STATUS PAGE
PROTOCOL **11-325**

Closed To New Accrual

Closure Effective Date: 08/06/2018
Reason: Study Accrual Goal Met

No new subjects may be enrolled in the study- as described above. Any questions regarding this closure should be directed to the study's Principal Investigator

DFCI Protocol No: 11-325

Front Sheet

Report Generated: 05/10/2018 12:01 PM

Title: Evaluation of the validity of BIS as a tool for quantification of lymphedema through comparison with perometry and self-report

Overall Institution: Massachusetts General Hospital

Overall Principal Investigator	Email	Institution
Taghian, Alphonse G.	ataghian@partners.org	Massachusetts General Hospital

Primary Contact(s) for Questions	Email	Phone
Daniell, Kayla	kdaniell@mgh.harvard.edu	617-643-1306

Sponsor Name	Sponsor Protocol No	Roles	Grant Number(s)
DF/HCC Investigator		Regulatory	
Dana-Farber/Harvard Cancer Center		Funding	

Total Study-Wide Enrollment Goal: 270 **Total DF/HCC Estimated Enrollment Goal:** 270

Phase: III

Age: Adults

Age Ranges: Age-Adults (18-64); Age-Adults (65+)

Will all subjects be recruited from pediatric clinics?

CTEP Study: No

Management Group(s): DF/HCC Breast Cancer
MGH Breast Cancer
MGH Regulatory Coordinators

Primary Management Group: DF/HCC Breast Cancer

Investigational Drug? This study does not use a Drug/Biologic.

Investigational Device? This study does not use an Investigational Device.

IRB of Record:

Risk Category: Minimal Risk

Protocol Involves: Medical Record Review; Quality of Life; Questionnaires/Surveys/Interviews

Date Range: (Medical Record Review and Specimen Collection studies)

Participating Sites under the DFCI IRB

Institution: Massachusetts General Hospital

Participating Institutions Under Other IRB

None

Protocol Number: 11-325

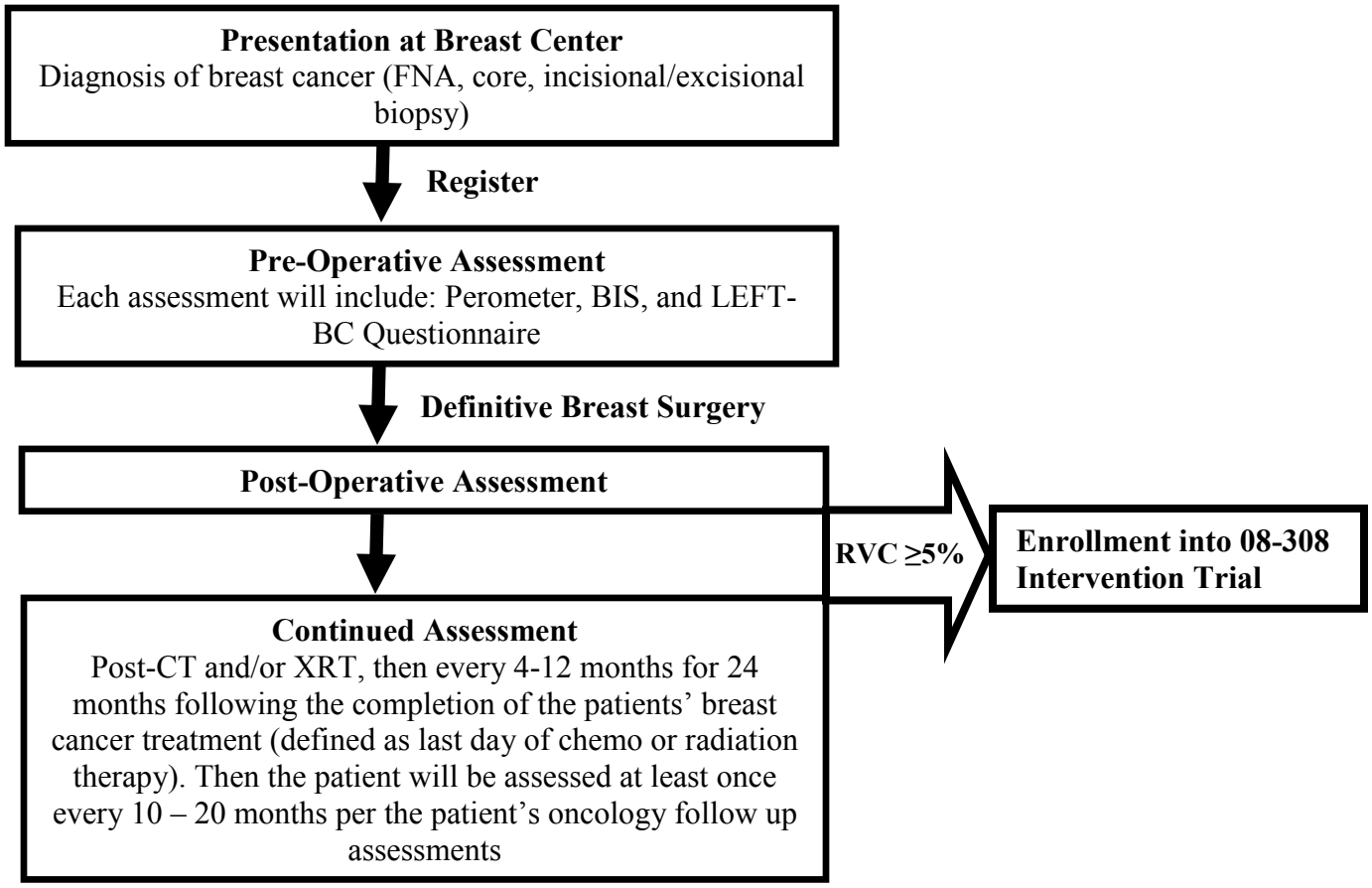
Approval Date: 10/10/11 (IRB meeting date when protocol/consent approved or conditionally approved)

Activation Date: 12/28/11 (Date when protocol open to patient entry)

Approval signatures are on file in the Office for Human Research Studies, tel. 617-632-3029.

Date Posted	Revised Sections	IRB Approval Date	OHRS Version Date
01/12/12	Protocol replaced due to Amendment #1	01/12/12	-
05/29/12	Protocol and Front Sheet replaced due to Amendment #2	05/25/12	-
07/23/12	Consent Form replaced due to Amendment #3	07/19/12	07/20/12
08/30/12	Study Renewal/ Consent Form replaced due to Continuing Review #1	08/22/12	08/30/12
08/01/13	Protocol and Front Sheet replaced due to Amendment #4	07/19/13	n/a
08/20/13	Study Renewal/ Consent Form replaced due to Continuing Review #2	07/23/13	08/12/13
07/22/14	Study renewal/ Consent Form footer replaced due to Continuing Review #3	06/25/14	N/A
06/23/15	Study renewal/ Consent Form footer replaced due to Continuing Review #4	06/09/15	N/A
Date Posted	**Revised Sections**	**IRB Approval Date**	**OnCore Version Date**
07/16/15	Consent Form, Protocol and Front Sheet replaced due to Amendment #6	06/30/15	07/15/15
09/14/15	Consent Form, Protocol and Front Sheet replaced due to Amendment #7	09/04/15	09/10/15
06/07/16	Study renewal/ Consent Form footer replaced due to Continuing Review #5	05/25/16	06/07/16
07/05/16	Protocol and Consent Form replaced due to Amendment #8	06/20/16	07/01/16
08/04/16	Consent Form, Protocol and Front Sheet replaced due to Amendment #9	08/04/16	08/04/16
Date Posted	**Revised Sections**	**Approved Date**	**Version Date (OnCore)**
03/23/17	Consent Form and Front Sheet replaced due to Amendment #10	03/20/2017	03/21/17
04/28/17	Study renewal/ Consent Form footer replaced due to Continuing Review #6	04/28/17	04/28/17
07/24/17	Consent Form and Front Sheet replaced due to Amendment #11	06/28/17	06/28/17
04/30/2018	ON HOLD; All research must stop due to lapsed Continuing Review. Study approval expired 04/28/2018	N/A	N/A
05/03/2018	ON HOLD removed: Study renewal/Consent Form footer replaced per Continuing Review #7	05/03/2018	05/03/2018
05/10/2018	Front Sheet replaced per Amendment #13	05/08/2018	N/A
06/11/2018	Consent Form, Protocol replaced per Amendment #12	06/05/2018	06/08/2018
08/07/2018	Study Closed – Study Accrual Goal Met	08/06/2018	n/a
03/04/2019	Study renewal/Consent Form footer replaced per Continuing Review #8	03/04/2019	03/04/2019

SECTION 1: Protocol Schema



SECTION 2: BODY OF PROTOCOL

TABLE OF CONTENTS

1.0 INTRODUCTION

1.1 Overview

Prior studies of bioimpedance spectroscopy for the detection of lymphedema have left significant gaps in the literature regarding its use as a tool for the early detection of breast cancer-related lymphedema and its relationship with previously established measurement methods and self-reported symptoms. The purpose of our study is to assess for lymphedema pre- and post- treatment (surgery, +/- radiation, +/- chemotherapy) through the concurrent use of perometry, bioimpedance spectroscopy, and self-report. From these assessments we will:

1) Determine if BIS is a valid tool for early detection of lymphedema through comparison with the perometer and self-reported symptoms
2) Evaluate the relationship between impedance ratios obtained through bioimpedance, volume changes measured by perometry and quantified using the relative volume change equation (RVC), and self-reported symptoms.

From this data we will determine if bioimpedance spectroscopy is a valid tool for detecting and monitoring of early lymphedema. Furthermore we aim to determine the relationship between diagnostic indices utilized by perometry and BIS such that measurements with BIS can be related to the previously established definitions of lymphedema and used in a clinically meaningful way.

1.2 Background and Rationale

1.2.1 Study Disease

Lymphedema is an abnormal collection of protein-rich fluid that rests in the interstitial tissues (1). The development of upper extremity lymphedema following treatment for breast cancer is well documented (2-6). The impact of lymphedema on quality of life is supported by research and clinical experience in treating patients with this distressing condition that is often a constant reminder of their cancer treatment (7). Symptoms of pain, stiffness and loss of function typically accompany the onset of lymphedema, and have been found to compound changes in quality of life (8-11).

Despite its known impact on patients and prevalence in the literature, reported rates of lymphedema vary significantly (12,13). While it has been reported that lymphedema occurs in at least 25% of patients who have had surgery and radiation treatment for breast cancer (14-16), others report rates as high as 50% (17). The wide range in lymphedema incidence rates can be attributed to the lack of a standard method of measurement or index for diagnosis of lymphedema, which may lead to misdiagnosis or delay in treatment (18,19). In light of recent evidence which demonstrates the importance of early detection for successful management of lymphedema, it is important to determine the relationship among measurement techniques and diagnostic indices to establish a universal method of measurement and definition for lymphedema (20).

Previously, lymphedema resulting from breast cancer treatment has been assessed as using limb circumference or volume to estimate the excess size of the affected limb as

compared to the unaffected limb (21). Circumferential measurements are obtained using tape measurements at various point(s) along the limb, from which volume is calculated using the truncated cone method. Limb volume may be directly measured with optoelectric perometry or water displacement (volumetry). Common criteria for diagnosis of lymphedema include >2cm circumference difference, >200 ml volume difference, or 10% limb volume change between arms or between the same arm before and after surgery, as well as self-report of symptoms(12).

More recently, bioelectrical impedance analysis (BIA) has also been utilized for the detection of breast cancer-related lymphedema. BIA measures the opposition to flow of an electric current passed through the body at single or multiple frequencies, and resistance to the flow of this current is reported as an impedance value. The level of impedance to a current depends upon the capacitive and inductive properties of the medium through which the current is passed (22). Single-frequency bioimpedance analysis (SF-BIA) devices pass an electrical current through the body at only one frequency (23), whereas multiple frequency bioimpedance analysis (MF-BIA) and bioimpedance spectroscopy (BIS) utilize multiple frequencies and can detect fluid volume changes specifically related to extracellular fluid (22). Increased fluid in the extracellular space of the limb, as occurs in lymphedema, decreases resistance to current flow and results in a lower impedance value (24,25). It has been established that increased limb volume based upon circumferential measurements correlates with a decreased impedance value obtained via BIA (24).

To quantify lymphedema using bioimpedance analysis, the ratio of impedance values of the affected to unaffected limb is calculated. The difference between the measured impedance ratio and an established normal range is then assessed as standard deviations from the norm, and 3+ deviations is considered to be indicative of lymphedema (23). Since there is no direct mathematical relationship between impedance (in ohms) and volume (in ml) of the limb, it is not possible to directly compare impedance values obtained using BIA with limb volume changes obtained from circumferential or volumetric measurements (24).

1.2.2 Previous Studies

Within the MGH-Gillette Breast Center, lymphedema screening has been provided to all patients prospectively through Perometric arm volume measurements during and after treatment. Since July 2005, over 2200 patients have undergone a pre-operative baseline measurement, and 1123 patients have two additional measurements thereafter with a median follow-up of 22.4 months after surgery. Through the development of this screening program, continuous research and analysis of interim data has been completed under Partners Protocols 2005P-001038 and 1999P-009256. As part of this evaluation, the Lymphedema Studies Team has developed an equation for Relative Volume Change (RVC), which quantifies the percent of change in arm volume on the affected/treated side as compared to the initial pre-operative measurements (26).

To further understand the detrimental effect that fear of lymphedema development as well as the presentation of this complication may have on a patient, our team has developed a longitudinal screening and questionnaire protocol (Partners Protocol #2008P-000540). Under this protocol, women who complete a preoperative perometer

measurement will, in addition to periodic measurements, complete the Lymphedema Evaluation Following Treatment for Breast Cancer Questionnaire (LEFT-BC) which will allow for the evaluation of changes in functionality, upper extremity utilization (fear associated avoidance), and quality of life. Screening visits (involving both a perometer measurement and completion of the LEFT-BC) occur pre-operatively, at the initiation and conclusion of each type of treatment (surgery, chemotherapy and radiation), and every 4-7 months following the completion of treatment.

Additionally, in order to evaluate the efficacy of early intervention for mild and moderate edema, our team developed DFHCC Protocol #2008P-000308, in which a sample of women who experience mild and moderate volume changes are randomized to postoperative compression. If during the course of a patient's screening visits as part of Protocol 2008P-000540 they are found to have an RVC of ≥ 5%, which remains above 5% at a verification measurement within 4-8 weeks, the patient may enroll in the intervention arm of the study. Dependent upon their RVC, these patients are randomized either within Group I –Mild Lymphedema (5-<10% RVC) or Group II – Moderate Lymphedema (≥10-20% RVC). Patients with mild lymphedema are randomized either to observation or compression, and those with moderate lymphedema are randomized either to compression or compression with night compression bandaging.

In the proposed study, we aim to prospectively screen a cohort of patients with bioimpedance spectroscopy, in addition to the perometer and LEFT-BC questionnaire to determine if BIS is a valid clinical tool for assessing lymphedema in breast cancer patients. Through the collection of concurrent longitudinal measurements with the perometer and BIS, we will establish the relationship between these assessment methods, as well as evaluate the symptoms, functional disability, and changes in quality of life that accompany these measurements. This study will be and all previous studies were supported by 2 NIH grants totally >$2.2M / 5 years [Award Number R01CA139118 (PI: Dr. Taghian), Award Number P50CA089393 (PI: Dr. Taghian)].

1.2.3 Literature Review

The earliest publication describing BIS occurred in 1992, in which Ward et al described the results of assessment for lymphedema using bioimpedance and limb volume calculated from circumferences in a cohort of women with and without clinical lymphedema (24). Their data showed that impedance values did not entirely discriminate between women with lymphedema and control subjects. In a subsequent study (1996) assessing the utility of BIA devices in comparison with circumferential measurements, Cornish et al demonstrated a 3 to 4-fold increased sensitivity of BIA compared to circumferential measurements (27). In 2001, a large prospective trial assessing breast cancer patients with BIA and circumferential measurements confirmed the suitability of BIA as a reliable diagnostic procedure for early detection of lymphedema, and sensitivity of BIA and circumferences for early detection were shown to be 100% and 5%, respectively (23). A study by Hayes comparing circumferences and BIA reported sensitivities of 35% and 65%, respectively, for detection of lymphedema in an analysis of 176 breast cancer patients 6 months post-surgery (28).

Several studies have also assessed the utility of BIA as compared to optoelectronic perometry in the detection of lymphedema. In 2009, Ward showed that impedance ratios were highly correlated with limb volume ratios measured using perometry in an analysis of 45 breast cancer patients with clinical lymphedema and 21 women without lymphedema (29). In a comparison of physical measurement methods and self-report in a small cohort of patients post-breast cancer treatment (n=10), Jain et al also showed a high concordance among measurements with BIA and perometry, as well as a moderate correlation of these methods with self-report (22).

An examination of the relationship among several methods of lymphedema detection including BIS, perometry, circumferences, and self-report has demonstrated a strong concordance among these techniques. In a comparison of these methods in a cohort of women with and without clinically diagnosed lymphedema, Czernic (25) and Ridner (30) and found statistical agreement among methods in the detection of clinical lymphedema (n= 25, n= 51, respectively).

1.2.4 Impact of Proposed Study

As one of the most recent devices to be applied in the assessment of breast cancer-related lymphedema, it is important to validate BIS as an effective tool for early detection of lymphedema and to establish the relationship of its index with traditional volume-based measurement techniques. This study would be significant because it would prospectively screen a large cohort of women for development of early lymphedema with the concurrent use of several assessment methods including BIS, perometry, and self-reported symptoms via the LEFT-BC Questionnaire. Though a concordance among BIA and perometry for detection of clinically diagnosed lymphedema has been established, previous studies use small sample sizes, lack pre-surgical assessment and adequate follow-up, and do not define or evaluate the criteria for classification of lymphedema based upon assessment methods. If bioimpedance is to be applied for early detection of lymphedema in the clinical setting, it is important to determine how the diagnostic scale utilized by BIA correlates with traditionally established definitions of lymphedema. The concurrent and regular assessment of at-risk women using BIS, perometry, and self-report will allow for analysis of the utility of BIS as well as the correlation among definitions of lymphedema corresponding with each assessment technique.

2.0 OBJECTIVES

2.1 Primary Objectives:

-To assess the validity of BIS as a tool for quantification of lymphedema through comparison with perometry

-To determine relationship between impedance ratios, relative volume changes (RVC), and self-reported symptoms

2.2 Secondary Objectives:

-Compare diagnostic criteria for lymphedema correlating with each assessment method

-Define the natural history of lymphedema and determine a threshold for intervention using BIS

3.0 RESEARCH SUBJECT SELECTION

Eligibility and exclusion criteria are similar to those for Partners Protocol 2008P-000540 and DFHCC Protocol #2008P-000308.

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Participants must have histologically or cytologically confirmed invasive or in-situ carcinoma of the breast.
3.1.2 Participants must have undergone sentinel node mapping or axillary dissection.
3.1.3 Age >18 years.
3.1.4 Life expectancy of greater than 1 year.
3.1.5 Ability to understand and the willingness to sign a written informed consent document.
3.1.6 Willingness to comply with required follow up perometer and BIS measurements and completion of LEFT-BC questionnaire.
3.1.7 Participant must be either English or Spanish speaking

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study:

3.2.1 Patients who have known metastatic disease or other locally advanced disease in the thoracic or cervical regions.
3.2.2 Any patient who will not be returning routinely for follow-up at MGH or DFHCC.
3.2.3 Participants with known brain metastases will be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.
3.2.4 History of primary lymphedema.
3.2.5 History of prior surgery or radiation to the head, neck, upper limb, or trunk.
3.2.6 Participants who have evidence that axillary lymph node malignancy is causing lymphedema due to recurrence as per physician discretion.
3.2.7 Any patient who has bilateral lymph node mapping or dissection**.**
3.2.8 Any patient with a current case of cellulitis.
3.2.9 Patients with a history of a different malignancy are ineligible except for the following circumstances. Individuals with a history of other malignancies are eligible if they have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy. Individuals with

the following cancers are eligible if diagnosed and treated within the past 5 years: cervical cancer *in situ*, and basal cell or squamous cell carcinoma of the skin.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

No exclusions will be made on the basis of race or ethnicity. Efforts will be made by the Lymphedema Clinical Research Staff to enroll all eligible participants and special effort will be given to the enrollment of minorities.

4.0 RESEARCH SUBJECT ENTRY

The Clinical Research Coordinators will be responsible for consenting the subjects at the time of the pre-operative assessment with Perometry, BIS, and the LEFT-BC Questionnaire. All clinical research staff will be trained to utilize both devices and to administer the questionnaire.

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to initiation of study processes or completion of study materials by participants.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol processes. If a participant does not complete study processes and/or materials following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. If a participant must be registered during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:
1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.
2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.
3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.
4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.
5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

5.0 STUDY DESIGN AND METHODS

5.1 Design / Study Type

This will be a prospective trial to assess arm edema using Bioiompedance Spectroscopy (BIS), perometry, and a comprehensive self-report questionnaire (LEFT-BC) in a cohort of patients who have had sentinel lymph node mapping or axillary dissection as part of breast cancer surgery. All patients will have their first baseline assessment after diagnosis for breast cancer (core biopsy, FNA or incisional/ excisional biopsy) and before their definitive breast surgery. Patients will be assessed for lymphedema at the initiation and completion of each treatment process, and every 4-12 months throughout follow-up during the first 24 months following completion of their breast cancer treatment. Subsequently they will be assessed at least once every 10-20 months following this 24 month post treatment time period. This research will be done for 5 years throughout the patient's follow-up for breast cancer, or as long as the patient returns to MGH for care related to breast cancer. This trial aims to accrue a total of 200 patients in 5 years.

5.2 Selection of Instruments

Bioimpedance Spectroscopy (BIS)

BIS has been proposed to be the new standard for early detection of lymphedema in breast cancer patients through quantification of extracellular fluid content of the arm (19). It is purported to be highly specific, accurate, sensitive, and have a high inter-rater reliability and repeatability within and between testing centers (19). The L-Dex U400 is the BIS device to be used in this protocol, and received U.S. FDA clearance in 2008 for aiding in the clinical assessment of unilateral lymphedema of the arm in breast cancer patients (31).

Assessment with the BIS device will be conducted by a Lymphedema Studies Clinical Research Staff member. Electrodes will be placed in specifically designated locations while the patient maintains a supine position. According to manufacturers, the actual amount of electrical current passed through the body is imperceptible to most patients, is applied non-invasively and is applied over a brief period (less than 1 second) (31). Measurements will be taken pre- and post-operatively, as well as at screening visits per study design, and each measurement takes about 2-3 min. including electrode placement.

Perometer

The perometer is a well-validated instrument for quantifying volume in a limb, and has been a regular part of the standard of care for MGH breast cancer patients since 2005. Patients are routinely measured (1) at diagnosis, (2) after surgery, (3) after chemotherapy, (4) after radiation, (5) at four to seven month follow-up visits that continue for five years, and (6) any time a patient reports with new symptoms of swelling or arm discomfort outside these time frames. The perometer provides highly reliable and valid arm volume measurements, with no physical discomfort or inconvenience to the patient. It utilizes infrared lamp-light receiver pairs contained within a frame which is moved along the extremity. As indicated by our preliminary analyses and the literature, the perometer calculates volume within 1% accuracy (33). This calculation of volume is accurate within a standard deviation of 8.9 ml and a .55% difference with repeated measurements (33). The perometer can give detailed information about arm volume in milliliters, the percent difference between the volumes of both arms, the location of the swelling in the arm as well as a follow-up clearly showing progression of the lymphedema over time.

Measurements of arm volume with the perometer will be taken pre- and post-operatively, as well as at screening visits per study design. All arm volume measurements will be converted to a percent RVC. The RVC calculation will indicate volume changes in the affected arm as compared to the baseline measurement. This value will indicate whether or not a patient is experiencing lymphedema for the purposes of this study and will determine patient eligibility for enrollment into Partners Protocol 08-308.

Questionnaire

The primary source of data on symptoms, functionality, arm use and quality of life will be derived from a questionnaire completed at each lymphedema assessment. Patients who are enrolled in the study will complete the questionnaire at their initial point of enrollment (after diagnosis and prior to definitive breast surgery), and at all subsequent assessments.

This questionnaire is currently being utilized as part of Partners' Protocols 08-540 and DFHCC Protocol #08-308 and as such has been completed by over 500 patients on protocol since 2009. It was developed to analyze symptoms, functionality, fear avoidance behavior, and quality of life. This questionnaire is referred to as the Lymphedema Evaluation Following Treatment for Breast Cancer Questionnaire (LEFT-BC), and it has been pilot tested for clarity, readability, and validity. This pilot testing was completed with a sample of 20 patients currently undergoing perometer measurements as a standard of care within the MGH Gillette Breast Center. After completion of the pilot, adjustments were made to the questionnaire to increase clarity and readability. The complete questionnaire is included in Appendix 2.

In order to minimize respondent burden the questionnaire was limited to 6 written pages and took between 5-12 minutes to complete during the pilot study. We will utilize tablet style PCs for questionnaire completion within the clinic. Dr. Kevin Hughes and Brian Drohan, MS developed the LEFT-BC Questionnaire program by formatting the

questionnaires for the tablet PCs, and a corresponding database for data logging. The questionnaires will be completed by patients in a point and click manner. In the event that tablet PCs are not available, paper copies of the questionnaire will be available for participant visits. Questionnaire responses from paper based questionnaires will be manually entered into the database.

Risk Assessment

At each lymphedema assessment, patients will be verbally asked a short series of questions to provide further information for an analysis of the risk factors involved in the development of lymphedema (see Appendix 3). These questions include: number of blood draws, blood pressures, or injections on the affected arm since the last lymphedema assessment. Also recorded is the number of flights, total hours in flight, and whether a sleeve was worn while flying since the last lymphedema assessment.

5.3 Description of Intervention

Results of assessment with BIS will be blinded such that only a ≥5% RVC measured using the perometer will be considered indicative of lymphedema. If at any time while enrolled in this study a patient is detected to have an RVC≥ 5% by perometry, a verification measurement including assessment with perometry, BIS, and the LEFT-BC questionnaire will be conducted at a 4-8 week interval. If at this time the patient's RVC measured by perometry is confirmed above 5%, the patient will be offered enrollment into the DFHCC 08-308 Intervention Protocol and/or referred to a clinician for appropriate care. Patients that enroll into Protocol #08-308 will continue to be measured using BIS at the time of each assessment as required by the protocol. Patients that refuse enrollment into the intervention protocol will remain in the current study.

5.4 Data Collection

Patients will be assessed pre-operatively, at the initiation and conclusion of each type of treatment (surgery, chemotherapy and radiation), and every 4-12 months following the completion of treatment for a period of 24 months. Subsequently they will be assessed at the time their follow-up appointments with their oncologists, with no more than 20 months between measurements. At the time of each assessment, the patient will be measured with the perometer, bioimpedance spectroscopy, and will complete the LEFT-BC questionnaire. Data collected at each visit includes arm volume measurements obtained via perometry and quantified using the RVC equation, bioimpedance ratios collected via BIS, self-reported symptoms obtained via the LEFT-BC questionnaire.

5.5 Description of Study Process

The proposed study will incorporate the use of bioimpedance spectroscopy (BIS) to evaluate its validity for detecting and monitoring lymphedema. Patients will be assessed for lymphedema in a prospective manner using perometry, BIS, and the LEFT-BC questionnaire, accruing a total of 200 patients in 5 years. The entire study will be

completed at the MGH main campus, and all patients who present for a baseline (pre-operative) arm measurement and meet the eligibility criteria will be offered the opportunity to participate in this trial. At this time the purpose of the trial will be explained, and any patient that wishes to participate will be assessed using the perometer, BIS, and provided with the LEFT-BC questionnaire to complete prior to surgery. Patients who do not wish to participate in the proposed trial will be asked to participate instead in Partners Protocol #2008P-000540, which involves regular assessment with the perometer and completion of the LEFT-BC questionnaire at the time of each perometer measurement.

5.5.1 Instrument Administration

The perometer, bioimpedance spectroscopy (BIS) device, and the LEFT-BC questionnaire will all be administered by a Lymphedema Studies Clinical Research Staff. Patients will be notified upon arrival to the clinic that they will undergo a lymphedema assessment on that date using the perometer, BIS, and LEFT-BC questionnaire. Perometry measurements will be conducted in a room specifically allocated for its use, and require about 5-10 minutes for completion. BIS assessments will be conducted in a clinical room and require 2-3 minutes to complete. The LEFT-BC questionnaire will be administered on a tablet PC in a clinical room or given as a paper copy for the patient to complete in the event that tablet PC's are not available. The questionnaire takes 5-12 minutes to complete.

5.5.2 Intervention Administration

As stated previously, results of assessment with BIS will be blinded. Patients that experience a ≥5% RVC determined by measurement with perometry and maintain a ≥5% RVC at the 4-8 week verification measurement will be eligible for enrollment into DFHCC Protocol #08-308 Intervention Trial. These patients will continue to be measured using BIS at the time of each assessment as required by the protocol, and intervention will be administered as dictated by DFHCC Protocol #08-308. Patients that refuse enrollment into the intervention protocol will be referred to a clinician for appropriate care and will remain on the current study.

5.5.3 Special Concerns

Please see sections 5.6.2 and 5.6.3 for anticipated reactions and resolution strategies.

5.5.4 Compensation

No compensation is considered.

5.60 Adverse Reactions and their Management

5.6.1 Reporting Adverse or Unanticipated Events

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology

Criteria for Adverse Events version 3.0 (CTCAE v3.0) that is available at http://ctep.cancer.gov/reporting//ctc.html.

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Adverse events experienced by participants will be collected and reported from initiation of treatment, throughout the study, and within 30 days of the last follow-up visit. Participants who experience an ongoing adverse event or related to a study procedure beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator. Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

- Adverse Event (AE)

  An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol. For the purpose of this study we will be defining adverse events as any of the following that pertain to the patient's breast cancer-related lymphedema:

  - Psychological distress caused by heightened awareness of lymphedema and the potential of developing the condition

- Serious adverse event (SAE)

  A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:
  - Results in death
  - Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more sever form.
  - Requires or prolongs inpatient hospitalization
  - Results in persistent or significant disability/incapacity.
  - Is a congenital anomaly or birth defect; or

  jeopardizes the participant and require medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

- Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

- Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

- Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

- Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.

- Unrelated - The AE is clearly NOT related to the study treatment.

5.6.1.1 Procedures for AE and SAE Recording and Reporting

Reporting participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

5.6.1.2 Reporting Requirements

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

5.6.1.3 Reporting to the Study Sponsor
N/A. Single site study.

5.6.1.4 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

5.6.1.5 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

5.6.1.6 Reporting to the Institutional Review Board (IRB)

Each adverse event will be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local policies, and federal guidelines and regulations as appropriate. It is the responsibility of the participating investigator to notify the Principal Investigator (or Protocol Chair), IRB, and others of all serious adverse events as required in the protocol. The Principal Investigator (or Protocol Chair) will provide information with respect to adverse events and safe use of the study treatment (e.g., safety reports, Action Letters) to all participating investigators as soon as the information becomes available. Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

5.6.2 Anticipated Reactions

Since completion of the LEFT-BC questionnaire is voluntary, it is foreseeable that the use of the questionnaires may heighten the awareness of lymphedema and possible symptoms.

Additionally, assessment with BIS is voluntary and may increase awareness of lymphedema and cause distress regarding the potential development of the condition. Use of the device is considered safe and has regulatory clearance in the United States to “support the measurement of extracelluar fluid volume differences between the arms to aid in the clinical assessment of unilateral lymphedema of the arm in women” (31). According to manufacturers, “the actual amount of electrical current passed through the body is imperceptible to most patients, is applied non-invasively and is applied over a brief period (less than 1 second)” (31).

5.6.3 Reaction Management

In the event that a participant does feel an increased level of distress or discomfort, the social work team within the breast cancer center have confirmed their willingness and ability to provide additional counseling if necessary. Julie Berrett, MSW has confirmed that she will be available to any patients who experience such adverse effects.

Julie Berrett, LICSW
P. (617) 643-2355
JBERRETT@PARTNERS.ORG

6.0 STATISTICAL ANALYSIS

6.1 Primary and Secondary Endpoints

The primary aims of the study are to assess the validity of BIS measurements by comparison with perometery and determine the relationships of BIS measurements to perometer measurements and to self-reported symptoms. The secondary aims will be to compare diagnostic criteria for lymphedema for each assessment method, assess the natural history of lymphedema using BIS, and determine a threshold for intervention using BIS. Thus primary endpoints will subsist in volumetric and BIS measurements of each arm at the baseline examination and during follow-up visits, as well as data captured by LEFT-BC questionnaires. The changes of arm volumes will be quantified using established RVC formula (26), and we will use a similar formula for quantification of BIS changes after evaluating the statistical distribution of BIS measurements.

6.2 Sample Size and Statistical Power

The sample size will be determined with the prospect of primary aim of this study, i.e, to evaluate the correlation between arm volume changes measured by perometry and quantified using RVC formula (26) and using relative changes of impedance measured by biompedance spectroscopy (BIS). We want to evaluate this correlation for all subjects enrolled, and separately, for a subgroup of those subjects who develop lymphedema with RVC≥5%. The first analysis will evaluate overall agreement between these two techniques and the second analysis will evaluate agreement between assessment of lymphedema grade by both techniques. We plan to quantify the relationship between these two measurement methods using Kendall's tau coefficient (34).

We chose to use a non-parametric correlation coefficient to account for a possible non-linear form of the relationship between the two measurements, and for a possible non-normal distribution of BIS measurements. We expect a moderately high correlation between these measurements, tau=0.50 . The choice of sample size is motivated by a need to evaluate the correlation with sufficient precision rather than by a hypothesis test: we want to obtain a lower bound of 95% confidence interval for the estimate of tau of no less than 0.2 in the LE group and of no less than 0.42 overall. We assume that 10% of enrolled subjects will develop lymphedema with RVC≥5%. Furthermore, we expect that up to 20% of paired measurements may be missing due to non-compliance or technical problems.

Sample size calculations are based on approximate confidence intervals for Kendall's tau (35). The minimum number of measurements, to attain the required precision in the LE group is n=16; however, accounting for missing data we need to enroll 20 patients with LE and 200 patients overall. We thus expect to have 160 non-missing pairs of measurements overall, this allows us to determine Kendall's tau with 95% confidence interval from 0.426 to 0.567.

Of note, patients that are enrolled pre-operatively and subsequently undergo bilateral breast surgery, rendering them ineligible for the study, will not be counted towards the overall accrual goal of 200 subjects.

6.3 Stratification Factors

N/A: this is not a randomized study.

6.4 Stratification factors and their impact on design

The analysis will be stratified on the time of follow-up, volumetric and BIS changes, as well as self-reported symptoms will be correlated at the corresponding time points.

6.5 Early stopping rules, if appropriate

N/A: the study will not have early stopping rules.

6.6 Definition of and allowance in design for unevaluable / ineligible participants

Only eligible patients, as specified by inclusion and exclusion criteria, will participate in this study. In the event that a participant is found to be ineligible according to the exclusion criteria after enrollment into the study, the patient will be removed and the QACT will be notified. All data corresponding to these patients will be excluded in the analyses. If a participant becomes ineligible according to the exclusion criteria while actively enrolled in this study, the participant will be removed and the QACT will be notified. Any data corresponding to these patients collected prior to removal will be included in the analyses. The sample size for this study takes into account potential unevaluable/ ineligible participants by aiming to accrue 200 participants, when only 160 non-missing pairs of measurements overall are needed to meet the desired confidence interval for statistical analysis.

6.7 Analysis plan

The statistical analysis in this study will subsist in 1) calculating the Kendall's correlation coefficient with 95% confidence intervals for each time point, separately for all subjects and in the subgroup with RVC≥5%, 2) plotting graphically the relationship between changes in arm volumes and BIS measurements, by time point, 3) calculate overall Kendall's tau stratifying by time point, i.e., evaluating concordant and discordant pairs within each time point only (35), 4) determining the change of BIS measurements

corresponding to RVC=5% of volumetric measurements, 5) calculating area under ROC curve, for predicting volumetric RVC≥5% using BIS measurements, and tabulating diagnostic indices including specificity, sensitivity, positive prognostic value, 6) evaluating diagnostic characteristics of lymphedema diagnosis based on BIS using 3 sigma method, and 7) assessing the association between patient-reported symptoms and each measurement method (using area under ROC and other diagnostic criteria). We will also evaluate the statistical distribution of BIS measurements and based on the shape of the distribution determined if BIS changes are better captured as absolute or as relative differences.

6.8 Handling of missing data in the analysis

RVC for volumetric changes and a corresponding quantity for BIS changes will be calculated only with patients with measurements both at the baseline and during follow-up. Time points with missing data will be excluded from the evaluation of the correlation between volumetric and BIS changes and, separately, between BIS changes and patient-reported symptoms for those patients who complete the LEFT-BC questionnaire.

7.0 REFERENCES

1. Clark B. SJ, Harlow W. Incidence and Risk of Arm Oedema Following Treatment for Breast Cancer: A Three-Year Follow-up Study. *Q J Med.* 2005;98:343-348.
2. *Guide to Physical Therapy Practice.* Vol 81. 2nd ed: American Physical Therapy Association; 2001.
3. Armer J HP. Post-Breast Cancer Lymphedema in Aging Women: Self-Management and Implications for Nursing. . *Journal of Gerontological Nursing.* 2005;31(5):29-39.
4. Morrell RM, Halyard MY, Schild SE, Ali MS, Gunderson LL, Pockaj BA. Breast cancer-related lymphedema. *Mayo Clin Proc.* Nov 2005;80(11):1480-1484.
5. Ozaslan C, Kuru B. Lymphedema after treatment of breast cancer. *Am J Surg.* Jan 2004;187(1):69-72.
6. Warmuth MA, Bowen G, Prosnitz LR, et al. Complications of axillary lymph node dissection for carcinoma of the breast: a report based on a patient survey. *Cancer.* Oct 1 1998;83(7):1362-1368.
7. Paskett ED, Naughton MJ, McCoy TP, Case LD, Abbott JM. The epidemiology of arm and hand swelling in premenopausal breast cancer survivors. *Cancer Epidemiol Biomarkers Prev.* Apr 2007;16(4):775-782.

8. Armer JM, Radina ME, Porock D, Culbertson SD. Predicting breast cancer-related lymphedema using self-reported symptoms. *Nurs Res.* Nov-Dec 2003;52(6):370-379.
9. Leduc O, Leduc A. Rehabilitation protocol in upper limb lymphedema. *Ann Ital Chir.* Sep-Oct 2002;73(5):479-484.
10. Kwan W, Jackson J, Weir LM, Dingee C, McGregor G, Olivotto IA. Chronic arm morbidity after curative breast cancer treatment: prevalence and impact on quality of life. *J Clin Oncol.* Oct 15 2002;20(20):4242-4248.
11. Pain SJ, Vowler SL, Purushotham AD. Is physical function a more appropriate measure than volume excess in the assessment of breast cancer-related lymphoedema (BCRL)? *Eur J Cancer.* Oct 2003;39(15):2168-2172.
12. Armer JM, Stewart BR: A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. Lymphat Res Biol 3:208-17, 2005
13. Rockson SG, Rivera KK (2008) Estimating the population burden of lymphedema. *Ann NY Acad Sci* 1131: 147–154
14. Cheville, A., McGarvey, C., Petrek., Russo, S., Thiadens, S., Taylor, M. The Grading of Lymphedema in Oncology Clinical Trials. Seminars in Radiation Oncology 2003; 13(3):214-225.
15. Vignes, S., Arrault, M., Dupuy, A. Factors Associated with Increased Breast Cancer-Related Lymphedema Volume. Acta Oncologica 2007; 1-5.
16. Williams, A., Franks, P., Moffatt, C. Lymphoedema: Estimating the Size of the Problem. Palliative Medicine 2005; 19:300-313.
17. Petrek, J., Senie, R., Peters, M., Rosen, P. Lymphedema in a Cohort of Breast Carcinoma Survivors 20 Years After Diagnosis. Cancer 2001; 92(6):1368-1377.
18. Hayes SC, Janda M, Cornish B, et al: Lymphedema after breast cancer: incidence, risk factors, and effect on upper body function. J Clin Oncol 26:3536-42, 2008
19. Ward LC. Is BIS ready for prime time as the gold standard measure? Journal of Lympheodema 2(2): 53-56, 2009
20. Stout Gergich NL, Pfalzer LA, McGarvey C, et al: Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. Cancer 112:2809-19, 2008
21. Armer, J. The Problem of Post-Breast Cancer Lymphedema: Impact and Measurement Issues. Cancer Investigation 2005; 1:76-83.
22. Jain MS, Danoff JV, Paul SM: Correlation between bioelectrical spectroscopy and perometry in assessment of upper extremity swelling. Lymphology 43:85-94, 2010
23. Cornish BH, Chapman M, Hirst C, et al: Early diagnosis of lymphedema using multiple frequency bioimpedance. Lymphology 34:2-11, 2001
24. Ward LC, Bunce IH, Cornish BH, et al. Multifrequency bioelectrical impedance augments the diagnosis and management of lymphedema in post-mastectomy patients. Eur J Clin Invest 1992; 22:751-754.

25. Czerniec SA, Ward LC, Refshauge KM, et al: Assessment of breast cancer-related arm lymphedema--comparison of physical measurement methods and self-report. Cancer Invest 28:54-62, 2010
26. Ancukiewicz M, Russell TA, Otoole J, et al: Standardized method for quantification of developing lymphedema in patients treated for breast cancer. Int J Radiat Oncol Biol Phys 79:1436-43, 2011
27. Cornish BH, Bunce IH, Ward LC, et al: Bioelectrical impedance for monitoring the efficacy of lymphoedema treatment programmes. Breast Cancer Res Treat 38:169-76, 1996
28. Hayes S, Cornish B, Newman B: Comparison of methods to diagnose lymphoedema among breast cancer survivors: 6-month follow-up. Breast Cancer Res Treat 89:221-6, 2005
29. Ward LC, Czerniec S, Kilbreath SL: Operational equivalence of bioimpedance indices and perometry for the assessment of unilateral arm lymphedema. Lymphat Res Biol 7:81-5, 2009
30. Ridner SH, Montgomery LD, Hepworth JT, et al: Comparison of upper limb volume measurement techniques and arm symptoms between healthy volunteers and individuals with known lymphedema. Lymphology 40:35-46, 2007
31. http://impedimed.com/knowledge-center/faqs/
32. Petlund C. Lymph Stasis: Pathophysiology, Diagnosis and Treatment. *Volumetry of Limbs*. Boston: Olszewski & Waldeman; 1991:443-451.
33. Tierney S, Aslam M, Rennie K, Grace P. Infrared optoelectronic volumetry, the ideal way to measure limb volume. *Eur J Vasc Endovasc Surg.* Nov 1996;12(4):412-417
34. Hollander M, Wolfe DA (1999). Nonparametric Statistical Methods, Wiley-Interscience, 2nd ed.
35. Newson R (2006). Confidence intervals for rank statistics: Somers' D and extensions. The Stata Journal 6:339-334

8.0 APPENDICES

8.1 Appendix 1: Partners/ DFHCC Lymphedema Studies

8.1.2 Partners Protocol #: 1999-P-009256

Study Outline:

Data collection protocol for Breast Cancer database
All patients who received treatment at MGH are eligible for entry
Data includes: clinical and pathological data for surgical, radiation and medical oncology
treatment, as well as basic demographic and risk factor information

8.1.3 Partners Protocol#: 2005P-001038

Study Outline:

Data collection protocol for perometer measurements/database
All patients who undergo a perometer measurement are eligible for entry

Data includes: clinical and pathological data for surgical, radiation and medical oncology treatment, perometer measurements as well as basic demographic and risk factor information.

8.1.4 Partners Protocol#: 2008-P-000540
Study Outline:
Open to patients who undergo a pre-operative perometer reading and complete a pre-operative questionnaire
At baseline measurement:
1. Study explained
2. Questionnaires with "Consent Fact Sheet" provided to patient
3. Complete questionnaire prior to having perometer measurement
Follow-up measurements:
1. Patients asked to complete the LEFT-BC questionnaire at with follow-up visits
2. Follow-ups defined as: after surgery, after chemotherapy, after radiation, 4-6 month follow-up for 5 years, with any new symptoms outside of those time frames

8.1.5 DFHCC Protocol #08-308
Study Outline:
Open to patients currently participating in Protocol# 2008-P-000540, who undergo two consecutive perometer measurements with RVC≥5% at a 4-8 week interval. Patients with RVC 5-<10% are randomized within Group I –Mild Lymphedema (5-<10% RVC) to either observation or compression. Patients with RVC≥10% are randomized within Group II – Moderate Lymphedema (≥10-20% RVC) to compression or compression with night compression bandaging. Treatment intervention is for a duration of 12 weeks, after which patients undergo two follow-up measurements (week 16 and week 22-24) and subsequently return to screening per Protocol # 2008-P-000540.

8.2 Appendix 2: LEFT- BC Questionnaire

Lymphedema Evaluation Following Treatment for Breast Cancer Questionnaire

Thank you for taking the time to complete this questionnaire. You can skip any questions that you do not want to answer. **Lymphedema** means swelling of the arm, hand, shoulder or upper body on the side where your cancer was treated.

The following questions will ask you about changes that have happened to your arm or body in the last month.

Have you had a change in arm size?
☐ Larger ☐ Smaller ☐ Constantly Changes ☐ No change

Have you had a change in shoulder size?
☐ Larger ☐ Smaller ☐ Constantly Changes ☐ No change

Have you had a change in neck size?
☐ Larger ☐ Smaller ☐ Constantly Changes ☐ No change

Have you had a change in how your sleeve fits?
☐ Looser ☐ Tighter ☐ Constantly Changes ☐ No change

How has the way your sleeve cuff fits changed?
☐ Looser ☐ Tighter ☐ Constantly Changes ☐ No change

How has the way your ring fits changed?
☐ Looser ☐ Tighter ☐ Constantly Changes ☐ No change

The following questions will ask you about arm, breast, and chest symptoms you have experienced in the last month:

Are you experiencing:	None	Mild	Moderate	Severe	Not Applicable
Tenderness?	0	1	2	3	
Swelling?	0	1	2	3	
Redness?	0	1	2	3	
Firmness/tightness?	0	1	2	3	
Increased warmth in your arm?	0	1	2	3	
Heaviness?	0	1	2	3	
Numbness?	0	1	2	3	
Stiffness?	0	1	2	3	

Aching?	0	1	2	3	
Chest wall swelling?	0	1	2	3	
Breast swelling?	0	1	2	3	
Other symptoms Please describe:					

Cording

The next few questions will ask you about Cording. As your body heals following treatment for breast cancer, sometimes bands of tissue can form in your armpit or down you arm that look like strings or thin ropes. This is called **cording**. Please indicate if you have experienced any of the following symptoms.

Do you feel pulling in any of the following areas? Check all that apply.

- ☐ In your armpit that extends into the inside of your upper arm
- ☐ Across the inside of your elbow
- ☐ Into your forearm and wrist
- ☐ Under your breast
- ☐ None of the above

Do you see or feel a thin cord or string in any of the following areas? Check all that apply.

- ☐ In your armpit that extends into the inside of your upper arm
- ☐ Across the inside of your elbow
- ☐ Along your forearm or wrist
- ☐ Under your breast extending towards your abdomen
- ☐ None of the above

Beliefs About Arm Use:

The questions in this section ask about your beliefs about the use of your affected arm. Your affected arm is the side which you had or will be having surgery. Some questions in this section will ask about strenuous activities, examples of strenuous activities are: playing racquetball, cross country skiing, shoveling snow or cleaning a closet.

Arm swelling affects some women after breast cancer treatment. We are interested in how you feel about this potential side-effect of treatment. Please circle the number according to how strongly you agree or disagree with the statement.

	Strongly Agree	***Agree***	***Disagree***	***Strongly Disagree***	***Don't Know***
a. Having arm swelling would or does significantly change my lifestyle	1	2	3	4	5
b. The possibility of developing arm swelling or making it worse worries me	1	2	3	4	5
c. Doing strenuous activities with my affected arm puts me at risk of developing arm swelling or making it worse.	1	2	3	4	5
d. Strenuous work is part of my lifestyle so I must do it regardless of any advice given.	1	2	3	4	5
e. I plan to avoid any strenuous arm activities	1	2	3	4	5
f. I am more careful with my arm now than I was before my breast cancer treatment	1	2	3	4	5
g. I do not protect my arm in any way.	1	2	3	4	5

Use of Your Arm:
The questions in this section ask about how you use your affected arm (the side which you had or will be having surgery).
Please rate how well you could perform each of the activities when using your affected side, even if it is not your dominant arm or hand. Circle the number closest to how well you are able to complete each activity.

	Easily	***With Some Difficulty***	***With Great Difficulty***	***Unable to do***	***Never Attempted, or Would Not Attempt***
a. Placing something on a shelf above my head	1	2	3	4	5
b. Drive a car for more than 30 minutes	1	2	3	4	5
c. Pull a tight shirt on over my head	1	2	3	4	5
d. Unscrew a tight lid on a jar	1	2	3	4	5
e. Put on a bra that clips in the back	1	2	3	4	5
f. Carry a 10 pound grocery bag for 10 minutes	1	2	3	4	5

g. Sleep on my affected side for more than 10 minutes	1	2	3	4	5
h. Pull wet clothes out of the washing machine	1	2	3	4	5
i. Push a heavy piece of furniture	1	2	3	4	5
j. Dry my back with a towel	1	2	3	4	5
k. Chop potatoes into small cubes	1	2	3	4	5
l. Push open a heavy door	1	2	3	4	5
m. Clean a window above shoulder height	1	2	3	4	5
n. Vacuum for 30 minutes	1	2	3	4	5
o. Iron clothes for 15 minutes	1	2	3	4	5
p. Scrub a surface for 5 minutes	1	2	3	4	5
q. Catch a falling object with my affected hand	1	2	3	4	5
r. Carry a 10 pound bag over my shoulder	1	2	3	4	5
s. Type on a keyboard for 20 minutes	1	2	3	4	5

The questions in the next section will ask you about exercises for your affected arm. Your affected arm is the arm on the same side of your body that you had or will be having surgery as party of your breast cancer treatment.

Did you do any exercises for your affected arm within the first few months after surgery? (Circle the letter that describes your exercise)

a. Yes
b. No

Do you currently do any exercises for your affected arm?

a. Yes
b. No

If you are still doing your exercises: How often are you doing exercises for your affected arm?

a. Daily
b. A few times per week
c. About once a week
d. About once a month

e. Other. Please describe how often: _____

Is there anything that may prevent or limit you from doing your arm exercises? Circle all of the statements that apply.

a. Nothing prevents or limits me from arm exercises
b. The exercises were too difficult
c. I have arm pain
d. My arm is too swollen
e. I don't have time
f. I worry that the exercises might make my arm swell
g. I am too tired
h. I am too confused about what to do
i. Other. Please explain what other things may limit your exercise:

_____

Would you consider your regular daily activities strenuous on your arm(s)?

a. Yes
b. No
c. Don't know

About You:

The questions in this section include a list of statements that other people with your illness have said are important. When discussing illness, we are asking about breast cancer. By circling one (1) number per line, please indicate how true each state has been for you during the past 7 days.

Your Physical Well-Being

	Not at all	*A little bit*	*Somewhat*	*Quite a bit*	*Very much*
a. I have a lack of energy	0	1	2	3	4
b. I have nausea	0	1	2	3	4
c. Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
d. I have pain	0	1	2	3	4
e. I am bothered by side effects of treatment	0	1	2	3	4
f. I feel ill	0	1	2	3	4
g. I am forced to spend time in bed	0	1	2	3	4

Your Social/Family Well-Being

	Not at all	***A little bit***	***Somewhat***	***Quite a bit***	***Very much***
a. I feel close to my friends	0	1	2	3	4
b. I get emotional support from my family	0	1	2	3	4
c. I get support from my friends	0	1	2	3	4
d. My family has accepted my illness	0	1	2	3	4
e. I am satisfied with family communication about my illness	0	1	2	3	4
f. I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box □ and go to the next section. g. I am satisfied with my sex life.	0	1	2	3	4

Your Emotional Well-Being

	Not at all	***A little bit***	***Somewhat***	***Quite a bit***	***Very much***
a. I feel sad	0	1	2	3	4
b. I am satisfied with how I am coping with my illness	0	1	2	3	4
c. I am losing hope in the fight against my illness	0	1	2	3	4
d. I feel nervous	0	1	2	3	4
e. I worry about dying	0	1	2	3	4
f. I worry that my condition will get worse	0	1	2	3	4

Your Functional Well-Being

	Not at all	***A little bit***	***Somewhat***	***Quite a bit***	***Very much***
a. I am able to work (including work at home)	0	1	2	3	4
b. My work (including work at home) is fulfilling	0	1	2	3	4
c. I am able to enjoy life	0	1	2	3	4

d. I have accepted my illness	0	1	2	3	4
e. I am enjoying the things I usually do for fun	0	1	2	3	4
f. I am content with the quality of my life right now	0	1	2	3	4

Additional Concerns

	Not at all	***A little bit***	***Somewhat***	***Quite a bit***	***Very much***
a. I have been short of breath	0	1	2	3	4
b. I am self-conscious about the way I dress	0	1	2	3	4
c. One or both of my arms are swollen or tender	0	1	2	3	4
d. I feel sexually attractive	0	1	2	3	4
e. I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
f. I worry about the effect of stress on my illness	0	1	2	3	4
g. I am bothered by a change in weight	0	1	2	3	4
h. I am able to feel like a woman	0	1	2	3	4
i. I have certain parts of my body where I experience significant pain	0	1	2	3	4

8.3 Appendix 3: Risk Assessment

Lymphedema Risk Assessment:
MRN:
Date:
Blood Draws on Affected Side: ____
Blood Pressure Taken on Affected Side: ___
Injections: ____
Flights: ____ Total Hours: ___
Sleeve: _____
Trauma to Arm: ____
RVC: _____

Study ID#: _____

Date Completed: _____

Lymphedema Evaluation Following Treatment for Breast Cancer Questionnaire

Thank you for taking the time to complete this questionnaire. You can skip any questions that you do not want to answer. **Lymphedema** means swelling of the arm, hand, shoulder or upper body on the side where your cancer was treated.

The following questions will ask you about changes that have happened to your arm or body in the last month.

Have you had a change in arm size?
☐ Larger ☐ Smaller ☐ Constantly Changes ☐ No change

Have you had a change in shoulder size?
☐ Larger ☐ Smaller ☐ Constantly Changes ☐ No change

Have you had a change in neck size?
☐ Larger ☐ Smaller ☐ Constantly Changes ☐ No change

Have you had a change in how your sleeve fits?
☐ Looser ☐ Tighter ☐ Constantly Changes ☐ No change

How has the way your sleeve cuff fits changed?
☐ Looser ☐ Tighter ☐ Constantly Changes ☐ No change

How has the way your ring fits changed?
☐ Looser ☐ Tighter ☐ Constantly Changes ☐ No change

→ **Continue on to the next page** →

The following questions will ask you about arm, breast, and chest symptoms you have experienced in the last month:

Are you experiencing:	None	Mild	Moderate	Severe	Not Applicable
Tenderness?	0	1	2	3	
Swelling?	0	1	2	3	
Redness?	0	1	2	3	
Firmness/tightness?	0	1	2	3	
Increased warmth in your arm?	0	1	2	3	
Heaviness?	0	1	2	3	
Numbness?	0	1	2	3	
Stiffness?	0	1	2	3	
Aching?	0	1	2	3	
Chest wall swelling?	0	1	2	3	
Breast swelling?	0	1	2	3	
Other symptoms Please describe:					

Cording

The next few questions will ask you about Cording. As your body heals following treatment for breast cancer, sometimes bands of tissue can form in your armpit or down you arm that look like strings or thin ropes. This is called **cording**. Please indicate if you have experienced any of the following symptoms.

Do you feel pulling in any of the following areas? Check all that apply.

- ☐ In your armpit that extends into the inside of your upper arm
- ☐ Across the inside of your elbow
- ☐ Into your forearm and wrist
- ☐ Under your breast
- ☐ None of the above

→ Continue on to the next page →

Do you see or feel a thin cord or string in any of the following areas? Check all that apply.

- ☐ In your armpit that extends into the inside of your upper arm
- ☐ Across the inside of your elbow
- ☐ Along your forearm or wrist
- ☐ Under your breast extending towards your abdomen
- ☐ None of the above

Beliefs About Arm Use:

The questions in this section ask about your beliefs about the use of your affected arm. Your affected arm is the side which you had or will be having surgery. Some questions in this section will ask about strenuous activities, examples of strenuous activities are: playing racquetball, cross country skiing, shoveling snow or cleaning a closet.

Arm swelling affects some women after breast cancer treatment. We are interested in how you feel about this potential side-effect of treatment. Please circle the number according to how strongly you agree or disagree with the statement.

	Strongly Agree	***Agree***	***Disagree***	***Strongly Disagree***	***Don't Know***
a. Having arm swelling would or does significantly change my lifestyle	1	2	3	4	5
b. The possibility of developing arm swelling or making it worse worries me	1	2	3	4	5
c. Doing strenuous activities with my affected arm puts me at risk of developing arm swelling or making it worse.	1	2	3	4	5
d. Strenuous work is part of my lifestyle so I must do it regardless of any advice given.	1	2	3	4	5
e. I plan to avoid any strenuous arm activities	1	2	3	4	5
f. I am more careful with my arm now than I was before my breast cancer treatment	1	2	3	4	5
g. I do not protect my arm in any way.	1	2	3	4	5

→ Continue on to the next page →

Use of Your Arm:

The questions in this section ask about how you use your affected arm (the side which you had or will be having surgery).

Please rate how well you could perform each of the activities when using your affected side, even if it is not your dominant arm or hand. Circle the number closest to how well you are able to complete each activity.

	Easily	*With Some Difficulty*	*With Great Difficulty*	*Unable to do*	*Never Attempted, or Would Not Attempt*
a. Placing something on a shelf above my head	1	2	3	4	5
b. Drive a car for more than 30 minutes	1	2	3	4	5
c. Pull a tight shirt on over my head	1	2	3	4	5
d. Unscrew a tight lid on a jar	1	2	3	4	5
e. Put on a bra that clips in the back	1	2	3	4	5
f. Carry a 10 pound grocery bag for 10 minutes	1	2	3	4	5
g. Sleep on my affected side for more than 10 minutes	1	2	3	4	5
h. Pull wet clothes out of the washing machine	1	2	3	4	5
i. Push a heavy piece of furniture	1	2	3	4	5
j. Dry my back with a towel	1	2	3	4	5
k. Chop potatoes into small cubes	1	2	3	4	5
l. Push open a heavy door	1	2	3	4	5
m. Clean a window above shoulder height	1	2	3	4	5
n. Vacuum for 30 minutes	1	2	3	4	5
o. Iron clothes for 15 minutes	1	2	3	4	5
p. Scrub a surface for 5 minutes	1	2	3	4	5
q. Catch a falling object with my affected hand	1	2	3	4	5
r. Carry a 10 pound bag over my shoulder	1	2	3	4	5
s. Type on a keyboard for 20 minutes	1	2	3	4	5

→ Continue on to the next page →

The questions in the next section will ask you about exercises for your affected arm. Your affected arm is the arm on the same side of your body that you had or will be having surgery as party of your breast cancer treatment.

Did you do any exercises for your affected arm within the first few months after surgery? (Circle the letter that describes your exercise)

a. Yes
b. No

Do you currently do any exercises for your affected arm?

a. Yes
b. No

If you are still doing your exercises: How often are you doing exercises for your affected arm?

a. Daily
b. A few times per week
c. About once a week
d. About once a month
e. Other. Please describe how often: _____

Is there anything that may prevent or limit you from doing your arm exercises? Circle all of the statements that apply.

a. Nothing prevents or limits me from arm exercises
b. The exercises were too difficult
c. I have arm pain
d. My arm is too swollen
e. I don't have time
f. I worry that the exercises might make my arm swell
g. I am too tired
h. I am too confused about what to do
i. Other. Please explain what other things may limit your exercise: _____
_____

Would you consider your regular daily activities strenuous on your arm(s)?

a. Yes
b. No
c. Don't know

→ Continue on to the next page →

About You:

The questions in this section include a list of statements that other people with your illness have said are important. When discussing illness, we are asking about breast cancer. By circling one (1) number per line, please indicate how true each state has been for you <u>during the past 7 days</u>.

Your Physical Well-Being

	Not at all	*A little bit*	*Somewhat*	*Quite a bit*	*Very much*
a. I have a lack of energy	0	1	2	3	4
b. I have nausea	0	1	2	3	4
c. Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
d. I have pain	0	1	2	3	4
e. I am bothered by side effects of treatment	0	1	2	3	4
f. I feel ill	0	1	2	3	4
g. I am forced to spend time in bed	0	1	2	3	4

Your Social/Family Well-Being

	Not at all	*A little bit*	*Somewhat*	*Quite a bit*	*Very much*
a. I feel close to my friends	0	1	2	3	4
b. I get emotional support from my family	0	1	2	3	4
c. I get support from my friends	0	1	2	3	4
d. My family has accepted my illness	0	1	2	3	4
e. I am satisfied with family communication about my illness	0	1	2	3	4
f. I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box □ and go to the next section. g. I am satisfied with my sex life.	0	1	2	3	4

→ Continue on to the next page →

Your Emotional Well-Being

	Not at all	*A little bit*	*Somewhat*	*Quite a bit*	*Very much*
a. I feel sad	0	1	2	3	4
b. I am satisfied with how I am coping with my illness	0	1	2	3	4
c. I am losing hope in the fight against my illness	0	1	2	3	4
d. I feel nervous	0	1	2	3	4
e. I worry about dying	0	1	2	3	4
f. I worry that my condition will get worse	0	1	2	3	4

Your Functional Well-Being

	Not at all	*A little bit*	*Somewhat*	*Quite a bit*	*Very much*
a. I am able to work (including work at home)	0	1	2	3	4
b. My work (including work at home) is fulfilling	0	1	2	3	4
c. I am able to enjoy life	0	1	2	3	4
d. I have accepted my illness	0	1	2	3	4
e. I am enjoying the things I usually do for fun	0	1	2	3	4
f. I am content with the quality of my life right now	0	1	2	3	4

Additional Concerns

	Not at all	*A little bit*	*Somewhat*	*Quite a bit*	*Very much*
a. I have been short of breath	0	1	2	3	4
b. I am self-conscious about the way I dress	0	1	2	3	4
c. One or both of my arms are swollen or tender	0	1	2	3	4
d. I feel sexually attractive	0	1	2	3	4
e. I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
f. I worry about the effect of stress on my illness	0	1	2	3	4
g. I am bothered by a change in weight	0	1	2	3	4
h. I am able to feel like a woman	0	1	2	3	4
i. I have certain parts of my body where I experience significant pain	0	1	2	3	4