Acupuncture for chronic lymphedema: A randomized wait-list controlled trial

PROTOCOL FACE PAGE FOR MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Table 1. Protocol Summary	
Study Title	Acupuncture for chronic lymphedema: A randomized wait-list controlled trial
Primary Objective	To determine the effectiveness of acupuncture for breast cancer-related lymphedema (BCRL) as measured by arm circumference after 6 weeks of acupuncture treatment
Secondary Objectives	To assess differences between treatment group in bioimpedance scores To determine the safety of acupuncture for the treatment of BCRL To determine whether changes in lymphedema resulting from acupuncture treatment are sustained at 3-months (12 weeks) following completion of acupuncture treatment To determine whether time since lymphedema diagnosis affects response to acupuncture To determine whether stage affects response to acupuncture
Patient Population	Breast cancer patients with a diagnosis of chronic lymphedema (defined as a diagnosis of lymphedema, with affected arm >2cm larger than the unaffected arm, for at least 6 months and no more than 5 years) and stage II or higher lymphedema.
Number of Evaluable Patients Required	82 patients (41 randomized to each arm)
Study Design	Randomized prospective wait-list controlled trial
Treatment: Acupuncture Treatment Group	Acupuncture treatment twice weekly for 6 weeks
Treatment: Wait-List Control Group	No treatment for six weeks (wait-list). After 6 weeks, the wait-list control patients will cross over and receive acupuncture twice weekly for 6 weeks.
Time to Completion	Participants in the acupuncture treatment group will receive six weeks of acupuncture treatment. Assessments will be conducted prior to initiation of treatment, after six weeks of treatment, and again three months after conclusion of treatment. Patients in the wait-list control group will be on a waiting list for six weeks and then will cross-over and receive acupuncture treatment twice weekly for 6 weeks. Assessments will be conducted at baseline, after 6 weeks on the wait-list prior to onset of acupuncture treatment, after 6 weeks of acupuncture, and 3 months after completion of treatment.

Table 2. Protocol Schema															
Week	0	1	2	3	4	5	6	7	8	9	10	11	12	~18	~24
Acupuncture Group															
Acupuncture Treatment (2x/week)		X	X	X	X	X	X								
Lymphedema Staging	X														
Arm Measurement	X						X							X	
Pregnancy Test*	X														
Bioimpedance	X						X							X	
BMI	X						X							X	
Other Lymphedema Treatments Used by Patients	X →	→	→	→	→	→	→	→	→	→	→	→	→	→	
Side Effects		X →	→	→	→	→	→	→	→	→	→	→	→	→	
Wait-List Control Group															
Acupuncture Treatment (2x/week)	X							X	X	X	X	X	X		
Lymphedema Staging	X														
Arm Measurement	X						X						X		X
Pregnancy Test*	X														
Bioimpedance	X						X						X		X
BMI	X						X						X		X
Other Lymphedema Treatments Used By Patients	X →	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Side Effects							X →	→	→	→	→	→	→	→	→

*Pregnancy test only for women of childbearing potential

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective: To determine the effectiveness of acupuncture for the treatment of breast cancer-related lymphedema (BCRL) as measured by arm circumference after 6 weeks of acupuncture treatment.

Secondary Objectives:

- To assess differences between treatment group in bioimpedience scores
- To determine the safety of acupuncture treatment for BCRL

- To determine whether changes in lymphedema resulting from 6 weeks of acupuncture treatment are sustained over a 3-month follow-up period

- To determine whether time since lymphedema diagnosis affects response to acupuncture

- To determine whether stage affects response to acupuncture

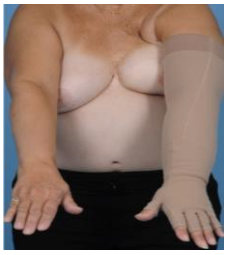
Our working hypothesis, that acupuncture will decrease objective measures of BCRL, is based on our preliminary pilot research that demonstrated no SAEs and showed that more than 1/3 of patients showed at least a 30% reduction in lymphedema following acupuncture treatment. [1]
We plan now to test this hypothesis with a randomized, prospective wait-list controlled clinical trial.

3.0 BACKGROUND AND RATIONALE

3.1 Lymphedema

Lymphedema, the chronic swelling of a limb after lymph node removal, is a dreaded complication of breast cancer treatment.[2] Lymphedema is more common than secondary tumors or heart damage resulting from chemotherapy or radiation.[2] In fact, up to 50% of patients who undergo axillary lymph node removal develop lymphedema, and the World Health Organization estimates that 3-5 million Americans suffer from this problem. [3-6] Even minor lymphatic injury can result in lymphedema, thereby exposing nearly every breast cancer survivor to the risk of this complication.[7] The incidence of lymphedema is likely to increase due to increased rates of obesity, use of radiation therapy, and an aging population, each of which independently increases the risk of this complication.[3,8]

Lymphedema can have devastating consequences. Many patients have frequent arm infections, often requiring hospitalization for antibiotics. Lymphedematous arms are heavy, swollen and stiff, with thickened, rough skin. Courses of daily, intensive physiotherapy lasting 6 weeks at a time are usually required to massage the lymphatic fluid out of the affected arm. These treatments often need to be repeated if lymphedema recurs. In addition, patients are obligated to wear tight, uncomfortable elastic stockings on their arm to prevent worsening of the swelling (**Figure 1**). These garments serve as a constant reminder to patients of their cancer diagnosis, decreasing quality of life and increasing anxiety.[9-15]



Lymphedema is a significant source of biomedical expenditure. Managing lymphedema-related problems increases overall treatment costs by more than $10,000 a year per patient.[16] These costs are a significant source of hardship for many patients as insurance coverage is limited and often inadequate for the lifetime palliative treatments currently available.

Figure 1. Elastic garment for left arm lymphedema

3.2 Acupuncture for Lymphedema

Early clinical trials, as well as our own preliminary data, show that acupuncture can decrease limb swelling and improve the symptoms of lymphedema in both lower and upper extremities.[1,17-19] The value and safety of acupuncture is documented in the growing body of literature on acupuncture treatment for chronic pain,[20-24] osteoarthritis,[25] migraine,[26] and the relief of procedural anxiety.[27,28] In addition, acupuncture may effectively treat a range of problems associated with cancer and cancer treatments, such as hot flashes,[29,30] chronic fatigue,[31] neuropathy,[32] nausea and vomiting,[33,34] xerostomia,[35] and dysphagia.[36] These results, plus our positive published pilot data, represent the foundations on which this protocol was constructed. We aim to further test the safety and effectiveness of acupuncture as a treatment for lymphedema in a larger, randomized trial.

Because current treatment options for lymphedema are time consuming, expensive and palliative, there is pressing need for effective means to treat this problem. Our preliminary research demonstrates that acupuncture decreases lymphedema by nearly 30% in patients with BCRL.[1]

3.2.1 Preliminary study

Following IRB approval, we conducted a preliminary trial to assess the safety of acupuncture in patients with breast cancer-related lymphedema. Per the stopping rule for this study (at least 40% of patients achieved at least 30% reduction in comparative arm circumference), the pilot was stopped at N=9 and the data published [1]. We continued the trial up to the total of 33 patients on whom the preliminary data are reported here. Patients were identified, screened, and, following informed consent and their oncologists' approval, enrolled in the trial. Inclusion criteria included women age ≥18 years, unilateral lymphedema (>2cm circumference difference between affected and unaffected arms) resulting from surgery and/or radiation therapy for breast cancer, and clinical diagnosis of lymphedema for at least 6 months and no more than 5 years. The >2cm circumference difference between the affected and unaffected arms was used as the cutoff for lymphedema because a difference of 2cm or more at any point compared with the unaffected arm is considered to be clinically significant by experts and has been used in previous studies at MSKCC and elsewhere[7,49]. The 6 month – 5 year timeframe was determined as optimal for both the pilot and the current RCT because it allows ample time for any surgically related nonlymphedema swelling to subside by 6 months post-surgery, while a cap of 5 years captures the broadest range of cases, and has been used as a timeframe in several studies. [7] [48]

Acupuncture technique. Traditional Chinese Medicine (TCM) acupuncture treatment was performed by certified, licensed MSKCC staff acupuncturists with extensive clinical experience in treating cancer patients. Alcohol swabs were applied prior to insertion of sterile single-use filiform needles (32-36 gauge; 30-40mm in length) that penetrate 5-10 mm into the skin. A total of 14 needles were inserted in both the affected and unaffected limbs. The points were stimulated manually by gentle rotation of the needles with lift and thrust. The selected acupuncture points (**Figure 2**) were based on historical context, the published literature, and the consensus of our experienced group of MSKCC staff acupuncturists.[17-19,32,35] Many of these local points are used to treat pain, weakness and motor impairment; others are traditionally used to drain "dampness", a TCM concept similar to edema. Each treatment was 30 minutes in duration and acupuncture was performed twice weekly for 4 consecutive weeks.

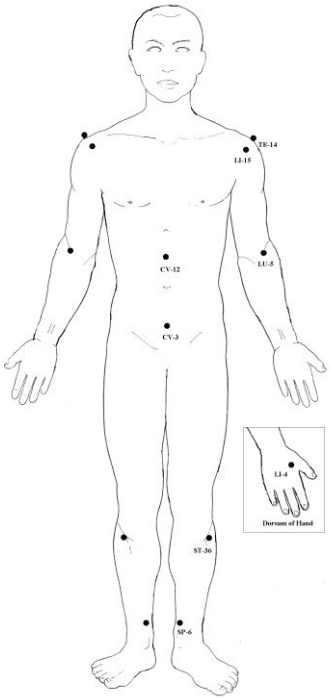


Figure 2. Acupuncture Points

Lymphedema measurements. We selected two arm circumference measurements for our objective analysis because this is the most widely used method to diagnose upper-extremity lymphedema, and based on data that 2-point measures have high sensitivity and specificity (80% and 71%, respectively) with high correlation with limb volume calculations using water displacement [37] and a threshold of 5% change in arm circumference.[38] Further, circumference measurements have excellent responsiveness enabling reliable measurement of differences of >0.4cm.[39] Measurement of two points compares favorably with the sensitivity and specificity of multiple point measurements with high test-retest and inter-rater reliability.[38,40,41] Further, water displacement techniques have potential for inaccuracy as well as practical difficulties (space issues, spillage, and the need for sterile technique for each measurement). Based on these considerations, circumference measurements of the affected and unaffected arms were performed before initiation of treatment and after each treatment session using our previously published methods.[1,7,40] Measurements were performed by trained research assistants10cm above (upper arm) and 5cm below (lower arm) the olecranon process using non-stretch tape measures.

We used our published technique to calculate the extent of lymphedema by determining the difference in circumference of the affected and unaffected arms and then expressing changes after treatment as a percentage of pre-treatment levels.[1,7] This measure enables us to determine the response to treatment and adjusts outcomes for baseline arm circumference. Monthly phone calls were made for 6 months to determine whether patients developed any complications.

Results of preliminary study.

1. 31 of the 33 patients showed decrease in lymphedema.
2. 11 of 31 pts (35%) showed decrease of 30% or more compared to unaffected arm.
3. the remaining 20 pts showed a decrease of an average of 16% compared to unaffected arm.
4. no reversion back to pre-acupuncture treatment circumference occurred over time.
5. no SAEs.

There were no serious adverse events (infections or severe exacerbation) after hundreds of treatment sessions and 6-month follow-up interviews. Complaints were minor and comprised primarily of mild bruising or minor pain/tingling in the arm, shoulder, or acupuncture site. Two patients had slight transient swelling of the lower arm. In summary, our preliminary work demonstrates that acupuncture for the treatment of BCRL is safe, well tolerated, and may decrease lymphedema.

3.3 Summary of rationale for the proposed study

Lymphedema is a prevalent complication of breast cancer treatment. Available treatments are burdensome, not curative and do not produce substantive reduction is arm circumference. Preliminary data suggest that acupuncture is safe, well tolerated and may decrease breast cancer-related lymphedema. Therefore, a randomized trial is warranted.

Successful completion of the proposed research could lead to significant benefits:

- Study subjects may see a reduction or disappearance of lymphedema.
- A novel, effective, inexpensive modality may be added as a treatment option.
- Reduction of health care costs (as noted, lymphedema treatment costs average $10,000 a year per patient).[16]
- Patients may experience a decrease in related physical and emotional problems.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a randomized, prospective, wait-list controlled design to test the hypothesis that acupuncture is a safe and effective treatment for BCRL. A secondary aim is to determine whether improvements in lymphedema resulting from acupuncture are sustained over a 3-month follow-up period after the completion of treatment.

4.2 Intervention

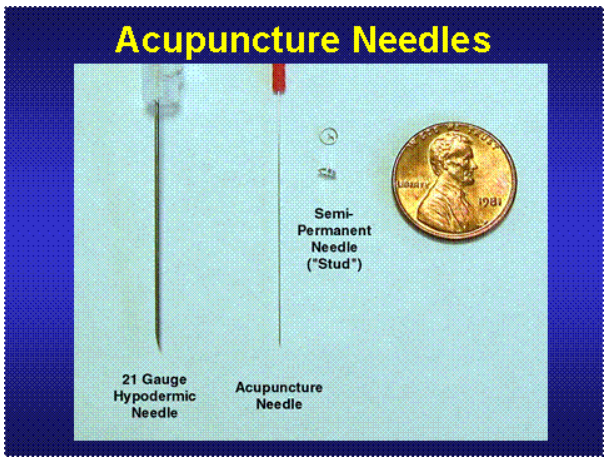
Eligible patients will be randomized to either the Acupuncture or Wait-list Control group. A synopsis of the study design and schema are given in Tables 1 and 2 in Section 1.0. Patients in the acupuncture group will receive acupuncture treatment twice weekly for six consecutive weeks at no cost. After approximately six weeks, those in the wait-list control group will cross over and receive acupuncture twice weekly for 6 consecutive weeks at no cost. Patients will be advised to continue any standard lymphedema exercises and/or use of compression garments they had been following prior to clinical trial participation. The acupuncture point prescription applied in our pilot study will be used in this RCT. Point selection was based on historical context, the published literature, and the consensus of our experienced group of MSKCC staff acupuncturists.[17-19,32,35] In addition to our

research, the Integrative Medicine Service has a history of safe and effective clinical acupuncture work with MSKCC outpatients and inpatients for over a decade.

The length of treatment for the proposed study was increased to six weeks from the pilot study's four weeks. This increase is intended to maximize treatment effectiveness based on the consensus of our experienced acupuncture faculty plus preliminary study patient interviews.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Acupuncture treatment will be given by certified, licensed MSKCC staff acupuncturists. All have extensive clinical experience in treating cancer patients. Alcohol swabs are applied prior to insertion of sterile, single-use, filiform needles (32-36 gauge; 30-40mm in length) that penetrate 5-10 mm into the skin. The adjacent photo indicates the relative size of acupuncture needles.



A total of 14 needles will be inserted in the affected and unaffected limbs (Fig. 2). The points will be stimulated manually by gentle rotation of the needles with lift and thrust. These points are easily accessible with the patient lying supine. The point prescription, described in the table below (Table 3), is based on that used in our pilot study, historical context, the published literature and the consensus of our experienced group of MSKCC staff acupuncturists.[17-19,32,35] Many of these points are used to treat pain, weakness and motor impairment; others are traditionally used to drain "dampness", a Traditional Chinese Medicine concept similar to edema. Acupuncture treatments will be given twice a week for 6 consecutive weeks. Each treatment will last 30 minutes. Patients randomized to the Acupuncture group will be treated for the first six weeks of the study. Patients randomized to the Wait-List Control group will wait approximately six weeks from baseline and then cross-over to receive acupuncture treatment. All patients will be asked not to receive acupuncture treatment, other than that performed for the study, while they are on study.

Table 3.

Point	Location	Function/Action
LI-15	Antero-Inferior to the acromion	Alleviates pain in shoulder [17]
LI 4	Dorsum of the hand (midpoint of 2nd MC bone in 1st interosseous m	Activates the channel and alleviates pain [38]
TE-14	Posterior and inferior to the acromion	Alleviates pain and benefits the shoulder joint [17]
CV-12	Midline abdomen between umbilicus and xiphoid	Regulates Qi and alleviates pain [16, 17]
CV-3	Midline abdomen, 4 inches below umbilicus	Drains "dampness" and dispels stagnation [16, 17]
LU 5	On the cubital crease, radial side of the tendon of m. biceps brachii	Regulates the water passages and relaxes the sinews [39]
SP-6	Posterior border/ medial aspect of the tibia, 3 inches above malleolus	Resolves dampness, activates the channel and alleviates pain [16, 17]
ST 36	Lateral to the anterior tibial crest and inferior to the lateral patella.	Activates the channel and alleviates pain [16, 17]

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Women age 18 or older
- Lymphedema in an arm as a result of surgery, chemotherapy, and/or radiation therapy for breast cancer per breast surgeon or medical oncologist
- Patients must have received a clinical diagnosis of lymphedema for at least 6 months and no more than 5 years. This timeframe allows ample time for any surgically related nonlymphedema swelling to subside by 6 months post-surgery, while a cap of 5 years will capture the broadest range of cases, and has been used as a timeframe in several studies including our pilot study. [1, 7, 48]
- The affected arm must be >2cm larger than the unaffected arm. Differences of 2 cm or more between the affected and unaffected arm are considered by experts to be clinically significant [7,49]. Each affected arm will be measured in two areas: upper arm and forearm. The larger of the two measures—upper arm or forearm— will be used for analysis.
- Classified as International Society of Lymphology (ISL) stage II or higher as determined by an MSKCC Certified Lymphedema Therapist (CLT)

6.2 Subject Exclusion Criteria

- Bilateral lymphedema
- Previous acupuncture treatment for lymphedema
- Concurrent diuretic use
- History of primary (congenital) lymphedema
- Pregnant or planning to become pregnant during the course of the study

- Has an implanted electronically charged medical device

7.0 RECRUITMENT PLAN

Recruitment Plan (with Limited waiver of Authorization)

Patients will be identified and referred to the study RSA for accrual and consent by a member of the patient's treatment team or by protocol investigators. Patients may also be self-referred, referred by other clinicians, or referred by a physician from other hospitals. Information about the protocol will appear in lay language on MSKCC's web site and clinicaltrials.gov. Printed material (flyers, shown in Appendix 1) will be posted in MSKCC clinic areas and distributed to potential referral sources. In addition, patients with a diagnosis of lymphedema (identified via MSKCC's DataLine) will be sent a standard letter (Appendix 2) to introduce the study. The recruitment letter to patients states that we are conducting a trial of "Acupuncture for the Treatment of Chronic Lymphedema" and if interested in learning more, the patient should contact the research study assistant for the trial. This recruitment method, similar to that used in the pilot study (IRB# 09-136), is widely applied. It is known to increase recruitment and decrease physician workload. Integrative Medicine RSAs will schedule and complete screening and consenting appointments. Because a large number of breast cancer patients are treated at MSKCC, and because our pilot study was completed in short order, reflecting patient interest, we do not anticipate accrual difficulties for this trial.

Initial contact with prospective subjects typically will be made by a member of the treatment team, a study investigator or research staff in consultation with the treatment team. The recruitment process presents no more than minimal risk to patient privacy, and minimal PHI will be maintained on screening logs. For these reasons, we seek a (partial) limited waiver of authorization to (1) review medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) converse with patients regarding possible enrollment; (3) handle PHI contained in those records and provided by potential subjects; and (4) maintain minimal PHI information in a screening log of patients approached.

8.0 PRETREATMENT EVALUATION

Attendings will approve potential patients per eligibility requirements noted above. Baseline measures to assess lymphedema (arm circumference, bioimpedance) , and BMI will be collected by trained study RSAs. A pregnancy test will be performed for women of child-bearing potential. There is no known risk of bioimpedance testing for pregnant women but the device has not been approved for use on pregnant women so women who are pregnant or intending to become pregnant during the course of the study will be excluded. Lymphedema staging will be performed by MSKCC's Certified Lymphedema Therapists. In addition, type of surgery (mastectomy/limited), type of axillary surgery (SLNB alone or followed by axillary lymph node dissection), age at axillary surgery and at study entry, radiation therapy (yes/no) and chemotherapy (yes/no) will be recorded by the RSA and maintained in MSKCC's clinical research database (CRDB).

Lymphedema Staging. All participants will be evaluated and their lymphedema will be staged by a Certified Lymphedema Therapist (CLT) employed by MSKCC. Staging will be based on the International Society of Lymphology (ISL) staging system. Lymphedema staging will be drawn from a lymphedema evaluation in MSKCC's Electronic Medical Record (EMR) if it occurred within 6

months of the onset of acupuncture treatment, or an assessment by a Certified Lymphedema Therapist at MSKCC's Evelyn H. Lauder Breast and Imaging Center (BAIC) will be conducted. All lymphedema evaluations in the EMR are performed by Certified Lymphedema Therapists who are employees of MSKCC. Participants who are classified as stage II or higher will be eligible to participate in the study.

Arm Circumference will be measured in the standard fashion. Patients' upper arm and forearms will be measured for both the affected and unaffected arms. The greater difference between affected and unaffected arms (either the forearm or the upper arm) will be used to determine eligibility. This measurement will also serve as the baseline measure of arm circumference for enrolled patients. Measurement frequency is detailed below in section 10.0, "Evaluation During Treatment/Intervention."

Bioimpedance measurement will be performed using the Impedimed L-Dex U400. This device measures the rate of electrical current transmission through tissues and estimates fluid content in a lymphedematous limb compared with the normal limb. Bioimpedance has high inter and intra-rater reliability, is highly sensitive and specific for lymphedema (100% and 98%, respectively), and is highly correlated with circumference measurements making it an excellent method to confirm our objective findings.[42-44] Further, bioimpedance is a useful way of analyzing subclinical changes in lymphatic transport (i.e. not measurable by circumference analysis).[42] This analysis will therefore be useful in identifying patients who report subjective improvements in lymphedema but do not have significant changes in arm circumference. The Bioimpedience equipmment will be donated by the distributor for this study. Measurement frequency is detailed below in section10.0, "Evaluation During Treatment/Intervention."

9.0 TREATMENT/INTERVENTION PLAN

Acupuncture treatment will be given at the Integrative Medicine Outpatient Center on 74th Street and First Avenue and/or at MSKCC's Breast and Imaging Center (300 East 66th Street, between First and Second Avenues). Each treatment will be 30 minutes in duration. Patients will receive two acupuncture treatments each week for six consecutive weeks. Patients will be advised to continue their standard lymphedema treatments such as exercise or use of compression garments if these were in use prior to clinical trial participation. Patients will be asked to contact the RSA should any side effects occur, and at each study visit, the RSA will ask patients about side effects and about the any other lymphedema treatments they are using.

All Integrative Medicine Service acupuncturists are licensed, credentialed employees of MSKCC.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

The study schema is presented in Section 1.0. Table 2. For participants in the acupuncture treatment group, followup objective assessments (limb circumference, bioimpedance) of lymphedema will be performed after 6 weeks of acupuncture treatment (within 1 week of the last acupuncture treatment) and again about three months after conclusion of treatment (3 months +/- 1 week from the last acupuncture treatment). For participants in the wait-list control group, follow-up objective assessments of lymphedema will be performed after approximately 6 weeks on the wait-list (6 weeks +/- 1 week from the patient's consent), before onset of acupuncture treatment, following 6

weeks of acupuncture treatment (within 1 week of the last acupuncture treatment) and about 3 months after completion of treatment (3 months +/- 1 week from the last acupuncture treatment). BMI will be measured at the same timepoints. Other treatments for lymphedema used by the patient while on study will be recorded, as will side effects; other lymphedema treatments tend to be consistent across most MSKCC patients, as all are encouraged to receive manual lymph drainage, exercise, etc.. All assessments, including circumference measurements of the affected and unaffected arms, bioimpedance, and BMI will be performed by trained research study assistants. Study staff responsible for measuring subjects' arms will not be blinded to treatment assignments for logistic reasons and because it is not possible for patients themselves to be blinded.

11.0 TOXICITIES/SIDE EFFECTS

Patients will be monitored for side effects at each visit. Any adverse events will be reported according to standard procedures. Although the only published studies of acupuncture for lymphedema found neither infection nor other side effects [17 19], study participants will be instructed to contact the study RSA with any problems, such as infection, that might arise.

Acupuncture is a generally safe treatment modality when performed by qualified practitioners. After 760,000 treatments in 97,733 patients receiving acupuncture in Germany, only six cases of serious adverse events were reported.[47] No serious adverse events were reported in our pilot study.

Most common side effects (<5%):

- Minor bleeding at acupuncture sites
- Bruises at acupuncture sites
- Pain or an unfamiliar sensation at acupuncture sites (local or radiating)

Less Common side Effects (<1%):

- Local allergic reaction (urticaria)
- Drowsiness, sleep disturbances (insomnia)
- Anxiety, nervousness
- Vasovagal reaction (fainting, dizziness, nausea, vomiting)

Rare but more serious side effects (<0.1%):

- Local skin Infection
- Organ puncture

Severity will be graded as "serious" or "non-serious". Serious AEs are those that require hospitalization, lead to death or disability or require urgent medical attention to prevent death or disability. The intensity of non-serious AEs will be graded as mild, moderate or severe.

Causality will be assessed as follows. The AE will be described as "Probable" if all of the following apply: there is a rational relationship between the occurrence of the AE and the time of treatment; the AE has already been described as an AE of acupuncture or could reasonably be anticipated to be an acupuncture AE; regression or disappearance of the AE (unless permanent) after discontinuation of treatment or dose reduction; AE cannot be plausibly be explained in terms of other causal factors. The AE will be described as "Possible" if all of the following apply: there is a rational

relationship to the time of treatment administration; the AE has already been described as an AE of acupuncture; the AE could be explained by other factors. The AE will be described as "Improbable" if the following apply: there is no rational relationship to the time of treatment administration; the AE has not been reported so far as a side effect of treatment and cannot reasonably be expected as an acupuncture side-effect and any of the following: non-permanent AE persists after discontinuation of the treatment or dose reduction; repeated exposure does not lead to reappearance of the AE; AE could be explained by numerous other factors. The AE will be described as "No relationship" if all of the following apply: there is no rational relationship to the time of treatment administration; AE is evidently caused by other factors, e.g. symptom of a concomitant disease. The AE will be described as "Unable to evaluate" if the amount and content of data do not permit a judgment of the relationship to the treatment.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Patients will be considered evaluable if they provide both a baseline and follow-up arm circumference measure. Patients will be analyzed according to randomization allocation regardless of the number of treatments received.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from the study if they experience unacceptable adverse events from acupuncture. If at any time the primary oncologist believes it is in the best interest of the participant to be withdrawn from the study, the participant will be withdrawn. Study subjects also may elect to withdraw from the study. Patients who withdraw will be asked for their reasons. These will be defined as: acupuncture treatment inconvenience; belief that treatment is ineffective; data collection inconvenience; medical reasons; other. Patients who discontinue participation in the study will be asked if they are willing to provide follow-up data or whether they wish to withdraw completely.

14.0 BIOSTATISTICS

Primary Aim

The primary aim is to establish the difference in the extent of lymphedema between patients receiving acupuncture and patients receiving no treatment. Extent of lymphedema is defined as the greater difference between the affected and unaffected arms (either the forearm or the upper arm). The extent of lymphedema post-treatment and at the 3 month follow-up timepoint will be from the same site as that determined at baseline. The difference in the extent of lymphedema between groups will be assessed with an analysis of covariance (ANCOVA) model with extent of lymphedema after 6 weeks as the outcome with treatment group and baseline extent of lymphedema as covariates. We will report a two-tailed p-value and a 95% confidence interval for the difference between groups.

Based on a previous study, we expect the baseline extent of lymphedema to be 4cm. In the sample size calculation, however, we assume the baseline extent to be 3.6cm due to regression to the mean. The observed correlation between extent of lymphedema at baseline and after 6 weeks of acupuncture is approximately 0.95. The standard deviation is 2.1cm. Using bootstrap methods, the 75th percentile of the standard deviation is estimated to be 2.23cm. To be conservative this inflated

standard deviation was used in the sample size calculation. To detect a minimally significant difference of 0.5cm in the extent of lymphedema, a trial with 90% power and an alpha of 5% requires 41 patients per treatment arm. We believe that the high correlation does not preclude finding an even greater effect size for this RCT.

The trial will accrue until it is anticipated that 41 patients per treatment arm will have evaluable data. We expect that, due to dropouts, this will involve accruing approximately 46 patients per treatment arm. Sensitivity analyses will be performed to assess the effect of patient withdrawal on the primary analysis. Towards this end, we will impute a spectrum of possible outcomes for the missing values and see how/if our inference changes.

Because of its clinical relevance, we will also report the proportion of patients in each group whose extent of lymphedema decreases 30% or more from baseline. The 30% goal was derived from our extensive clinical experience, in the absence of any consistent definition found in the clinical literature, and because that result or better was achieved in our pilot study, where 1/3 of patients showed at least a 30% reduction in lymphedema following acupuncture treatment. [1]

Predicted Accrual Rates

Because a large number of breast cancer patients are treated at MSKCC, we do not anticipate difficulties accruing patients to this trial. Over 1300 patients currently in the MSKCC database meet the basic eligibility criteria for the study (Initial diagnosis of lymphedema no more than 5 years ago, Diagnosis of breast cancer, Age ≥18 years, Alive Status=Alive, and Pt did not participate in our pilot study). Based on accrual rates in our previous study, we anticipate that it will require approximately 1 ½ years to accrue the required sample.

Secondary Aims

ANCOVA models will be used to assess differences between treatment group for bioimpedance. The 6-week score will be the outcome and treatment group, baseline score, and randomization stratum will be included as covariates. We will report the two-tailed p-value and a 95% confidence interval for the difference between groups.

To assess how the effects of acupuncture on lymphedema change after the cessation of acupuncture, we will calculate a difference in the extent of lymphedema and 95% confidence interval after 6 weeks of treatment and 3 months after the cessation of acupuncture. This analysis will include data from patients randomized to acupuncture and patients who crossed-over after the initial waiting period.

To determine whether time since diagnosis affects response to acupuncture, chronicity and an interaction between chronicity and treatment group will be entered into each of the ANCOVA models proposed in the primary and secondary aims.

An ANCOVA model will be utilized to assess whether the baseline stage of lymphedema modifies the effect of acupuncture on BCRL. An interaction term between treatment group and stage will be

added as a covariate to a model with extent of lymphedema after 6 weeks as the outcome and treatment group, baseline lymphdema stage, and baseline extent of lymphedema as covariates. The p-value for the interaction term will be reported along with mean differences in BCRL from baseline to 6 weeks by stage and treatment arm.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

Randomization will be conducted using MSKCC's Clinical Research Database (CRDB). Patients will be randomized to the intervention or wait-list control group stratified by baseline lymphedema (>=5cm vs. < 5cm) using blocks of randomly permuted length.

16.0 DATA MANAGEMENT ISSUES

The Research Study Assistant (RSA) assigned to this study will be responsible for project compliance, data collection, abstraction and entry, data reporting, regulatory and quality control monitoring, problem identification and prioritization. Coordination of study team activities will be the responsibility of our Research Coordinator and/or Research Manager.

The Integrative Medicine Service Research Manager (RM) will oversee the project and the research staff. The Research Coordinator and RM will work with the RSA on problem resolution, organization and quality control. The RM will hold regular meetings, attended by the research assistants and the Principal Investigators to review study progress and to manage any difficulties encountered. In addition, the RM will facilitate the timely submission of all required regulatory reports.

All data and forms gathered for this study will be collected and stored in a secure location in facilities of the Integrative Medicine Service. The data collected for this study will be entered into a secure

database (CRDB). Source documentation will be available to support the computerized patient data. The confidentiality of patient information will be carefully protected. Following data entry by Integrative Medicine Service research staff, data will be maintained in a secure location in the Integrative Medicine offices.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. 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.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Benefits: Study subjects may see a reduction or disappearance of lymphedema.

Risks: We know of no reports of serious adverse events from acupuncture in the research literature. In the more than ten-year experience of Integrative Medicine acupuncture treatment, we have never had a serious AE.

Side-effects: It is conceivable that a patient may feel some discomfort from the acupuncture needles, or that the needles may cause a minor bruise. However, these would likely be very minor, as acupuncture needles are filiform and hair-thin, much smaller than standard hypodermic needles.

They are also sterile, single-use and applied following alcohol swab. There may be other unforeseeable risks.

Consent Process: Participation in this trial is voluntary. All study subjects will be required to sign a statement of informed consent, which will conform to local IRB guidelines. Participation in this study will take place only after signed informed consent is obtained.

Costs: Study subjects will not be charged for acupuncture received in this study.

Confidentiality: Every effort will be made to maintain confidentiality of the study subjects. Research and hospital records are confidential. Subject's names or any other personally identifying information will not be used in reports or publications resulting from this study. Authorized agencies (e.g., qualified monitors from NCI etc.), and appropriate personnel may review subject's records as required. All forms are kept in a locked file cabinet when not in use. Identifiers are numeric and only study personnel will be allowed access to the names. Clinical data will be kept in a centralized database with restricted access to study personnel. Data will be entered into MSKCC's clinical research database (CRDB). Individual identifying information will be omitted from figures used in publications resulting from this research. No genetic tests will be performed in this study. Data will be reported in the aggregate.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any

events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

1. Patient Letter

2. Flyer