariance structure.

For binary outcomes, based on the 3 repeated observations with a conservative estimate for the assumed correlation of r = .5 between observations, alpha = .05, sample size of n = 50 per treatment arm will have power of 80% to detect odds ratios of the difference between groups ranging from 2.6 to 3.5 (small to medium effects).

Adequacy of sample size will be monitored during the analyses in three ways: 1) assessing sufficiency to estimate the number of model parameters identified by preliminary analyses, 2) examining model fit indices (e.g. Intra-class correlation coefficient to assess fit of random effects) to ensure data adequately support models generated, and 3) assessing the adequacy to accurately estimate model parameters by generating confidence intervals.

Data Analysis for Demographic and Clinical Data. Descriptive statistics for all variables will be calculated for participants in the control and intervention group. To confirm that randomization created equal distributions of variables that could affect treatment outcome, the two groups will be compared on demographic and cancer treatment characteristics using t-tests or chi squared analyses as appropriate. If necessary, these variables will be used as covariates in the subsequent analyses.

Data Analysis for Specific Aim #2. We hypothesize that participants who receive The-Optimal-Lymph-Flow ™ intervention will improve significantly in the following outcome variables: pain, symptoms related to lymphedema, Limb Volume Difference by infra-red perometer, BMI, and quality of life. Distributions of the outcome variables and other covariates will be summarized graphically and numerically. Bivariate relationships among the variables will be assessed using correlation, point-biserial correlation or phi coefficient to identify potential covariates for inclusion into statistical models. Linear mixed effects models will be used to analyze continuous outcomes (e.g. pain ratings) and generalized linear mixed models will be used to analyze binary outcomes (presence of symptoms). These models will incorporate fixed effects for time, group and any identified covariates. As indicated by preliminary models to estimate variance effects, models will include random effects for subject-specific slopes and intercepts. A statistically significant fixed effect group by time interaction will indicate a treatment effect, with the direction of difference determined from mean values. We will also compare pain at week 8 and at 12 between the two groups. Models will be compared for goodness of fit and modifications to link functions, distributional form and correlation structure will be made as necessary.

Methods for Handling Missing Data and Non-Adherence to Protocol. Data from participants who are missing >20% of any scale will be excluded from calculation of that scale, though remaining data meeting requirements for completeness will be retained. Analysis of missing data will first determine whether it can be assumed to be missing at random (MAR) or not missing at random (NMAR). Based on the results of this step, appropriate methods will be selected for addressing missing data (e.g. Heckman Selection for NMAR, Multiple Imputation for data which are MAR).

Further, mixed effects regression models are robust in the presence of missing data.

Unlike traditional repeated measures designs (e.g. repeated measures ANOVA) which employ listwise deletion, excluding all records for individuals who miss a single observation, mixed effects models are capable of incorporating all completed observations for estimations. Though our previous studies suggest that we will have a limited number of missed observations, individuals need not have the same number of observations. This maximizes the statistical power of our analyses and reduces the likelihood of systematic bias in estimates.

- *Identify the method used to control for other factors outside this project (e.g., use of a control group)*

We have designed the pilot clinical trial with an intervention and control group. The intervention group will receive The-Optimal-Lymph-Flow *™ program* and control group will receive the Arm Precaution program. *The goal for both The-Optimal-Lymph-Flow* ™ and control Arm Precaution group is the absence of pain or reduction of pain severity at 12 weeks post intervention.

The-Optimal-Lymph-Flow **™ Intervention Group.** Patients assigned to The-Optimal-Lymph-Flow ™ group will have access to the web-base*d* The-Optimal-Lymph-Flow *™* program includes information about lymphedema, diagnosis and measurement of lymphedema, lymphatic system, risk of lymphedema, risk reduction for Optimal Lymph Flow, self-monitoring, and tips for an optimal life. Patients will also have the access to the 8 videos that provide step-by-step instructions for The-Optimal-Lymph-Flow exercises to promote shoulder and limb mobility and optimize lymph flow. In addition, the patients will be introduced to the App, and the patient can choose to use either the web-based program or the App for self-monitoring and exercise. However, patients **will not** have access to the section "Risk Reduction-Arm Precautions."

Control Arm Precaution Group. Patients assigned to the control Arm Precaution group will have access to the website section that emphasizes precautionary lifestyle behaviors, such as avoidance of repetitive limb movement, lifting weighted objects, needle punctures, blood draw, and the use of compression garments for air travel in the affected limb [20-21]. Patients will have access to the following contents of the web-site: information about lymphedema, diagnosis and measurement of lymphedema, risk of lymphedema, risk reduction for Arm Precautions. However, patients **will not** have access to The-Optimal-Lymph-Flow *™* program.

ii. Quantify the amount of change expected from this project in terms of your target audience
Primary Endpoint. The primary endpoint for the study is absence of pain reported by the participants at week 12 post intervention.

iii. Indicate how you will determine if the target audience was fully engaged in the project.

Strategies to encourage participants' engagement:
Skill Training. To ensure that there are no skill barriers for the participants in both intervention and control group to access to the web-based program and the App, a laptop with internet connection will be provided in the research lab. First, the participants will be required to complete the web-based program during the first visit in the research lab where a research assistant will be available to help if a participant has any questions or needs for navigation of the web-based program. To ensure that participants are competent to navigate the web-based and the App program, each participant will be given a list of tasks to navigate and find the

information and videos on the website and download the App based on the treatment group assigned: The-Optimal-Lymph-Flow ™ intervention or Arm Precaution. It takes 30-40 minutes to complete the program. Second, the participants will have ongoing access to the program during the study period to review the material as needed; the participants have the option to use their own computers or laptops or iPad or other electronic tablets, or smartphones or use the research laptop for the study to review the intervention materials. Third, if needed, the research coordinator will help the participants who have laptop, iPad or any electronic tablets, or smart phones to access to the program and download the App.

Ongoing Engagement. From our previous experience, "too much trouble," that is when a project requires a daily log or researchers frequently contact the participants, is a major reason for potential participants to decline study participation and for participants to drop out of a study. In addition, from our previous qualitative study, we understand that patients desire self-care behaviors that work for them, can be part of their daily routine, and are perceived as their own initiative and motivation, rather than the behaviors that they have to adhere to because the clinicians or researchers want them to do so [26]. Furthermore, one goal of this proposed pilot clinical trial is to discern which behaviors are initiated, continued or discontinued by the participants in terms of pain management. We have designed the study to only assess the self-care behaviors at the study endpoint of 12-week after intervention with the intention that participants would initiate and sustain the behaviors that work for them in their daily lives for pain management. We will follow the procedures of our successful one-arm trial with only 4% attrition rate that allows patients to take the charge to report their pain and symptom experience and enhance their learning of the self-care strategies by accessing the web-based intervention as needed. The following strategies will be used to encourage participants' active engagement during the study period:

Monthly Online Pain and Symptom Report.

We will encourage participants to report their pain and symptom experience monthly or as needed during the study period. Upon the completion of online self-report of pain and symptoms related to lymphedema, regardless whether the patients are in The-Optimal-Lymph-Flow *™* or Arm Precaution group, patients will receive an instant motivational message according to their pain or symptoms experience, such as "Keep up your great work;" "Are you ready to do more to reduce your pain or other symptoms" "Congratulations! You have no pain and symptoms related to lymphedema. Keep doing what you have been doing," "Please visit the website for strategies to help you to manage your pain or other symptoms."

Ask an Expert. From our previous experience, we understand that patients usually have questions during the study period time. We will develop a section named as "Ask an Expert" to encourage patients to submit their questions through the website. The PI and the research nurse will determine the nature of the question whether it is personal or relevant to other patients. The patient who asks the question will receive an email within 24 hours regarding her question. If the question is interested to other patients, the question will be posted anonymously with the answer to the question by the PI or the research nurse.

Referral Plan. Participants who report pain or no reduction of pain severity at 12 week are considered treatment failures and will be referred to their oncologists for further medical intervention through an existing physician-nurse referral system. If the web-based The-Optimal-Lymph-Flow *™* is demonstrated to be effective when compared to the control, then patients

who receive the control will be offered The-Optimal-Lymph-Flow ™ intervention after the conclusion of the trial since pain and symptoms related to lymphedema are long-term adverse effects from cancer treatment.

iv. Describe how you plan for the project outcomes to be broadly disseminated.
Following the project's completion, we plan to widely disseminate the findings of the project to health care professionals and patients. For health care professionals, we will submit our findings to relevant conferences (e.g. Multinational Association of Supportive Care for Cancer, American Society of Clinical Oncology, San Antonio Breast Cancer Symposium, and Oncology Nursing Society. We plan to prepare for publications in peer-reviewed journals (e.g., Annals of Surgical Oncology, Annals of Clinical Oncology, CA-Cancer, New England Journal of Medicine, or Lymphology). We are confident that the proposed project will add to the track record of success of our previous projects [1,3,6-,13,18-19,26].

For patients, we plan to develop and refine an interactive and instructional application [App] based on current avatar videos capable of ensuring patients' continuing engagement in using The-Optimal-Lymph-Flow™ and self-care to promote lymph flow, manage pain and symptoms during Year 1 and Year 2. In Year 3, the final version of the App supported by Apple and Android devices will be completed based on the feedback from our patients and healthcare providers and made publically available for free if feasible or at a very low cost (e.g., $2.99) on Apple App stores and on Google App store.

5. Detailed Workplan and Deliverables Schedule:
We plan to accomplish the proposed project in 30 months or 2.5 years.

Month 1-3

- ✓ Complete the development of an initial version of an interactive and instructional application (App) that patients can use on their apple (iPhone or iPad) or Android devices for symptom assessment and exercise scheduling, instruction and record keeping.
- ✓ Obtain Institutional Review Approval and prepare for the project.

Month 4-24

- ✓ Implement *Evaluation Protocol* to evaluate pain and symptoms related to lymphedema. We plan to evaluate 1,000 patients to recruit 120 patients for *Intervention Protocol*.
- ✓ Implement *Intervention Protocol* to conduct a pilot randomized clinical trial to evaluate the effectiveness of The-Optimal-Lymph-Flow.™ self-care strategies.
- ✓ Follow up patients at week 8 and 12 after intervention
- ✓ Accomplish *Intervention Protocol* using the developed App as well as the web-based platform.
- ✓ Continue to improve the App based on the feedbacks from the patients and other involved practitioners' (nurses and doctors) and research findings.
- ✓ Prepare presentations and manuscripts for publication

Month 24-30

- ✓ Further improve the App based on the feedback from previous years to develop a final version. This version will be made available on the Apple App store and Google App store for Android devices.
- ✓ Prepare presentations and manuscripts for publications
- ✓ Submit a multi-site randomized clinical trial to the National Institute of Health

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D. Organizational Detail (not to exceed 3 pages)

1. Leadership and Organizational Capability:

The New York University College of Nursing (NYUCN) has a well-earned international reputation for excellence that is integral to our priority of addressing healthcare disparities both in the U.S. and globally. NYU College of Nursing offers world-class nursing programs (BS, MS, DNP, and PhD) provide the educational foundation to prepare the next generation of nursing leaders. NYUCN's graduates are leading the way into a new era of nursing, where playing a leadership role in achieving excellent patient outcomes and a healthier global society are priorities. NYUCN's overall mission is consistent with high-quality innovations for the nursing profession. Faculty pride themselves on living their mission and values.

The College is currently ranked 6th in research funding from the National Institute of Health (NIH), thanks to the strength of our research mission and our highly credentialed and published research and clinical faculty members. At NYU College of Nursing, teaching and research work hand-in-hand to provide students with a dynamic environment that promotes learning and professional development. Global leadership is expanding dramatically; faculty and students are conducting grant-funded initiatives to strengthen health care in 18 countries around the world. To meet growing demands for advanced degrees in the nursing profession, the College offers a DNP (Doctor of Nursing Practice) degree program, which graduated its first class in 2011. College of Nursing faculty are developing inter-professional collaborations, with NYU College of Dentistry and School of Medicine to prepare the next generation of health leaders.

The NYU Cancer Center is an urban medical center in New York City. The center provides treatment for women diagnosed with breast cancer, including traditional breast surgery, breast-conserving surgery, sentinel lymph nodes biopsy, radiation therapy, chemotherapy, and hormonal therapy. At NYU Cancer Center, approximately 1,000 newly diagnosed breast cancer patients are seen each year, providing a large patient pool for the proposed project. Also at NYU Cancer Center, available shared resources for our proposed study include Analytical Chemistry; Biostatistics; Core Clinical Laboratory; Experimental Pathology; Flow Cytometry Unit; Proteomics, RNAi Core Facility.

The New York University School of Medicine also provides institutional shared resources, including Division of Laboratory and Animal Resources; The Ehrman Medical Library; Research Computing Resource; DNA Synthesis and Sequencing Facility; Protein Analysis Facility; Transgenic Mouse Facility; and Information Technology Group.

Dr. Mei R. Fu's Nursing Research Laboratory is located at the NYU Cancer Center where the clinics for the breast surgeons are located. The location of the laboratory makes it efficient for participants to come for both routine clinical follow-up and research follow-up visits at the same time. The laboratory is equipped with an infra-red perometer, a Full Body Sensor Body Composition Monitor and Scale, an examination table, a computer specifically for the study, and supply cabinets.

NYU Polytechnic School of Engineering: Co-PI Yao Wang is in the Department of Electrical and Computer Engineering, NYU Polytechnic School of Engineering, located at 2 Metrotech Center, Brooklyn. This location is within 45 minutes by public transportation to the NYU Clinical Cancer

Center in Manhattan, and 30 minutes to Dr. Fu's office in Washington Square in Manhattan. The Brooklyn location is equipped with state-of-the-art office and computer facilities. All the offices and classrooms have high speed Internet connection and are served by dedicated servers.

Dr. Yao Wang leads the Video Lab in department of Electrical and Computer Engineering, Polytechnic School of Engineering School. The Lab currently has 10 Ph.D. Students. The students are housed inside the CATT/NYU WIRELESS center, located on the 9th floor of 2 Metrotech Center, Brooklyn, NY 11201. All students have cubicle office space. Dr. Wang has an office adjacent to the graduate students space on the same floor. The computers are provided for each student, plus a dedicated server computer for the lab. There is gigabit Ethernet connectivity at all student desks. There are shared printers and copiers in the center for all the faculty members and students.

2. Staff Capacity:

Dr. Mei R. Fu (PhD, RN, ACNS-BC, FAAN), the Principal Investigator, is Tenured Associate Professor of Nursing at the New York University. She is also a Fellow of American Academy of Nursing, a Fellow of Geriatrics at the Hartford Institute of Geriatrics, and a Fellow of New York Academy of Medicine. Her scientific focus is cancer-related symptoms and management of chronic illnesses. Her research incorporates qualitative and quantitative methods, genomic and biomarker approaches and cutting edge measurement technology along with innovative behavioral interventions. Her productive research has been supported by National Institute of Health, Oncology Nursing Society, the Hartford Institute of Geriatric Nursing, Avon Foundation, Vital Fund, Judges and Lawyers for Breast Cancer Alert. Dr. Fu's award-winning research informs effective ways of performing symptom assessment and implementing risk-reduction behaviors that have profound sustained effect on national and international clinical practice for lymphedema care.

Joan Scagliola (RN, MS), Senior Director of Nursing, Ambulatory Oncology, NYU Cancer Center, will ensure the administrative and clinical support for the project. Please see her commitment letter.

Dr. Deborah Axelrod (M.D.), Clinical Associate Professor of surgery, NYU School of Medicine, board certified surgeon specialized in breast diseases and breast cancer, the Director of Clinical Breast Services and Breast Surgery and Medical Director of Community Cancer Education and Outreach at NYU Cancer Institute. As a senior surgeon, Dr. Axelrod has extensive clinical, surgical, and research expertise on breast surgery including sentinel lymph node biopsy, and post breast cancer treatment outcomes, patient education on the recognition of lymphedema and risk reduction. She will contribute to the proposed project by sharing her clinical and surgical expertise needed for the success of the project.

Program Coordinator [To be Determined], the program coordinator will help Dr. Fu to coordinate the project, recruit and consent potential participants for the proposed project. She will also help in answering participants' questions submitted to "Ask an Expert," patient contact for follow-ups, data collection, management, and storage.

Oncology Research Nurse [To be Determined], will be hired and trained to conduct data including the questionnaires and narrative responses, as well as limb volume measurement by the perometer, Body Mass Index by a bioimpedance device.

Dr. Yao Wang (PhD), Tenured Professor of Electrical and Computer Engineering, Polytechnic School of Engineering of New York University will supervise a Graduate Student to develop instant messages and interactive applications described below in year 1 and 2. She is a recognized expert in video coding, networked video applications, medical imaging, and pattern recognition. She will be supervising a graduate student to program the delivery of instant message upon the participants' completion of online report of pain and symptoms related to lymphedema. She will also supervise the student to develop an interactive and instructional application [App] based on current avatar videos capable of ensuring patients' continuing engagement in using The-Optimal-Lymph-Flow™ and self-care to promote lymph flow, manage pain and symptoms.

Research Assistant for Technology [To be Determined], will spend 3 month efforts in Year 1 and 2, respectively. In Year 1, under the supervision of Dr. Wang, the Research Assistant will create software that enables the delivery of instant message upon the participants' completion of online report of pain and symptoms related to lymphedema. The research assistant will also develop interactive and instructional application [app] guiding the patients through the exercises based on the current avatar videos, with features such as enabling the patient to create an exercise schedule, tracking the actual exercise time and frequency, generating motivating messages to the patients based on the record, etc. In Year 2, the Research Assistant, under the supervision of Dr. Wang, will refine the app for The-Optimal-Lymph-Flow ^{TM} group based on the feedback from the patients, practitioners, and researchers. A final version will be produced in Year 3 based on feedbacks from Year 2. In Year 3, the final version of app supported by Apple and Android devices will be completed and made publically available for free if feasible or at a very low cost (e.g., $2.99) on Apple App stores and on Google App store.

Dr. Jason Fletcher (PhD), Senior Biostatistician, a is a quantitative researcher with more than 15 years' experience conducting evaluation research in the fields of community and public health. His methodological interests include item-response theory, differential item analysis, multilevel modeling and analysis of longitudinal data. He has extensive experience conducting analyses using biomedical data. Dr. Fletcher has been actively involved in the preparation of the proposed project. He will collaborate with the PI and be responsible for comprehensive data management, statistical data analyses, data interpretation, and preparation of reports and manuscripts as co-author.

Dr. Winslow Burleson (PhD), Associate Professor, NYU College of Nursing. He is a known expert for technology applications. He will collaborate with Dr. Jeremy Rowe in providing and developing design and evaluation assistance regarding motivation and effectiveness of the training and instruction as well as app development.

Dr. Jeremy Rowe, Research Scientist (PhD), will work in collaboration with the PI and Dr. Winslow Burleson in providing and developing design and evaluation assistance regarding motivation and effectiveness of the training and instruction.

NYU Langone
MEDICAL CENTER

October 7, 2014

Dear Dr. Fu,

I am writing to express my enthusiastic support for your proposed study "**The Optimal Lymph Flow.**" Lymphedema is a serious and widespread complication resulting from breast cancer treatment. It is particularly tragic that, for so many, this dreaded condition is avoidable with the proper exercise. The challenge is getting this evidence-based information into the hands of patients and the health services community in general. So, what you now seek to accomplish by taking your proven research to the Internet is exciting and extremely timely.

Over the years, I have enjoyed working with you on several of your projects and I am very impressed and pleased to see the impact of your research on patients. As the Senior Director of Ambulatory Oncology Services, I have discussed your study with the Director of our Research Program and our Clinical Oncology Team and we are interested in and supportive of this study. We believe your research has the potential to provide information that will help guide the development of individualized nursing interventions to help breast cancer patients to reduce their risk of lymphedema.

The Perlmutter Cancer Center, an NCI designated cancer center and a division of NYU Medical Langone Center, is dedicated to improving cancer prevention and treatment through basic science and applied clinical research. At the Perlmutter Cancer Center, we have approximately 1000 women per year under treatment for breast cancer. The Perlmutter Cancer Center is an ideal setting for the project to recruit breast cancer survivors. Recognizing the importance of this research, clinicians, and other professionals at the Perlmutter Cancer Center will provide support to ensure the success of your project. In addition, the collaborative relationships you built among the nurses and physicians over the years will be a great asset for the proposed project.

Having collaborated so successfully with you on your prior clinical study that has led to "The Optimal Lymph Flow" I look forward to partnering with you again on this critical next step to exponentially bring relief from pain and disfigurement to so many women. You will have the full support of our oncology team to implement this important research project. Please let me know if I can be of further assistance.

Sincerely,

Joan Scagliola

Joan Scagliola, MSN, RN
Senior Director of Nursing
Ambulatory Oncology

NYU COLLEGE OF Nursing

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Office of the Dean

October 2, 2014

Dear Pfizer Scientific Review Committee:

As the Dean of the NYU College of Nursing, I am delighted to offer my enthusiastic support for Dr. Fu's proposed collaborative translational pilot project, *The Optimal Lymph Flow*, which responds to the pressing need for an e-health approach to improve outcomes and optimize healthcare utilization for breast cancer survivors suffering with chronic pain and lifelong disfigurement as a result of lymphedema.

The proposed study aims to leverage the near universality of the Internet to bring relief to so many who either already suffer with the pain and disfigurement caused by lymphedema, or are likely to contract this condition in the future. This has potential to be as cost-effective as it is innovative. Moreover, I believe the proposed study will provide the crucial foundation for a future efficacy multi-centered randomized clinical trial (RCT) from the National Institute of Health (NIH).

I have been impressed by Dr. Fu's dedication to research on behalf of breast cancer survivors. Certainly, the proposed project is a logical progression that builds upon her more than eight years here at the College of Nursing on collaborative projects responding to breast cancer-related symptoms and lymphedema risk reduction and management. The proposed study serves as a focal platform to garner the talents from different disciplines at NYU to advance the science of symptom management, including the departments of nursing, surgery, pathology, biostatistics, NYU Poly Tech, and the NYU Cancer Center. I am especially pleased that two of the most recent additions to our faculty who are well-known experts for technology applications (apps) will be responsible for packaging and developing *The Optimal Lymph Flow* apps.

Recognizing the importance of *The Optimal Lymph Flow*, I can assure you that the NYU College of Nursing Office of Research will facilitate post-award management if awarded the funding requested from the Pfizer Independent Grants for Learning & Change.

Also, based on the College's robust track record of evidenced-based research, we anticipate readily attracting additional partners to promote the visibility of the study. These include consumer groups, health professional organizations, disease-prevention foundations, public health education agencies, and patient-powered research networks.

Finally, a significant number of our faculty and staff serve on a diverse range of local, state, national, and international governmental policy-influencing panels and committees, including Medicare and Medicaid. We therefore anticipate that over the life of the proposed study the NYU College of Nursing will have numerous opportunities to report upon its progress and findings to a wide – and receptive – audience of policy-makers and stakeholders.

On behalf of the NYU College of Nursing, I look forward to partnering with Pfizer on this groundbreaking work that will address the urgent, but unmet, healthcare needs of breast cancer survivors at risk for lymphedema.

Sincerely,

Eileen M. Sullivan-Marx

Eileen M. Sullivan-Marx, PhD, RN, FAAN
Dean & Erline Perkins McGriff Professor