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| <b>13. ABSTRACT (Maximum 200 Words)</b><br><br>The <b>purpose</b> is to evaluate perioperative training for lymphedema protection. The <b>hypothesis</b> is that structured perioperative training in lymphedema protection will decrease lymphedema, and improve the QOL in patients undergoing axillary dissection and/or radiation therapy for breast cancer as compared to a control group. The <b>specific questions</b> are 1) what is the incidence of lymphedema and infection during the first three years after surgery among breast cancer patients who received perioperative training in lymphedema protection as compared to a control group? 2) What are the differences in the measured QOL among these breast cancer survivors? 3) What are the retention of information on lymphedema protection, and the compliance with arm precautions among these breast cancer survivors? <b>Major Findings:</b> In this interim report, the LE rate is 55%. Our rate for acute LE is 46.2%. Presentation of LE after the first year after surgery occurred in 8.9% of the study patients. There were 38.6% acute LE cases persisting to become chronic for a total chronic rate of 47.5%. <b>Significance:</b> LE is a significant problem. The identification of newer treatment plans and modalities that may obviate the need for injury to the lymphatics would help reduce the incidence of LE. |                                                                 |                                                                |                                                                         |                                  |
| <b>14. SUBJECT TERMS</b><br>Lymphedema, quality of life, education                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                 |                                                                |                                                                         | <b>15. NUMBER OF PAGES</b><br>34 |
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## INTRODUCTION

### Narrative:

**Subject:** Increasing numbers of breast cancer survivors are at risk for long-term sequelae from treatment. Axillary surgery or radiation therapy to the breast may alter lymph channels, leaving the survivor with a lifetime risk for developing lymphedema. Lymphedema is a swelling of the upper extremity, which causes pain, debility, and reduced quality of life (QOL) that impacts choices about work, social and sexual interactions and self-esteem. Protective measures to reduce the risk of lymphedema become important life-long skills. However, there is inconsistent teaching of protective measures, and inattention to lymphedema detection in clinical practice. **Purpose:** The purpose of this study is to test that structured perioperative training in lymphedema protection will decrease lymphedema, the episodes of infection, the time to detection of lymphedema and improve the QOL in patients undergoing axillary dissection and/or radiation therapy for breast cancer as compared to a control group. **Scope:** The specific aims are 1) what is the incidence of lymphedema and infection during the first three years after surgery among breast cancer patients who received perioperative training in lymphedema protection as compared to a control group? 2) What are the differences in the measured QOL among breast cancer patients during the first three years after surgery that received perioperative education in lymphedema protection as compared to a control group? 3) What are the retention of information on lymphedema protection, and the compliance with arm precautions among breast cancer patients who received perioperative lymphedema training as compared to a control group? **Methods:** Patients with resectable breast cancer also undergoing axillary lymph node surgery and/or radiation therapy to the breast will be prospectively randomized to two groups. In addition to receiving standard care (i.e., written breast rehabilitation materials and preoperative counseling by the breast surgeon), patients in Group 1, will receive structured education in Breast Surgery Rehabilitation including range of motion exercises, lymphedema arm precautions, and management of complications. Patients in Group 2 will receive standard care (written material and preoperative counseling by the surgeon). For both groups, preoperative and then quarterly volume measurements and exams of the upper extremities will be done for three years after surgery in order to determine lymphedema and infection incidence. The QOL will be measured longitudinally by the Functional Assessment of Cancer Therapy-Breast (FACT-B) and the Medical Outcome Study Short Form Health Survey (MOS SF-36) and sexuality subscales of Cancer Rehabilitation Evaluation System (CARES). The knowledge of and practice of lymphedema protective skills will be measured by periodic testing longitudinally as well.

## BODY

### Part 1: Response to Reviewer's comments from Year III report:

#### Format/Editorial Issues

1. *"The Principal Investigator (PI) has commendably addressed each subtask in the approved Statement of Work (SOW), but has provided very little data to document progress or "complete accomplishment" of many subtasks."*

**Response:** In this report, data corresponding to specific subtasks are provided throughout to document the progress of accomplishment of the subtasks.

Subtask data is also presented as related to each of the Specific Aims of the study.

## BODY (continued)

2. *"The PI states on page 13 that the lymphedema rate found among totally evaluable subjects (49.6%) is higher than that "predicted in the literature" (more properly, "expected on the basis of rates reported in the literature"), but fails to identify what rates (or range of rates) have been reported. This should not have been difficult, as the draft article (Bland, Perczyk et al.) included as supporting data provides both a reported range (6%-30%) and a source (Petrek JA and MC Heelan, Incidence of breast carcinoma-related lymphedema, Cancer 83:2776-2781 [1998]) that could easily have been included as a reference in the report."*

**Response:** In this report, if there are any references to the literature, specific data from the literature will be included for the convenience of the reviewers.

### Technical Issues

1. *"Interim data and statistical analysis of such data were missing in the report."*

**Response:** In this report, interim data and statistical analysis of the data are included. We did not suffer a regional power outage as occurred last year.

**Part 2: Research accomplishments associated with each task outlined in the approved Statement of Work. Therefore, the Year IV report is cumulative through 7/31/04**

*(Some figures and tables will be embedded in the text, others in the appendix.)*

**Task 1. Start-up, Months 1-2.**

This was completely accomplished in 2000.

**Task 2. Introduce study to physicians, nurses and clerks in clinics, Months 1-2.**

This was completely accomplished in 2000.

**Task 3. Subject recruitment and data collection, Months 3-60.**

This is ongoing.

For Specific Aim 1, there are 158 evaluable patients which was the goal. This permits determination of interim LE and infection rates as the years of followup continue.

For Specific Aim 2, there are 153 evaluable patients since 5 did not complete the QOL questionnaires preoperatively, and will not be part of Spec. Aim 2 analysis. Interim determination of changes in QOL can be determined with this number while the followup continues.

For Specific Aim 3, there are 158 evaluable patients which permits determination of interim knowledge and compliance with LE protection measures while followup continues.

The data tables listed under **Task 11** show population and clinical characteristics of the study patients for the intervention and control groups for Specific Aims 1 and 3 (Tables 1 and 2)

**BODY (continued)**

**Task 4. Perioperative teaching sessions, Months 3-27.**

All patients randomized to the intervention group (n=71) underwent perioperative teaching by the LE study nurse, and underwent knowledge testing at the same time. See Appendix Item #1.

**Task 5. Quarterly measurements of subjects, Months 6-60.**

This is ongoing. Appendix Item #2 shows the measurement data of subjects in centimeters at multiple standardized sites along both upper extremities. If a patient is unable to complete a quarterly measurement, we see them at the next quarterly interval. See Appendix Item #2.

**Task 6. QOL questionnaires at 6 months, 1-, 2-, and 3-years postop, Months 9-60.**

This is ongoing. Tables 9 and 10 under *Task 11* show the population and clinical characteristics for the subjects for this group of data pertinent to Specific Aim 2. Interim analysis of the QOL data are shown under *Task 11*.

**Task 7. Booster training session for Group 1 subjects, Months 9-33.**

Appendix #3 lists the booster sessions attended by the intervention group. Of the intervention group, 15 did not attend the booster session. Of these 6 are still within the timeframe to receive the booster session now. This leaves 9 (12.7%) without the booster session. The impact of the booster sessions is tested yearly by knowledge and compliance questionnaires as part of Specific Aim 3. From the original grant application:

**"Sample Size Calculation.** A total of 158 evaluable patients (79 in each arm) will be studied. This sample size will allow detection of a reduction in the acute lymphedema incidence rate from 25% to 10% with 80% power, 5% overall type I error, and a one-sided hypothesis test. It will also detect changes in the QOL measures using a 2-sided  $\alpha$  at 0.05 and power at 0.8 for changes with  $3/4^{\text{th}}$ s of a standard deviation (43). Assuming an attrition rate of 10% due to dropouts, 176 patients will be needed to complete the accrual goal of 158 evaluable patients."

Therefore, we are continuing to evaluate eligible subjects so that 158 evaluable patients will have both the perioperative teaching (Task 4) and booster training (Task 7) completed.

**Task 8. Knowledge and compliance questionnaires, Months 9-60.**

This is ongoing. Interim data analysis is under *Task 11* for this item which tests Specific Aim 3.

**Task 9. Calculations of limb volumes and comparison of differences, Months 3-60.**

This is ongoing.

Weekly report sheets are created and reviewed which show cumulative data:

- a) volume changes
- b) >1cm measurement changes
- c) Symptoms

## **BODY (continued)**

### **Task 9 (continued)**

All subjects with >10% volume change, >1cm measurement change and/or persistent symptoms are evaluated by the LE study nurse. Appendix # 4 shows a weekly volume report.

### **Task 10. Quarterly data entry and print out by the Psychosocial and Behavioral Core, Months 3-60.**

This is ongoing. From the previous annual reports, the Psychosocial and Behavioral Core was dissolved by the reorganization at the Karmanos Cancer Institute. Data entry is now at least weekly by a data manager.

### **Task 11. Interim analysis of data after 1 year, 3 years, Months 14-16, 38-40.**

The interim analysis of data is being reported in this Year IV report due to the power outage last August (2003) in our section of the US. We were excused for the Year III report.

The study statistician performed the interim analyses which are summarized in the following tables and figure. The comparisons of various patient characteristics between the control and intervention arm or between patients with and without lymphedema were performed using 2-sample t-tests and chi-square tests. A multivariable logistic regression with a backward variable selection procedure was also utilized to determine the relationship between lymphedema and various risk factors.

The interim data are reported according to the Specific Aims. Discussion about the data appears in between the data tables and figures.

*Specific Aim 1) What is the incidence of lymphedema and infection during the first three years after surgery among breast cancer patients who received perioperative training in lymphedema protection as compared to a control group?*

**Table 1 Population Characteristics of Study Participants in the Intervention and Control Groups for LE Protection teaching (Specific Aim 1 and 3)**

|                                            | Intervention Group | Control Group   | Univariate                                                      |
|--------------------------------------------|--------------------|-----------------|-----------------------------------------------------------------|
| <b>N</b>                                   | 71                 | 87              |                                                                 |
| <b>Mean age, yrs <math>\pm</math> S.D.</b> | 53.6 $\pm$ 11.8    | 52.8 $\pm$ 11.6 | P=0.6671                                                        |
| <b>Gender (F, M)</b>                       | 70, 1              | 86, 1           |                                                                 |
| <b>Race</b>                                |                    |                 |                                                                 |
| African American                           | 31                 | 37              | P=0.8862                                                        |
| Caucasian                                  | 33                 | 38              |                                                                 |
| Hispanic                                   | 1                  | 2               |                                                                 |
| Arab/Chaldean                              | 1                  | 2               |                                                                 |
| Asian                                      | 0                  | 4               |                                                                 |
| Native American                            | 3                  | 1               |                                                                 |
| Other                                      | 2                  | 3               |                                                                 |
| <b>Highest education level</b>             |                    |                 | P=0.6838<br>For college<br>vs<br>no college                     |
| Less than high school                      | 9                  | 8               |                                                                 |
| High school/GED                            | 36                 | 43              |                                                                 |
| Associate degree                           | 0                  | 0               |                                                                 |
| Bachelor degree                            | 13                 | 16              |                                                                 |
| Masters degree                             | 3                  | 8               |                                                                 |
| Doctorate/professional school              | 3                  | 1               |                                                                 |
| Not answered                               | 7                  | 11              |                                                                 |
| <b>Annual income</b>                       |                    |                 | P=0.4864<br>For<br>< \$50,000<br>vs<br>≥ \$50,001               |
| < \$5,000                                  | 5                  | 9               |                                                                 |
| \$5,000-\$15,000                           | 9                  | 12              |                                                                 |
| \$15,001-\$30,000                          | 8                  | 10              |                                                                 |
| \$30,001-\$50,000                          | 8                  | 8               |                                                                 |
| \$50,001-\$75,000                          | 8                  | 9               |                                                                 |
| > \$75,001                                 | 16                 | 15              |                                                                 |
| Not answered                               | 17                 | 24              |                                                                 |
| <b>Marital Status</b>                      |                    |                 | P=0.3438<br>For<br>married/<br>cohabitating<br>vs<br>all others |
| Divorced/separated                         | 17                 | 17              |                                                                 |
| Married/Cohabitating                       | 34                 | 33              |                                                                 |
| Never married                              | 8                  | 11              |                                                                 |
| Widowed                                    | 8                  | 16              |                                                                 |
| Not answered                               | 4                  | 10              |                                                                 |
| <b>Religious Preference</b>                |                    |                 | P=0.1818<br>For<br>Christian<br>vs<br>Non-<br>Christian         |
| Catholic                                   | 18                 | 17              |                                                                 |
| Hindu                                      | 0                  | 1               |                                                                 |
| Jewish                                     | 2                  | 0               |                                                                 |
| Muslim                                     | 1                  | 1               |                                                                 |
| Protestant                                 | 19                 | 19              |                                                                 |
| Other                                      | 21                 | 34              |                                                                 |
| None                                       | 2                  | 4               |                                                                 |
| Not answered                               | 8                  | 11              |                                                                 |
| <b>Transportation</b>                      |                    |                 | P=0.5587<br>For<br>drive myself<br>vs<br>all others             |
| Usually drive myself                       | 45                 | 59              |                                                                 |
| Usually public transportation              | 8                  | 1               |                                                                 |
| Usually driven                             | 13                 | 14              |                                                                 |
| Other                                      | 0                  | 2               |                                                                 |
| Not answered                               | 5                  | 10              |                                                                 |

**Table 2 Clinical Characteristics of Study Participants in the Intervention and Control Groups for LE Protection teaching (Specific Aim 1).**

|                                                          | Intervention Group               | Control Group                    | Univariate                                                         |
|----------------------------------------------------------|----------------------------------|----------------------------------|--------------------------------------------------------------------|
| <b>N</b>                                                 | <b>71</b>                        | <b>87</b>                        |                                                                    |
| <b>Breast Cancer Stage</b>                               |                                  |                                  | <b>P=0.9984</b>                                                    |
| 0                                                        | 10                               | 9                                | <b>Stage 0,I<br/>Vs<br/>Stage IIA,<br/>IIB, IIIA, IIIB,<br/>IV</b> |
| I                                                        | 21                               | 29                               |                                                                    |
| IIA                                                      | 17                               | 19                               |                                                                    |
| IIB                                                      | 13                               | 16                               |                                                                    |
| IIIA                                                     | 6                                | 9                                |                                                                    |
| IIIB                                                     | 4                                | 5                                |                                                                    |
| IV                                                       | 0                                | 0                                |                                                                    |
| <b>Type of breast surgery)</b>                           |                                  |                                  | <b>P=0.8095</b>                                                    |
| <b>Mastectomy with axillary surgery</b>                  | <b>38</b>                        | <b>50</b>                        |                                                                    |
| <b>Lumpectomy with axillary surgery</b>                  | <b>28</b>                        | <b>30</b>                        |                                                                    |
| <b>Lumpectomy</b>                                        | <b>5</b>                         | <b>7</b>                         |                                                                    |
| <b>Radiation therapy</b>                                 |                                  |                                  | <b>P=0.9984</b>                                                    |
| Yes                                                      | 40                               | 49                               |                                                                    |
| No                                                       | 31                               | 38                               |                                                                    |
| <b>Number of LNs resected (mean <math>\pm</math> SD)</b> | <b>8.5 <math>\pm</math> 5.8</b>  | <b>9.9 <math>\pm</math> 6.5</b>  | <b>P=0.1786</b>                                                    |
| $\leq 8$ LNs submitted                                   | 37                               | 40                               | <b>P=0.4428</b>                                                    |
| $> 8$ LNs submitted                                      | 34                               | 47                               |                                                                    |
| <b>Number of LNs positive for ca</b>                     | <b>1.1 <math>\pm</math> 2.4</b>  | <b>1.6 <math>\pm</math> 3.0</b>  | <b>P=0.2795</b>                                                    |
| 0                                                        | 45                               | 52                               | <b>P=0.6332</b>                                                    |
| 1-3                                                      | 19                               | 22                               |                                                                    |
| $>4$                                                     | 7                                | 13                               |                                                                    |
| <b>Body Mass Index (BMI) (mean <math>\pm</math> SD)</b>  | <b>29.3 <math>\pm</math> 7.3</b> | <b>29.2 <math>\pm</math> 7.6</b> | <b>P=0.9165</b>                                                    |
| BMI $>25$                                                | 52                               | 61                               | <b>P=0.6651</b>                                                    |
| BMI $>30$                                                | 27                               | 35                               | <b>P=0.7780</b>                                                    |

**Discussion:** From Tables 1 and 2, it can be concluded that the intervention and control groups of subjects are similar by univariate analysis. This is expected in a prospective randomized study. Therefore any differences in LE rate, infection, time to LE will be due to other reasons.

**Table 3 Incidence of LE in the intervention and control groups (interim data) (Specific Aim 1)**

|                      | Secondary LE (n=87) | Without LE (n=71) | P=0.3503 |
|----------------------|---------------------|-------------------|----------|
| Intervention (n=71)  | 42                  | 29                |          |
| Control group (n=87) | 45                  | 42                |          |

**Table 4 Infection rate in the intervention and control groups, and in those with LE and without LE (interim data) (Specific Aim 1)**

|                      | Infection | No infection | P=1   |
|----------------------|-----------|--------------|-------|
| Intervention (n=71)  | 5         | 66           |       |
| Control group (n=87) | 3         | 84           |       |
|                      |           |              |       |
| LE (n=87)            | 7         | 80           | P=0.1 |
| No LE (n=71)         | 1         | 70           |       |

**Discussion:** From Table 3, the interim incidence of LE in the intervention group is not significantly different from the control group. From Table 4, the interim infection rate is similar in the intervention and the control group. However, there are more subjects with infection in the LE group than in the group without LE. The cases of infection may confound the effect of teaching and may need to be separated during the final analysis. Infection was predicted to increase the risk of LE<sup>1</sup>.

To investigate whether there are any variables more strongly associated with LE, multivariate analysis was performed with this interim data. For multivariate analysis, stepwise logistic regression using the backward selection method was performed to determine association with LE by variables in the clinical or population characteristics. LE (yes/no) was dependent, and the other variables were explanatory variables. From Table 5, the highest correlation with developing LE was with any lymph nodes positive or the number of lymph nodes removed at surgery. Being Christian had a protective effect (odds ratio <1). Being in the control arm did not correlate with higher LE (or being in the intervention arm did not correlate with lower risk for LE). In Table 6 and Table 7, the population and clinical characteristics of subjects with LE are compared with those of subjects without LE. Unlike a report from the literature<sup>2</sup>, there was no association between elevated body mass index (BMI) and the risk of LE in this study.

**Table 5 The LOGISTIC Procedure**

Analysis of Maximum Likelihood Estimates

| Parameter              | Wald       |            | 95%                        |        |
|------------------------|------------|------------|----------------------------|--------|
|                        | Pr > ChiSq | Odds Ratio | Confidence Limits for Odds |        |
| Intercept              | 0.0863     | -----      | -----                      | -----  |
| Control arm            | 0.2799     | 0.675      | 0.331                      | 1.377  |
| Ln submitted (>8)      | <.0001     | 4.864      | 2.302                      | 10.277 |
| Ln positive (>0)       | 0.0171     | 2.505      | 1.177                      | 5.329  |
| Mastectomy (vs. other) | 0.0754     | 0.507      | 0.240                      | 1.072  |
| Christian              | 0.0208     | 2.345      | 1.138                      | 4.830  |

**Table 6 Population Characteristics of Breast Cancer Survivors with and without Upper Extremity Secondary Lymphedema (LE) from the Walt Breast Center, Karmanos Cancer Institute, Detroit, MI**

|                                | With LE                        | Without LE                     | Univariate                                                     |
|--------------------------------|--------------------------------|--------------------------------|----------------------------------------------------------------|
| <b>N</b>                       | <b>87</b>                      | <b>71</b>                      |                                                                |
| <b>Mean age, yrs±SD(range)</b> | <b>53.5 ± 12.1 (29.3-80.2)</b> | <b>52.8 ± 11.2 (34.1-79.6)</b> | <b>P=0.7249</b>                                                |
| <b>Gender (F, M)</b>           |                                |                                |                                                                |
| <b>Race</b>                    |                                |                                |                                                                |
| African American               | 36                             | 32                             | <b>P=0.6411</b>                                                |
| Caucasian                      | 39                             | 32                             |                                                                |
| Hispanic                       | 3                              | 0                              |                                                                |
| Arab/Chaldean                  | 3                              | 0                              |                                                                |
| Asian                          | 1                              | 3                              |                                                                |
| Native American                | 1                              | 3                              |                                                                |
| Other                          | 4                              | 1                              |                                                                |
| <b>Employment status</b>       |                                |                                |                                                                |
| Working                        | 69                             | 48                             |                                                                |
| Not working                    | 16                             | 20                             |                                                                |
| Retired                        | 0                              | 0                              |                                                                |
| Not answered                   | 2                              | 3                              |                                                                |
| <b>Highest education level</b> |                                |                                | <b>P=0.7697<br/>for<br/>college<br/>vs<br/>no college</b>      |
| Less than high school          | 10                             | 7                              |                                                                |
| High school/GED                | 42                             | 37                             |                                                                |
| Associate degree               | 0                              | 0                              |                                                                |
| Bachelor degree                | 17                             | 12                             |                                                                |
| Masters degree                 | 5                              | 6                              |                                                                |
| Doctorate/professional school  | 3                              | 1                              |                                                                |
| Not answered                   | 10                             | 8                              |                                                                |
| <b>Annual income</b>           |                                |                                | <b>P=0.3775<br/>for<br/>&lt;\$50,000<br/>vs<br/>≥ \$50,001</b> |
| < \$5,000                      | 6                              | 8                              |                                                                |
| \$5,000-\$15,000               | 10                             | 11                             |                                                                |
| \$15,001-\$30,000              | 10                             | 8                              |                                                                |
| \$30,001-\$50,000              | 10                             | 6                              |                                                                |
| \$50,001-\$75,000              | 10                             | 7                              |                                                                |
| > \$75,001                     | 19                             | 12                             |                                                                |
| Not answered                   | 22                             | 19                             |                                                                |
| <b>Marital Status</b>          |                                |                                |                                                                |
| Married/Cohabiting             | 40                             | 37                             | <b>P=0.2646</b>                                                |
| Other responses                | 41                             | 26                             |                                                                |
| <b>Transportation</b>          |                                |                                |                                                                |
| Usually drive myself           | 58                             | 46                             | <b>P=0.8045</b>                                                |
| Other responses                | 29                             | 25                             |                                                                |
| <b>Religious Preference</b>    |                                |                                |                                                                |
| Christian                      | 46                             | 27                             | <b>P=0.0378</b>                                                |
| Non-Christian                  | 30                             | 36                             |                                                                |

**Table 7 Clinical Characteristics of Breast Cancer Survivors with and without Secondary LE**

|                                                                 | With LE                          | Without LE                       | Univariate                                       |
|-----------------------------------------------------------------|----------------------------------|----------------------------------|--------------------------------------------------|
| <b>N</b>                                                        | <b>87</b>                        | <b>71</b>                        |                                                  |
| <b>Breast Cancer Stage</b>                                      |                                  |                                  | <b>P=0.0241</b>                                  |
| 0                                                               | 5                                | 14                               | <b>For Stage 0,I vs IIA, IIB, IIIA, IIIB, IV</b> |
| I                                                               | 26                               | 24                               |                                                  |
| IIA                                                             | 20                               | 16                               |                                                  |
| IIB                                                             | 20                               | 9                                |                                                  |
| IIIA                                                            | 9                                | 6                                |                                                  |
| IIIB                                                            | 7                                | 2                                |                                                  |
| IV                                                              | 0                                | 0                                |                                                  |
| <b>Type of breast surgery)</b>                                  |                                  |                                  | <b>P=0.1705</b>                                  |
| Mastectomy with axillary surgery                                | 47                               | 41                               |                                                  |
| Lumpectomy with axillary surgery                                | 36                               | 22                               |                                                  |
| Lumpectomy                                                      | 4                                | 8                                |                                                  |
| <b>Radiation therapy</b>                                        |                                  |                                  | <b>P=0.5203</b>                                  |
| Yes                                                             | 51                               | 33                               |                                                  |
| No                                                              | 36                               | 38                               |                                                  |
| <b>Number of LNs resected (mean <math>\pm</math> SD)</b>        | <b>11.1 <math>\pm</math> 6.1</b> | <b>7.0 <math>\pm</math> 5.7</b>  | <b>P&lt;0.0001</b>                               |
| $\leq 8$ LNs submitted                                          | 29                               | 48                               | <b>P&lt;0.0001</b>                               |
| > 8 LNs submitted                                               | 58                               | 23                               |                                                  |
| <b>Number of LNs positive for ca (mean <math>\pm</math> SD)</b> | <b>1.6 <math>\pm</math> 3.0</b>  | <b>1.0 <math>\pm</math> 2.4</b>  | <b>P=0.2795</b>                                  |
| 0                                                               | 45                               | 52                               | <b>P=0.0137</b>                                  |
| 1-3                                                             | 30                               | 11                               |                                                  |
| >4                                                              | 12                               | 8                                |                                                  |
| <b>Body Mass Index (BMI) (mean <math>\pm</math> SD)</b>         | <b>29.7 <math>\pm</math> 7.1</b> | <b>28.8 <math>\pm</math> 7.8</b> | <b>P=0.4443</b>                                  |
| BMI >25                                                         | 49                               | 64                               | <b>P=0.5285</b>                                  |
| BMI >30                                                         | 36                               | 26                               | <b>P=0.5422</b>                                  |

**Discussion:** Univariate analysis of those with LE compared with those without LE in Tables 6 and 7 showed that LE was significantly associated with certain clinical characteristics. These included the number of mean number of lymph nodes resected at surgery (11.1 with LE vs 7.0 without LE,  $p<0.0001$ ), especially if >8 lymph nodes were resected ( $p<0.0001$ ). Furthermore, while the mean number of lymph nodes positive for metastatic cancer was not associated with increased risk for LE, the greater the number of lymph nodes positive for cancer (>4 vs 1-3 vs 0), the greater the risk of LE ( $p=0.0137$ ). This is supported by the increased risk with higher stage of breast cancer (Stage IIA and above vs Stage 0 or I,  $p=0.241$ ). The only population characteristic associated with those with LE was the religious preference of being a Christian. The reason for this is not determined.

For these interim data, there are new findings regarding the timing of LE occurrence which will be included in the final analysis of data next year.

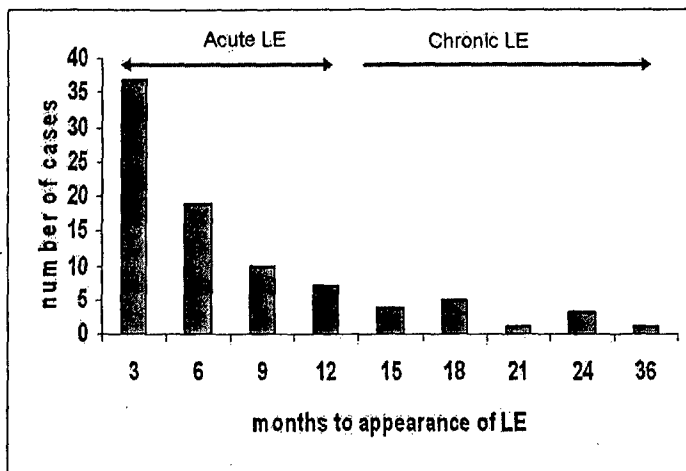
From Fig. 1, the frequency of occurrence of LE was highest in the first year after surgery. LE occurring in the first year is acute LE. If it doesn't resolve, it becomes chronic. However, there were also subjects that had the LE occur after the first year. Therefore, a pattern of LE occurrence is an important finding of the study and has not been previously reported in the literature. There are several reasons for this, including lack of prospective data collection, and the frequency of measurements (quarterly) within this study that would not ordinarily occur in clinical practice. Table 8 describes the patterns of LE occurrence which is new information that will be put into a paper this coming year. There were 73 subjects with LE occurring within the first year after surgery. For 6 of these, the LE resolved within the first year. For another 6 subjects, the LE eventually resolved within 36 months. However, for the majority (61 subjects), the LE occurred during the first year after surgery and persisted. (All cases of LE were referred to the LE clinic for treatment.) These 61 cases of LE are now persistent and chronic.

There were 14 subjects in whom LE occurred after the first year after surgery. Only 1 resolved within 2 years, and 13 remain with chronic LE.

These patterns of LE occurrence are important for several reasons:

- a) They show that careful postoperative measurements identify people with LE within the first year after surgery.
- b) LE that occurs after the first year may be different from LE that occurs within the first year and gives support to further study of these differences.
- c) The literature quotes 16-25.5% occurrence of LE in breast cancer survivors, with the greatest risk within 4 years of treatment<sup>3,4</sup>. However, there is no distinction between acute and chronic LE. Therefore the quoted LE rate is not accurate since it mixes LE occurrence from different times postoperatively. Our rate for acute LE is 46.2%. Presentation of LE after the first year after surgery occurs in 8.9% of the study patients. There are 38.6% acute LE cases persisting to become chronic for a total chronic rate of 47.5%.

The plan is to continue to perform measurements and then specifically perform subset analysis looking at the influence of race, age, stage, type of surgery, number of lymph nodes removed and how many positive for cancer, and radiation therapy while examining LE cases as acute, chronic or acute becoming chronic (persistent).



**Fig. 1. Determining when secondary LE occurs after breast cancer surgery.** Using quarterly prospective measurements after breast cancer surgery, secondary LE was determined by comparing volume changes to preoperative measurements. These were verified by a LE nurse specialist. The months to appearance of secondary LE are along the x-axis, and number of cases along the y-axis. By definition, acute LE presents and resolves within 12 months. Chronic LE presents after 12 months.

**Table 8** Patterns of secondary LE presentation, resolution and persistence in upper extremity of breast cancer survivors

| <i>Presents within the first 12 months after surgery (73 cases)</i> |                                                                                                                  |    |                              |
|---------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|----|------------------------------|
| Secondary LE Pattern                                                | Time of occurrence/pattern description                                                                           | N  | Mean followup $\pm$ SD (mos) |
| Acute LE only                                                       | 0-12 months<br>(Presents and resolves within 12 months after surgery)                                            | 6  | 17.0 $\pm$ 10.3              |
| Acute LE $\rightarrow$ chronic LE $\rightarrow$ resolved            | 0-12 month $\rightarrow$ resolved<br>(Presents within 12 months after surgery and resolves within 3 yrs)         | 6  | 25.0 $\pm$ 10.3              |
| Acute LE $\rightarrow$ chronic LE (persists)                        | 0-12 months $\rightarrow$ continues<br>(Presents within 12 months after surgery and persists) resolved)          | 61 | 20.1 $\pm$ 12.0              |
| <i>Presents more than 12 months after surgery (14 cases)</i>        |                                                                                                                  |    |                              |
| Secondary LE Pattern                                                | Time of occurrence/pattern description                                                                           | N  | Mean followup (mos)          |
| Chronic LE only                                                     | After 12 months<br>(Presents more than 12 months after surgery and persists)                                     | 13 | 27.2 $\pm$ 8.1               |
| Chronic LE resolved                                                 | After 12 months $\rightarrow$ resolved<br>(Presents more than 12 months after surgery and resolves within 3 yrs) | 1  | 30.0                         |
| Total                                                               |                                                                                                                  | 87 | 19.3 $\pm$ 11.1              |

*Specific Aim 2) What are the differences in the measured QOL among breast cancer patients during the first three years after surgery that received perioperative education in lymphedema protection as compared to a control group?*

For Specific Aim 2, there are 153 evaluable patients since 5 did not complete the QOL questionnaires preoperatively, and will not be part of Spec. Aim 2 analysis. Interim determination of changes in QOL can be determined with this number while the followup continues.

In Tables 9 and 10, the population and clinical characteristics of these 153 evaluable subjects are compared for the intervention and control groups.

Then in Table 11, the interim scores for the QOL instruments in this study are compared (FACT-B, MOS-SF36, and the sexuality and marital subscales of CARES). In Table 12, the interim longitudinal changes in the QOL scores are shown. In Table 13, the interim scores for the FACT-B subscales are shown that may give insight into the longitudinal changes in the FACT-B. In Table 14, the interim longitudinal change in the FACT-B scores are compared for the subscales.

**Table 9 Population Characteristics of Study Participants in the Intervention and Control Groups for LE Protection teaching (Specific Aim 2)**

|                                            | Intervention Group                | Control Group                     |
|--------------------------------------------|-----------------------------------|-----------------------------------|
| <b>N</b>                                   | <b>69</b>                         | <b>84</b>                         |
| <b>Mean age, yrs <math>\pm</math> S.D.</b> | <b>53.4 <math>\pm</math> 11.9</b> | <b>52.1 <math>\pm</math> 11.2</b> |
| <b>Race</b>                                |                                   |                                   |
| African American                           | 30                                | 34                                |
| Caucasian                                  | 32                                | 38                                |
| Hispanic                                   | 1                                 | 2                                 |
| Arab/Chaldean                              | 1                                 | 2                                 |
| Asian                                      | 0                                 | 4                                 |
| Native American                            | 3                                 | 1                                 |
| Other                                      | 2                                 | 3                                 |
| <b>Highest education level</b>             |                                   |                                   |
| Less than high school                      | 9                                 | 8                                 |
| High school/GED                            | 36                                | 42                                |
| Associate degree                           | 0                                 | 0                                 |
| Bachelor degree                            | 13                                | 16                                |
| Masters degree                             | 3                                 | 8                                 |
| Doctorate/professional school              | 2                                 | 1                                 |
| Not answered                               | 6                                 | 9                                 |
| <b>Annual income</b>                       |                                   |                                   |
| < \$5,000                                  | 5                                 | 8                                 |
| \$5,000-\$15,000                           | 9                                 | 12                                |
| \$15,001-\$30,000                          | 7                                 | 10                                |
| \$30,001-\$50,000                          | 8                                 | 8                                 |
| \$50,001-\$75,000                          | 8                                 | 9                                 |
| > \$75,001                                 | 15                                | 15                                |
| Not answered                               | 17                                | 22                                |
| <b>Marital Status</b>                      |                                   |                                   |
| Divorced/separated                         | 17                                | 17                                |
| Married/Cohabiting                         | 33                                | 33                                |
| Never married                              | 8                                 | 11                                |
| Widowed                                    | 7                                 | 15                                |
| Not answered                               | 4                                 | 8                                 |
| <b>Transportation</b>                      |                                   |                                   |
| Usually drive myself                       | 43                                | 58                                |
| Usually use public transportation          | 8                                 | 1                                 |
| Usually driven by someone else             | 13                                | 15                                |
| Other                                      | 0                                 | 2                                 |
| Not answered                               | 5                                 | 8                                 |
| <b>Religious Preference</b>                |                                   |                                   |
| Catholic                                   | 18                                | 17                                |
| Hindu                                      | 0                                 | 1                                 |
| Jewish                                     | 2                                 | 0                                 |
| Muslim                                     | 1                                 | 1                                 |
| Protestant                                 | 18                                | 18                                |
| Other                                      | 20                                | 34                                |
| None                                       | 2                                 | 4                                 |
| Not answered                               | 8                                 | 9                                 |

**Table 10 Clinical Characteristics of Study Participants in the Intervention and Control Groups for LE Protection teaching (Specific Aim 2).**

|                                  | Intervention Group | Control Group |
|----------------------------------|--------------------|---------------|
| <b>N</b>                         | <b>69</b>          | <b>84</b>     |
| <b>Breast Cancer Stage</b>       |                    |               |
| 0                                | 10                 | 8             |
| I                                | 20                 | 29            |
| IIA                              | 17                 | 18            |
| IIB                              | 12                 | 15            |
| IIIA                             | 6                  | 9             |
| IIIB                             | 4                  | 5             |
| IV                               | 0                  | 0             |
| <b>Type of breast surgery)</b>   |                    |               |
| Mastectomy with axillary surgery | 37                 | 48            |
| Lumpectomy with axillary surgery | 27                 | 30            |
| Lumpectomy                       | 5                  | 6             |
| Mean number of LN submitted      | 8.5 ± 5.8          | 9.9 ± 6.5     |
| BMI (mean ± SD)                  | 29.4 ± 7.4         | 29.3 ± 7.8    |

**Table 11. Interim QOL scores comparing the Intervention group with the Control group.**

|                                | Intervention Group<br><i>n=71</i> |              | Control Group<br><i>n=87</i> |              |
|--------------------------------|-----------------------------------|--------------|------------------------------|--------------|
|                                | N                                 |              | N                            |              |
| <b><u>FACT-B scores</u></b>    |                                   |              |                              |              |
| <b>Total</b>                   |                                   |              |                              |              |
| initial (mean)                 | 65                                | 122.06±6.49  | 79                           | 105.19±3.90  |
| 6-month (mean)                 | 46                                | 129.54±10.86 | 49                           | 113.19±4.88  |
| 12-month (mean)                | 32                                | 132.08±11.85 | 48                           | 115.42±3.68  |
| 24-month (mean)                | 17                                | 129.68±17.70 | 19                           | 135.86±13.69 |
| 36-month (mean)                | 6                                 | 99.67±18.26  | 13                           | 128.15±9.66  |
| <b><u>MOS-SF 36 scores</u></b> |                                   |              |                              |              |
| <b>Physical Scale</b>          |                                   |              |                              |              |
| initial (mean)                 | 60                                | 46.06±1.44   | 70                           | 47.92±2.20   |
| 6-month (mean)                 | 45                                | 43.05±6.06   | 48                           | 28.24±8.48   |
| 12-month (mean)                | 33                                | 48.25±3.50   | 44                           | 44.41±1.53   |
| 24-month (mean)                | 18                                | 46.38±2.24   | 18                           | 47.62±2.05   |
| 36-month (mean)                | 7                                 | 45.91±4.34   | 12                           | 47.81±2.41   |
| <b>Mental Scale</b>            |                                   |              |                              |              |
| initial (mean)                 | 60                                | 50.01±1.44   | 70                           | 46.05±1.50   |
| 6-month (mean)                 | 45                                | 58.48±9.77   | 48                           | 84.12±27.19  |
| 12-month (mean)                | 33                                | 49.18±2.43   | 44                           | 52.68±1.57   |
| 24-month (mean)                | 18                                | 51.27±2.14   | 18                           | 50.78±2.60   |
| 36-month (mean)                | 7                                 | 49.80±3.80   | 12                           | 48.48±4.10   |

Table 11 (continued)

**CARES scores****Sexuality Subscale**

|                 |    |                   |    |                     |
|-----------------|----|-------------------|----|---------------------|
| initial (mean)  | 54 | 7.39 $\pm$ 3.07   | 65 | 25.05 $\pm$ 13.07   |
| 6-month (mean)  | 38 | 77.55 $\pm$ 33.84 | 43 | 26.56 $\pm$ 15.43   |
| 12-month (mean) | 26 | 43.39 $\pm$ 26.68 | 34 | 68.85 $\pm$ 34.90   |
| 24-month (mean) | 10 | 77.90 $\pm$ 37.87 | 10 | 5.90 $\pm$ 2.46     |
| 36-month (mean) | 3  | 5.33 $\pm$ 2.73   | 4  | 123.75 $\pm$ 107.52 |

**Marital Subscale**

|                 |    |                     |    |                     |
|-----------------|----|---------------------|----|---------------------|
| initial (mean)  | 54 | 23.796 $\pm$ 20.629 | 65 | 50.12 $\pm$ 29.59   |
| 6-month (mean)  | 38 | 159.18 $\pm$ 74.945 | 43 | 57.23 $\pm$ 36.11   |
| 12-month (mean) | 26 | 91.00 $\pm$ 59.205  | 34 | 102.56 $\pm$ 61.37  |
| 24-month (mean) | 10 | 339.60 $\pm$ 169.46 | 10 | 7.60 $\pm$ 4.07     |
| 36-month (mean) | 3  | 3.67 $\pm$ 2.33     | 4  | 420.25 $\pm$ 261.75 |

Table 12 Interim Longitudinal changes in Quality of Life Scores for the Intervention Group and Control Group

|                                   | N  | Intervention Group  | N  | Control Group       |
|-----------------------------------|----|---------------------|----|---------------------|
| <b>FACT-B (total score)</b>       |    |                     |    |                     |
| 6-mon compare to 0 month change   | 44 | 13.01 $\pm$ 11.59   | 46 | 10.99 $\pm$ 5.62    |
| 12-mon compared to 0 month        | 31 | 17.42 $\pm$ 11.98   | 46 | 2.28 $\pm$ 6.20     |
| 24-month compare to 0 month       | 17 | 16.85 $\pm$ 18.51   | 18 | 26.64 $\pm$ 12.88   |
| 36-month compared to 0-month      | 6  | -26.44 $\pm$ 16.26  | 11 | 18.89 $\pm$ 9.88    |
| <b>MOS SF-36 (physical score)</b> |    |                     |    |                     |
| 6-mon compare to 0 month change   | 39 | -1.69 $\pm$ 1.64    | 38 | -9.36 $\pm$ 5.26    |
| 12-mon compared to 0 month        | 29 | -1.68 $\pm$ 2.03    | 36 | -5.26 $\pm$ 4.49    |
| 24-month compare to 0 month       | 16 | -3.86 $\pm$ 2.30    | 14 | 3.28 $\pm$ 2.17     |
| 36-month compared to 0-month      | 6  | -0.44 $\pm$ 2.92    | 11 | 4.78 $\pm$ 2.82     |
| <b>MOS SF-36 (mental score)</b>   |    |                     |    |                     |
| 6-mon compare to 0 month change   | 39 | -0.41 $\pm$ 1.87    | 38 | 12.94 $\pm$ 11.95   |
| 12-mon compared to 0 month        | 29 | 1.60 $\pm$ 2.23     | 36 | 5.96 $\pm$ 2.79     |
| 24-month compare to 0 month       | 16 | 3.08 $\pm$ 3.02     | 14 | -0.92 $\pm$ 2.41    |
| 36-month compared to 0-month      | 6  | -4.96 $\pm$ 4.61    | 11 | -1.31 $\pm$ 5.13    |
| <b>CARES (sexuality subscale)</b> |    |                     |    |                     |
| 6-mon compare to 0 month change   | 35 | 32.11 $\pm$ 24.16   | 39 | 16.18 $\pm$ 16.56   |
| 12-mon compared to 0 month        | 25 | 39.48 $\pm$ 27.97   | 32 | 67.09 $\pm$ 37.10   |
| 24-month compare to 0 month       | 10 | 75.80 $\pm$ 37.38   | 10 | 0.10 $\pm$ 3.53     |
| 36-month compared to 0-month      | 3  | 5.00 $\pm$ 2.517    | 4  | 117.50 $\pm$ 105.93 |
| <b>CARES (marital subscale)</b>   |    |                     |    |                     |
| 6-mon compare to 0 month change   | 35 | 83.63 $\pm$ 59.24   | 39 | 26.95 $\pm$ 28.73   |
| 12-mon compared to 0 month        | 25 | 90.36 $\pm$ 61.74   | 32 | 103.44 $\pm$ 65.37  |
| 24-month compare to 0 month       | 10 | 338.20 $\pm$ 169.74 | 10 | -5.50 $\pm$ 4.86    |
| 36-month compared to 0-month      | 3  | 3.67 $\pm$ 2.33     | 4  | 403.50 $\pm$ 260.99 |

Notes: Please be aware that the following p-values are not statistically significant because of the number of tests that were run (p-values should be less than 0.0005 to be statistically significant.)

|                                                     |                    |                 |                |
|-----------------------------------------------------|--------------------|-----------------|----------------|
| Total Fact B at baseline                            | Intervention (122) | Control (105)   | p-value=0.0280 |
| MOS-SF 36 Mental at baseline                        | Intervention (50)  | Control (46)    | p-value=0.0615 |
| CARES Sexuality at 24 months                        | Intervention (78)  | Control (6)     | p-value=0.0900 |
| CARES Marital at 24 months                          | Intervention (340) | Control (8)     | p-value=0.0818 |
| For those who answered 75% or more of the questions |                    |                 |                |
| CARES Sexuality at 24 months                        | Intervention (110) | Control (7)     | p-value=0.0837 |
| Dif. in Fact B 0 – 36 months                        | Intervention (-26) | Control (19)    | p-value=0.0230 |
| Dif. in MOS-SF 36 Physical 0 – 24 months            | Intervention (-4)  | Control (3)     | p-value=0.0335 |
| Dif. in CARES Sexuality 0 – 24 months               | Intervention (76)  | Control (0)     | p-value=0.0741 |
| Dif. in CARES Marital 0 – 24 months                 | Intervention (338) | Control (-6)    | p-value=0.0736 |
| MOS-SF 36 Mental at baseline                        | Lumpectomy (50)    | Mastectomy (46) | p-value=0.0582 |
| Dif. in Mental 0 – 12 months                        | Lumpectomy (-1)    | Mastectomy (9)  | p-value=0.0088 |
| CARES Dif. in Sexuality 0 – 24 months               | Lumpectomy (54)    | Mastectomy (0)  | p-value=0.0775 |

**Discussion:** From Table 11 and Table 12, The scores for the intervention group and the control group do not differ for this first level of analysis. This is expected if the prospectively randomized patients are to be compared. However, the impact of LE teaching on QOL is not determined without including the time of the LE diagnosis. This may impact on the QOL scores as was presented in the preliminary data for the grant. Therefore, the plan for the final analysis is to determine the changes in QOL scores based upon the time of LE diagnosis. This was tested in the data analysis for knowledge and compliance with protection methods to be presented next for Specific Aim 3. Therefore, it will be feasible for the QOL data analysis.

The CARES questionnaire has been particularly problematic with some of the subjects due to questions regarding marital and sexual relationships. Although these are not as detailed as other questionnaires, we observe that patients do not answer questions on the CARES questionnaires because they may not be in a relationship at the time. That is why the analysis examines those who have answered at least 75% of the questions in order to have meaningful data about those questions. At the same time, the number of subjects who feel they cannot respond to the questions is also noteworthy.

The following subscale analysis for FACT-B presented in Tables 13 and 14 also do not identify significant differences between the intervention group and the control group. This would be expected in a prospective randomized trial. However, specific attention to the time of diagnosis of LE in these analysis is planned.

**Table 13** Interim Subscale Scores for the FACT-B QOL Questionnaire comparing the Intervention Group with the Control Group

|                                   |    | Intervention Group |    | Control Group     |  |
|-----------------------------------|----|--------------------|----|-------------------|--|
|                                   |    | <i>n=71</i>        |    | <i>n=87</i>       |  |
|                                   | N  |                    | N  |                   |  |
| <b><u>FACT-B subscales</u></b>    |    |                    |    |                   |  |
| <b><u>Breast</u></b>              |    |                    |    |                   |  |
| initial (mean)                    | 65 | 28.17 $\pm$ 1.73   | 79 | 22.10 $\pm$ 2.63  |  |
| 6-month (mean)                    | 46 | 27.37 $\pm$ 3.61   | 49 | 24.82 $\pm$ 0.93  |  |
| 12-month (mean)                   | 32 | 25.91 $\pm$ 0.93   | 48 | 24.98 $\pm$ 1.21  |  |
| 24-month (mean)                   | 17 | 24.96 $\pm$ 1.74   | 19 | 29.83 $\pm$ 5.33  |  |
| 36-month (mean)                   | 6  | 26.00 $\pm$ 1.86   | 13 | 26.16 $\pm$ 1.65  |  |
| <br><b><u>GP (Physical)</u></b>   |    |                    |    |                   |  |
| initial (mean)                    | 65 | 20.69 $\pm$ 2.16   | 79 | 9.59 $\pm$ 8.87   |  |
| 6-month (mean)                    | 46 | 23.08 $\pm$ 0.70   | 49 | 21.63 $\pm$ 0.79  |  |
| 12-month (mean)                   | 32 | 23.22 $\pm$ 0.92   | 48 | 21.96 $\pm$ 1.47  |  |
| 24-month (mean)                   | 17 | 22.72 $\pm$ 1.21   | 19 | 24.63 $\pm$ 0.74  |  |
| 36-month (mean)                   | 6  | 7.83 $\pm$ 17.03   | 13 | 24.62 $\pm$ 1.08  |  |
| <br><b><u>GS (Social)</u></b>     |    |                    |    |                   |  |
| initial (mean)                    | 65 | 30.78 $\pm$ 4.82   | 79 | 39.01 $\pm$ 11.18 |  |
| 6-month (mean)                    | 46 | 38.68 $\pm$ 7.86   | 49 | 28.44 $\pm$ 3.83  |  |
| 12-month (mean)                   | 32 | 39.30 $\pm$ 9.14   | 48 | 27.00 $\pm$ 2.30  |  |
| 24-month (mean)                   | 17 | 28.25 $\pm$ 5.68   | 19 | 37.45 $\pm$ 11.38 |  |
| 36-month (mean)                   | 6  | 24.17 $\pm$ 1.45   | 13 | 33.91 $\pm$ 8.45  |  |
| <br><b><u>GE (Emotional)</u></b>  |    |                    |    |                   |  |
| initial (mean)                    | 65 | 18.65 $\pm$ 0.53   | 79 | 15.83 $\pm$ 1.46  |  |
| 6-month (mean)                    | 46 | 17.18 $\pm$ 2.18   | 49 | 18.82 $\pm$ 0.69  |  |
| 12-month (mean)                   | 32 | 19.16 $\pm$ 0.82   | 48 | 20.17 $\pm$ 0.67  |  |
| 24-month (mean)                   | 17 | -4.94 $\pm$ 23.21  | 19 | 20.42 $\pm$ 0.71  |  |
| 36-month (mean)                   | 6  | 20.87 $\pm$ 0.97   | 13 | 19.92 $\pm$ 0.72  |  |
| <br><b><u>GF (Functional)</u></b> |    |                    |    |                   |  |
| initial (mean)                    | 65 | 23.78 $\pm$ 2.04   | 79 | 18.67 $\pm$ 0.82  |  |
| 6-month (mean)                    | 46 | 23.24 $\pm$ 2.35   | 49 | 19.49 $\pm$ 1.02  |  |
| 12-month (mean)                   | 32 | 24.50 $\pm$ 3.38   | 48 | 21.32 $\pm$ 0.86  |  |
| 24-month (mean)                   | 17 | 58.71 $\pm$ 39.69  | 19 | 23.53 $\pm$ 1.10  |  |
| 36-month (mean)                   | 6  | 20.81 $\pm$ 1.98   | 13 | 23.54 $\pm$ 1.73  |  |

**Table 14 Interim Longitudinal changes in FACT-B Subscale scores for the Intervention group compared with the Control group.**

|                                 | N  | Intervention group | N  | Control group |
|---------------------------------|----|--------------------|----|---------------|
| <b>FACT-B (Breast Subscale)</b> |    |                    |    |               |
| 6-mon compare to 0 month change | 44 | 1.71+3.71          | 46 | 0.75+1.06     |
| 12-mon compared to 0 month      | 31 | -1.09+1.09         | 46 | 3.21+4.28     |
| 24-month compare to 0 month     | 17 | -0.15+2.37         | 18 | 4.08+5.65     |
| 36-month compared to 0-month    | 6  | -4.63+0.98         | 11 | 0.64+2.21     |
| <b>FACT-B (GP Subscale)</b>     |    |                    |    |               |
| 6-mon compare to 0 month change | 44 | 1.42+2.29          | 46 | 3.35+2.36     |
| 12-mon compared to 0 month      | 31 | -0.87+0.78         | 46 | 4.49+3.40     |
| 24-month compare to 0 month     | 17 | -1.13+1.02         | 18 | 1.99+1.17     |
| 36-month compared to 0-month    | 6  | -18.23+17.37       | 11 | 3.36+2.03     |
| <b>FACT-B (GS Subscale)</b>     |    |                    |    |               |
| 6-mon compare to 0 month change | 44 | 11.18+8.83         | 46 | 4.24+4.63     |
| 12-mon compared to 0 month      | 31 | 15.11+9.54         | 46 | -10.62+13.00  |
| 24-month compare to 0 month     | 17 | 3.19+5.58          | 18 | 15.79+11.57   |
| 36-month compared to 0-month    | 6  | -2.75+1.68         | 11 | 10.44+9.58    |
| <b>FACT-B (GE Subscale)</b>     |    |                    |    |               |
| 6-mon compare to 0 month change | 44 | -1.39+2.31         | 46 | 1.58+0.76     |
| 12-mon compared to 0 month      | 31 | 0.87+0.82          | 46 | 3.89+2.52     |
| 24-month compare to 0 month     | 17 | -23.12+23.02       | 18 | 2.78+1.09     |
| 36-month compared to 0-month    | 6  | 0.87+0.47          | 11 | 1.91+1.16     |
| <b>FACT-B (GF Subscale)</b>     |    |                    |    |               |
| 6-mon compare to 0 month change | 44 | 0.09+3.15          | 46 | 1.08+1.09     |
| 12-mon compared to 0 month      | 31 | 3.40+3.47          | 46 | 1.32+1.07     |
| 24-month compare to 0 month     | 17 | 38.06+40.09        | 18 | 2.00+0.80     |
| 36-month compared to 0-month    | 6  | -1.69+1.815        | 11 | 2.55+1.04     |

Notes: Please be aware that the following p-values are not statistically significant because of the number of tests that were run (p-values should be less than 0.0005 to be statistically significant.)

|                                  |                   |                 |                |
|----------------------------------|-------------------|-----------------|----------------|
| Breast Subscale at baseline      | Intervention (28) | Control (22)    | p-value=0.0563 |
| GE Subscale at baseline          | Intervention (19) | Control (16)    | p-value=0.0724 |
| GF Subscale at baseline          | Intervention (24) | Control (19)    | p-value=0.0224 |
| Dif. in Breast 0 – 36 months     | Intervention (-5) | Control (1)     | p-value=0.0483 |
| Dif. in GF 0 – 36 months         | Intervention (-2) | Control (3)     | p-value=0.0444 |
| Dif. in GP 0 – 24 months         | Intervention (-1) | Control (2)     | p-value=0.0540 |
| Breast Subscale at 36 months     | Lumpectomy (28)   | Mastectomy (23) | p-value=0.0438 |
| GF Subscale at baseline          | Lumpectomy (23)   | Mastectomy (19) | p-value=0.0541 |
| Dif. in GF Subscale 0 – 6 months | Lumpectomy (-3)   | Mastectomy (3)  | p-value=0.0874 |

*Specific Aim 3) What are the retention of information on lymphedema protection, and the compliance with arm precautions among breast cancer patients who received perioperative lymphedema training as compared to a control group?*

The knowledge questionnaires are given preoperatively and at 6 months, 12 months, 24 months and 36 months after surgery. There are 17 questions that cover several categories of protection methods to reduce the risk of LE. The compliance questionnaires are given at the same intervals as the knowledge questionnaires with the exception that no preoperative compliance questionnaire is given. There are 22 questions with each scored from 0 to 4 depending on the frequency of use of a particular protection method.

In Table 15, the interim scores for the knowledge and compliance questionnaires are compared for the intervention and control groups. These are not significantly different. However, in Table 16, the scores are compared for those with LE as compared to those without LE. In addition, the time of LE diagnosis was included so that those with LE at the time of the questionnaire were listed as LE positive. Then for each interval the number of subject who with or without LE changes as new cases are diagnosed (and some resolve). Still required is determining the scores for those with and without LE within the intervention and control groups. This will be a more precise method of reporting the impact of teaching on LE occurrence. We plan to continue these analyses as data are collected.

**Table 15. Interim analysis of knowledge and compliance questionnaires for the Intervention Group and Control Group (Specific Aim 3)**

|                                        |    | <b>Intervention Group</b> |    | <b>Control Group</b> |  |
|----------------------------------------|----|---------------------------|----|----------------------|--|
|                                        |    | <i>n=71</i>               |    | <i>n=87</i>          |  |
|                                        |    | N                         |    | N                    |  |
| <b><u>Knowledge Questionnaire</u></b>  |    |                           |    |                      |  |
| Pretest (mean)                         | 58 | 0.35±0.04                 | 71 | 0.37±0.04            |  |
| 6-month (mean)                         | 46 | 0.67±0.04                 | 51 | 0.67±0.04            |  |
| 12-month (mean)                        | 30 | 0.78±0.05                 | 44 | 0.74±0.04            |  |
| 24-month (mean)                        | 19 | 0.82±0.06                 | 19 | 0.73±0.06            |  |
| 36-month (mean)                        | 5  | 0.76±0.15                 | 12 | 0.79±0.06            |  |
| Dif. Pre Post                          | 39 | 0.37±0.06                 | 41 | 0.26±0.05            |  |
| <b><u>Compliance Questionnaire</u></b> |    |                           |    |                      |  |
|                                        |    | <b>Intervention</b>       |    | <b>Control</b>       |  |
| 6-month (mean)                         | 42 | 3.22±0.09                 | 46 | 3.12±0.12            |  |
| 12-month (mean)                        | 31 | 2.98±0.16                 | 46 | 3.04±0.10            |  |
| 24-month (mean)                        | 16 | 2.92±0.15                 | 19 | 3.10±0.14            |  |
| 36-month (mean)                        | 7  | 2.87±0.32                 | 11 | 2.96±0.18            |  |

**Table 16 Interim analysis of knowledge and compliance questionnaires for those with LE and those without LE (Specific Aim 3)**

|                                        | N  | Without LE | With LE      |
|----------------------------------------|----|------------|--------------|
|                                        |    |            | N            |
| <b><u>Knowledge Questionnaire</u></b>  |    |            |              |
| 6-month (mean)                         | 59 | 0.65±0.04  | 38 0.70±0.04 |
| 12-month (mean)                        | 41 | 0.71±0.04  | 33 0.81±0.04 |
| 24-month (mean)                        | 17 | 0.72±0.08  | 21 0.82±0.04 |
| 36-month (mean)                        | 4  | 0.57±0.15  | 13 0.85±0.05 |
| Dif. Pre Post                          | 47 | 0.32±0.05  | 33 0.30±0.06 |
| <b><u>Compliance Questionnaire</u></b> |    |            |              |
| 6-month (mean)                         | 51 | 3.09±0.11  | 37 3.27±0.11 |
| 12-month (mean)                        | 41 | 2.90±0.11  | 36 3.14±0.14 |
| 24-month (mean)                        | 15 | 2.76±0.15  | 20 3.22±0.12 |
| 36-month (mean)                        | 6  | 2.43±0.27  | 12 3.17±0.17 |

Notes: Please be aware that the following p-values are not statistically significant because of the number of tests that were run (p-values should be less than 0.0005 to be statistically significant.)

|                         |                                      |                |
|-------------------------|--------------------------------------|----------------|
| Knowledge at 36 months  | Lymphedema- (0.57) Lymphedema+(0.85) | p-value=0.0413 |
| Compliance at 24 months | Lymphedema- (2.76) Lymphedema+(3.22) | p-value=0.0204 |
| Compliance at 36 months | Lymphedema- (2.43) Lymphedema+(3.17) | p-value=0.0269 |

**Task 12. Analysis of data after 5<sup>th</sup> year, Months 61-65.**

Not yet applicable.

**Task 13. Annual report to USAMRMC, Months to be designated by USAMRMC.**

Year I, Year II and Year III and Year IV reports submitted.

**Task 14. Meeting in Baltimore, Maryland to disseminate results of DoD-sponsored Research during the second year, Month to be announced by USAMRMC.**

Attended September, 2003, Orlando, FL. Poster presentation.

**Task 15. Write journal articles. Submit abstract, Months 12-60+**

This is ongoing. We are preparing a paper describing the patterns of LE. Further QOL analysis will be performed during the year so that the data can be more quickly evaluated at the end of the next year for the final report.

During this fourth annual year report, the Tasks in the Statement of Work are being accomplished and data are being collected as described in the study. The data are being collected around each of the specific aims of the study. The Specific aims will be answered when all followup data still being collected in the fifth year will be analyzed for a final report.

**KEY RESEARCH ACCOMPLISHMENTS**

- **Patterns of lymphedema are identified:** acute LE cases that persist past the first year after surgery, and chronic LE cases that present after the first year from surgery. Paper in preparation.
- **Knowledge of and compliance with LE protection methods depend on the time of occurrence of LE**

**REPORTABLE OUTCOMES**

**Presentation (Poster)**

"Equality in Male Breast Cancer Care using Sentinel Lymph Node Biopsy", presented at the 2004 national meeting of the Association of VA Surgeons, Richmond Virginia (May, 2004).

**Funding Applied**

NIH: Linking Lymphedema to Disorders of Lymphangiogenesis (PI: Kosir) (Pending)

Komen: Linking Lymphedema to Disorders of Lymphangiogenesis (PI: Kosir)(Pending)

VACO: Linking Lymphedema to Inherited Disorders of Lymphangiogenesis (PI: Kosir) (Pending)

**CONCLUSIONS**

The identification of LE has been shown to require attention to measurement changes even during the first year after surgery. This pattern of LE occurrence leads to a persistent problem in a majority of patients. In this interim report, we have identified an overall LE rate of 55%. To be more precise, our rate for acute LE is 46.2%. Presentation of LE after the first year after surgery occurs in 8.9% of the study patients. There are 38.6% acute LE cases persisting to become chronic for a total chronic rate of 47.5%. This means that the problem of LE is a significant problem. The identification of newer treatment plans and modalities that may obviate the need for injury to the lymphatics would help reduce the incidence of LE.

**"So What Section"**

The awareness of lymphedema occurrence, protection, and treatment by many clinicians that are in contact with breast cancer survivors is not uniform. Furthermore, textbooks do not include enough detail regarding incidence, symptoms, measurement, and treatment, which lead to less attention to the

survivor's observations. This study must be completed to rebut current opinion in the medical literature. It will "rock the boat" and challenge current practice. Already, lymphedema in the first year postoperatively is underreported and this study will be able to add to the literature. We have already published a comparison of methods in detecting LE using our own rigorous detection as the "standard". The longitudinal collection of measurements in several dimensions (physical, quality of life, knowledge, behavior (compliance)) will provide strong data and conclusions that are absolutely necessary to shift established practices that have not really been the result of careful study. There are also several additional studies that will emanate from this study, with the potential to include additional disciplines in breast cancer research.

## REFERENCES

1. Petrek JA, Senie RT, Peters M, et al: Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. *Cancer* 92:1368-1377, 2001.
2. Werner RS, McCormick B, Petrek JA, et al: Arm edema in conservatively managed breast cancer: obesity is a major predictive factor. *Radiology* 180:177-184, 1991.
3. Petrek JA, Heelan MC: Incidence of breast carcinoma-related lymphedema. *Cancer* 83:2776-2781, 1998.
4. Ivens D, Hoe AL, Podd CR, et al: Assessment of morbidity from complete axillary dissection. *Br J Cancer* 66:136-1992.

## APPENDIX

Appendix Item 1- Task 4 Perioperative teaching session

Appendix Item 2- Task 5 Arm measurements

Appendix Item 3- Task 7 Booster teaching session

Appendix Item 4- Task 9 Weekly volume report

**Task 4 Perloperative teaching sessions  
(Intervention group) n=71**

| ID  | Type of Surg | Initial Class |
|-----|--------------|---------------|
| 6   | M+L          | x             |
| 7   | L+L          | x             |
| 9   | L+L          | x             |
| 13  | L+L          | x             |
| 15  | M+L          | x             |
| 19  | L+L          | x             |
| 21  | M+L          | x             |
| 26  | M+L          | x             |
| 28  | M+L          | x             |
| 29  | L+R          | x             |
| 33  | L+L          | x             |
| 35  | L+R          | x             |
| 40  | M+L          | x             |
| 42  | L+L          | x             |
| 46  | M+L          | x             |
| 47  | M+L          | x             |
| 51  | L+L          | x             |
| 55  | M+L          | x             |
| 56  | L+R          | x             |
| 57  | M+L          | x             |
| 58  | L+L          | x             |
| 59  | L+L          | x             |
| 60  | L+L          | x             |
| 62  | M+L          | x             |
| 67  | L+L          | x             |
| 73  | L+L          | X             |
| 74  | L+L          | x             |
| 77  | L+L          | X             |
| 78  | M+L          | X             |
| 84  | M+L          | X             |
| 85  | M+L          | X             |
| 86  | M+L          | X             |
| 90  | L+L          | X             |
| 92  | M+L          | X             |
| 93  | M+L          | X             |
| 97  | L+L          | X             |
| 98  | L+L          | X             |
| 111 | M+L          | X             |
| 113 | L+L          | X             |
| 114 | M+L          | X             |
| 117 | M+L          | X             |
| 118 | L+R          | X             |
| 120 | L+L          | X             |
| 122 | L+L          | x             |
| 124 | L+L          | x             |
| 128 | M+L          | x             |
| 132 | M+L          | x             |
| 133 | M+L          | x             |
| 134 | M+L          | x             |

|     |     |   |
|-----|-----|---|
| 136 | M+L | x |
| 139 | M+L | x |
| 146 | M+L | x |
| 150 | L+R | x |
| 153 | M+L | x |
| 157 | M+L | x |
| 158 | M+L | x |
| 160 | M+L | X |
| 161 | L+L | X |
| 164 | M+L | X |
| 165 | M+L | X |
| 168 | L+L | X |
| 175 | M+L | x |
| 176 | L+L | x |
| 177 | L+L | x |
| 179 | M+L | x |
| 184 | M+L | X |
| 186 | M+L | X |
| 188 | M+L | X |
| 189 | L+L | X |
| 190 | L+L | X |
| 194 | M+L | X |

## Task 5

Quarterly Measurements of Subjects  
(evaluable patients-Specific Aim 1)

Appendix Item #2-  
August, 2004

DAMD17-00-1-0

Annual Report

just three pages of the 30 page document are shown here for example.

| Patient Number | Interval | Current Weight | Affected Arm | Height | Handedness | Affected 1st Finger | Affected Hand (A) | Affected Wrist (B) | Affected 10 cm (C) | Affected 20 cm (D) | Affected Elbow (E) | Affected 30 cm (F) | Affected 40 cm (G) | Affected Grip | Affe Ext |
|----------------|----------|----------------|--------------|--------|------------|---------------------|-------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|---------------|----------|
| 001            | 0        | 305            | L            | 64     | R          | 7.00                | 19.00             | 18.40              | 24.50              | 30.50              | 31.50              | 36.80              | 52.80              | normal        | 180      |
| 001            | 3        | 302            | L            | 64     | R          | 7.50                | 20.00             | 18.30              | 23.50              | 31.00              | 33.00              | 39.30              | 51.00              | normal        | 180      |
| 001            | 6        | 309            | L            | 64     | R          | 7.50                | 20.00             | 18.00              | 23.00              | 29.00              | 31.00              | 34.00              | 48.00              | normal        | 180      |
| 001            | 15       | 309            | L            | 64     | R          | 7.50                | 20.50             | 17.80              | 23.60              | 29.50              | 30.50              | 35.80              | 49.80              | normal        | 180      |
| 001            | 24       | 265            | L            | 64     | R          | 7.40                | 20.00             | 17.40              | 22.50              | 27.90              | 29.00              | 33.50              | 46.80              | 50            | 180      |
| 001            | 36       | 180            | L            | 64     | R          | 7.00                | 19.30             | 16.20              | 19.80              | 24.70              | 25.40              | 29.10              | 37.80              | normal        | 180      |
| 002            | 0        | 172            | R            | 61     | R          | 6.40                | 19.40             | 15.50              | 23.90              | 28.60              | 27.50              | 32.60              | 37.80              | normal        | 180      |
| 002            | 3        | 160            | R            | 61     | R          | 6.50                | 19.70             | 16.00              | 23.30              | 28.70              | 28.50              | 31.00              | 37.70              | normal        | 180      |
| 002            | 6        | 158            | R            | 61     | R          | 7.10                | 19.80             | 16.70              | 22.00              | 28.00              | 27.90              | 30.50              | 36.50              | normal        | 180      |
| 002            | 9        | 155            | R            | 61     | R          | 6.80                | 19.00             | 16.40              | 27.90              | 27.90              | 27.40              | 30.00              | 35.90              | normal        | 180      |
| 002            | 12       | 172            | R            | 61     | R          | 6.80                | 19.00             | 16.10              | 22.70              | 27.80              | 27.00              | 29.70              | 36.00              | normal        | 180      |
| 002            | 24       | 167            | R            | 61     | R          | 7.00                | 19.50             | 16.30              | 27.90              | 28.70              | 29.90              | 34.30              | 39.20              | 15            | 180      |
| 002            | 33       | 172            | R            | 61     | R          | 6.80                | 19.20             | 16.30              | 25.30              | 28.40              | 27.90              | 32.40              | 36.60              |               | 180      |
| 002            | 36       | 164            | R            | 61     | R          | 6.90                | 18.90             | 15.90              | 23.80              | 28.00              | 28.00              | 30.40              | 37.90              | 60            | 180      |
| 004            | 0        | 127            | R            | 54     | R          | 5.50                | 19.00             | 14.30              | 17.40              | 22.80              | 22.80              | 22.50              | 25.80              | normal        | 180      |
| 004            | 3        | 118            | R            | 53.5   | R          | 5.40                | 17.50             | 14.80              | 15.70              | 20.80              | 22.00              | 21.50              | 24.00              | normal        | 180      |
| 004            | 12       | 127            | R            | 53.5   | R          | 6.10                | 18.50             | 14.50              | 16.50              | 21.60              | 23.00              | 22.00              | 23.50              | 38            | 180      |
| 005            | 0        | 226            | L            | 63.75  | R          | 7.10                | 20.70             | 17.50              | 22.10              | 28.40              | 27.80              | 31.80              | 40.80              | normal        | 180      |
| 005            | 3        | 229            | L            | 63.75  | R          | 5.50                | 18.60             | 15.60              | 20.60              | 26.50              | 26.30              | 29.70              | 37.90              | normal        | 180      |
| 005            | 6        | 224            | L            | 63.25  | R          | 6.40                | 17.00             | 16.00              | 20.00              | 27.00              | 26.70              | 29.00              | 36.00              | abnormal      | 180      |
| 005            | 9        | 224            | L            | 63.75  | R          | 6.40                | 17.00             | 16.00              | 20.00              | 27.00              | 26.70              | 29.00              | 36.00              | abnormal      | 180      |
| 005            | 12       | 227            | L            | 63.75  | R          | 6.40                | 20.60             | 16.00              | 20.00              | 27.00              | 27.00              | 29.60              | 37.00              | 45            | 180      |
| 005            | 15       | 226            | L            | 63.75  | R          | 6.40                | 20.00             | 16.10              | 21.10              | 27.30              | 26.80              | 30.70              | 39.00              | normal        | 180      |
| 006            | 0        | 185            | R            | 64     | R          | 7.50                | 20.30             | 16.50              | 22.00              | 27.90              | 27.90              | 29.10              | 33.50              |               | 180      |
| 006            | 6        | 190            | R            | 64     | R          | 6.50                | 20.00             | 17.00              | 21.00              | 29.00              | 28.00              | 28.90              | 34.70              | normal        | 180      |
| 006            | 12       | 183            | R            | 64     | R          | 6.50                | 20.40             | 16.00              | 20.60              | 27.50              | 27.00              | 28.30              | 32.50              | normal        | 180      |
| 007            | 0        | 180            | R            | 64     | R          | 7.50                | 20.00             | 18.00              | 22.60              | 22.60              | 28.20              | 30.00              | 33.00              |               | 180      |
| 007            | 3        | 170            | R            | 63.5   | R          | 7.00                | 18.80             | 16.00              | 18.00              | 24.30              | 26.00              | 26.50              | 31.00              | normal        | 180      |
| 007            | 6        | 170            | R            | 64     | R          | 6.80                | 18.40             | 15.90              | 17.90              | 24.00              | 24.40              | 24.70              | 27.00              | normal        | 180      |
| 007            | 12       | 170            | R            | 64     | R          | 6.90                | 18.10             | 15.10              | 17.90              | 23.50              | 24.50              | 24.70              | 28.40              | normal        | 180      |
| 007            | 24       | 167            | R            | 64     | R          | 7.00                | 18.60             | 15.50              | 18.90              | 24.20              | 25.00              | 25.10              | 30.00              | 40            | 180      |
| 007            | 36       | 176            | R            | 64     | R          | 7.00                | 18.00             | 15.40              | 20.40              | 25.00              | 25.00              | 26.80              | 31.90              | 50            | 180      |
| 007            | 67       | 177            | R            | 63.5   | R          | 6.90                | 18.50             | 15.50              | 20.70              | 25.70              | 25.50              | 27.90              | 32.20              | normal        | 180      |
| 008            | 0        | 107            | L            | 62     | R          | 5.90                | 15.40             | 13.80              | 16.00              | 21.50              | 21.00              | 23.00              | 26.00              | normal        | 90       |

|     |    |     |   |  |       |   |  |      |       |       |       |       |       |       |       |          |
|-----|----|-----|---|--|-------|---|--|------|-------|-------|-------|-------|-------|-------|-------|----------|
| 008 | 3  | 107 | L |  | 62    | R |  | 5.70 | 17.50 | 13.90 | 15.70 | 21.70 | 20.80 | 22.80 | 24.50 | abnormal |
| 008 | 6  | 107 | L |  | 62    | R |  | 6.00 | 17.00 | 13.80 | 16.00 | 22.00 | 21.60 | 21.00 | 25.50 | abnormal |
| 008 | 12 | 107 | L |  | 62    | R |  | 5.70 | 16.60 | 13.80 | 15.60 | 21.70 | 20.80 | 21.70 | 25.40 | normal   |
| 008 | 15 | 110 | L |  | 62    | R |  | 5.80 | 17.00 | 13.60 | 15.80 | 21.40 | 20.60 | 22.50 | 26.50 | normal   |
| 008 | 18 | 111 | L |  | 62    | R |  | 5.60 | 17.00 | 13.50 | 16.00 | 21.40 | 20.80 | 23.10 | 26.60 | normal   |
| 009 | 0  | 183 | R |  | 66    | R |  | 6.50 | 20.80 | 16.00 | 23.00 | 28.00 | 27.00 | 33.00 | 36.00 | normal   |
| 009 | 3  | 192 | R |  | 66    | R |  | 6.50 | 20.50 | 17.00 | 21.00 | 27.50 | 28.60 | 31.00 | 36.50 | normal   |
| 009 | 6  | 195 | R |  | 65    | R |  | 6.50 | 19.80 | 16.50 | 21.40 | 28.00 | 29.00 | 31.50 | 38.70 | normal   |
| 009 | 12 | 196 | R |  | 65    | R |  | 6.40 | 20.20 | 16.20 | 22.00 | 28.00 | 28.50 | 32.00 | 39.00 | 180      |
| 009 | 15 | 196 | R |  | 65    | R |  | 6.50 | 20.10 | 16.10 | 22.80 | 29.70 | 28.60 | 33.40 | 39.50 | normal   |
| 009 | 21 | 195 | R |  | 65    | R |  | 6.40 | 20.40 | 16.60 | 21.30 | 27.30 | 27.40 | 30.60 | 37.10 | normal   |
| 011 | 0  | 216 | R |  | 63.75 | R |  | 8.00 | 21.00 | 18.70 | 28.00 | 34.00 | 32.50 | 37.70 | 40.50 | normal   |
| 011 | 3  | 198 | R |  | 64    | R |  | 8.00 | 21.00 | 18.90 | 25.90 | 32.00 | 31.00 | 35.00 | 42.80 | abnormal |
| 011 | 6  | 198 | R |  | 64    | R |  | 4.30 | 16.80 | 15.20 | 25.30 | 28.60 | 27.60 | 34.20 | 40.50 | abnormal |
| 011 | 9  | 198 | R |  | 64    | R |  | 7.50 | 20.50 | 18.50 | 25.40 | 31.70 | 31.50 | 33.90 | 41.10 | 25       |
| 011 | 12 | 191 | R |  | 63.75 | R |  | 7.80 | 20.70 | 17.90 | 25.10 | 31.20 | 30.00 | 34.40 | 39.50 | normal   |
| 011 | 18 | 184 | R |  | 65    | R |  | 7.80 | 20.80 | 17.80 | 24.90 | 31.10 | 29.80 | 34.60 | 39.60 | normal   |
| 011 | 24 | 214 | R |  | 64    | R |  | 7.50 | 21.10 | 17.90 | 26.00 | 31.30 | 28.90 | 35.20 | 41.30 | 180      |
| 012 | 0  | 138 | R |  | 63    | R |  | 6.70 | 19.70 | 15.00 | 19.50 | 25.00 | 26.50 | 26.70 | 30.00 | normal   |
| 012 | 3  | 141 | R |  | 63    | R |  | 6.70 | 18.00 | 16.00 | 18.80 | 25.40 | 26.70 | 26.70 | 30.00 | normal   |
| 012 | 6  | 142 | R |  | 63    | R |  | 6.50 | 18.90 | 16.00 | 19.90 | 25.90 | 27.00 | 27.00 | 29.90 | normal   |
| 012 | 9  | 140 | R |  | 63    | R |  | 6.70 | 18.80 | 15.50 | 20.00 | 26.00 | 26.40 | 27.10 | 31.40 | 42       |
| 012 | 12 | 141 | R |  | 63    | R |  | 6.60 | 19.60 | 15.20 | 20.00 | 25.50 | 26.60 | 27.00 | 30.00 | 45       |
| 012 | 15 | 142 | R |  | 63    | R |  | 6.50 | 19.30 | 15.40 | 21.70 | 25.60 | 26.50 | 27.20 | 29.80 | normal   |
| 012 | 24 | 140 | R |  | 63    | R |  | 6.90 | 18.50 | 15.60 | 20.20 | 25.40 | 26.50 | 26.80 | 30.00 | 60       |
| 012 | 36 | 140 | R |  | 63    | R |  | 6.60 | 18.70 | 15.90 | 20.70 | 25.60 | 27.00 | 27.40 | 30.40 | 55       |
| 012 | 67 | 140 | R |  | 63    | R |  | 6.60 | 18.70 | 15.40 | 20.70 | 25.60 | 26.30 | 27.40 | 30.20 |          |
| 013 | 0  | 205 | R |  | 69    | R |  | 6.50 | 19.90 | 16.50 | 18.50 | 24.90 | 28.90 | 27.00 | 31.00 | normal   |
| 013 | 3  | 205 | R |  | 69    | R |  | 6.70 | 19.50 | 16.30 | 19.20 | 26.20 | 27.20 | 34.60 | 37.70 | normal   |
| 014 | 0  | 120 | L |  | 64    | R |  | 5.80 | 17.30 | 14.90 | 17.90 | 22.30 | 21.90 | 21.10 | 23.90 | normal   |
| 014 | 3  | 120 | L |  | 64    | R |  | 6.40 | 18.00 | 15.40 | 17.90 | 22.70 | 22.00 | 22.20 | 24.00 | normal   |
| 014 | 6  | 125 | L |  | 64    | R |  | 6.50 | 17.50 | 15.50 | 17.90 | 23.00 | 23.00 | 22.70 | 24.50 | normal   |
| 014 | 12 | 125 | L |  | 65    | R |  | 6.60 | 18.00 | 15.30 | 18.60 | 23.40 | 22.60 | 23.40 | 24.90 | normal   |
| 014 | 15 | 129 | L |  | 64.5  | R |  | 6.30 | 17.80 | 15.60 | 18.40 | 23.50 | 23.20 | 23.50 | 25.50 | normal   |
| 014 | 24 | 120 | L |  | 64    | R |  | 6.30 | 18.60 | 15.30 | 18.80 | 23.20 | 23.00 | 23.10 | 25.90 | 180      |
| 014 | 30 | 134 | L |  | 64    | R |  | 6.40 | 17.90 | 15.40 | 18.50 | 23.40 | 23.00 | 23.30 | 25.00 | 45       |
| 014 | 36 | 124 | L |  | 64    | R |  | 6.40 | 17.90 | 15.40 | 18.50 | 23.00 | 22.90 | 23.70 | 25.00 | 50       |
| 015 | 0  | 135 | L |  | 69    | R |  | 6.40 | 18.80 | 16.00 | 16.00 | 22.70 | 23.50 | 22.20 | 25.00 | normal   |
| 015 | 3  | 132 | L |  | 69    | R |  | 5.80 | 18.50 | 15.50 | 15.80 | 22.00 | 22.00 | 22.00 | 23.80 | normal   |
| 015 | 6  | 135 | L |  | 69    | R |  | 5.80 | 18.40 | 15.60 | 16.00 | 22.50 | 23.00 | 22.00 | 24.40 | normal   |

|     |  |    |     |   |  |      |   |  |      |       |       |       |       |       |       |       |          |     |
|-----|--|----|-----|---|--|------|---|--|------|-------|-------|-------|-------|-------|-------|-------|----------|-----|
| 015 |  | 9  | 137 | L |  | 69   | R |  | 5.80 | 18.40 | 15.60 | 16.50 | 23.10 | 23.70 | 22.50 | 25.00 | normal   | 180 |
| 018 |  | 0  | 143 | R |  | 66.5 | R |  | 6.70 | 19.00 | 15.00 | 17.00 | 23.50 | 23.70 | 22.80 | 28.50 | normal   | 180 |
| 018 |  | 3  | 148 | L |  | 66.5 | R |  | 6.10 | 18.70 | 15.00 | 17.70 | 24.00 | 23.00 | 23.00 | 27.40 | abnormal | 90  |
| 018 |  | 12 | 147 | R |  | 66.5 | R |  | 5.90 | 19.00 | 14.90 | 17.60 | 24.10 | 23.90 | 23.40 | 27.80 | 55       | 180 |
| 019 |  | 0  | 145 | L |  | 65   | R |  | 6.00 | 18.00 | 15.00 | 18.50 | 25.00 | 25.00 | 24.50 | 27.40 |          | 180 |
| 019 |  | 3  | 145 | L |  | 65   | R |  | 6.00 | 18.50 | 14.90 | 17.40 | 23.40 | 24.00 | 23.40 | 26.00 | normal   | 180 |
| 019 |  | 6  | 149 | L |  | 65   | R |  | 5.80 | 18.30 | 15.00 | 18.80 | 25.00 | 24.90 | 26.00 | 29.00 | normal   | 180 |
| 019 |  | 9  | 145 | L |  | 65   | R |  | 5.90 | 18.50 | 15.00 | 18.40 | 24.70 | 25.00 | 25.70 | 29.00 | normal   | 90  |
| 019 |  | 12 | 150 | L |  | 65   | R |  | 5.80 | 18.90 | 14.80 | 17.80 | 24.30 | 24.40 | 24.50 | 28.30 | 78       | 180 |
| 019 |  | 24 | 136 | L |  | 65   | R |  | 5.70 | 18.00 | 14.70 | 18.50 | 23.90 | 23.50 | 23.40 | 26.50 | 65       | 180 |
| 019 |  | 36 | 142 | L |  | 65   | R |  | 6.00 | 18.50 | 14.80 | 18.40 | 24.10 | 23.70 | 24.00 | 27.30 | 65       | 180 |

**Task 7**    **Booster Training Session**  
**for Group 1 subjects (n=71)**

| ID | Booster |
|----|---------|
| 6  | x       |
| 7  | x       |
| 9  | x       |
| 13 |         |
| 15 | x       |
| 19 | x       |
| 21 | x       |
| 26 | x       |
| 28 | X       |
| 29 | x       |
| 33 | x       |
| 35 | x       |
| 40 | X       |
| 42 | x       |
| 46 | x       |
| 47 | X       |
| 51 | X       |
| 55 | x       |
| 56 | X       |
| 57 | X       |
| 58 | x       |
| 59 | X       |
| 60 | x       |
| 62 | x       |
| 67 | x       |
| 73 | x       |
| 74 | x       |
| 77 | X       |
| 78 | X       |
| 84 | x       |
| 85 |         |
| 86 | x       |
| 90 |         |
| 92 |         |
| 93 | x       |

|     |   |
|-----|---|
| 97  | x |
| 98  | x |
| 111 | X |
| 113 | X |
| 114 |   |
| 117 |   |
| 118 |   |
| 120 |   |
| 122 | x |
| 124 | x |
| 128 | x |
| 132 | x |
| 133 | X |
| 134 | x |
| 136 | x |
| 139 |   |
| 146 | x |
| 150 | x |
| 153 | x |
| 157 | x |
| 158 | X |
| 160 | X |
| 161 | X |
| 164 | X |
| 165 | X |
| 168 | X |
| 175 | x |
| 176 | x |
| 177 | x |
| 179 | x |
| 184 |   |
| 186 |   |
| 188 |   |
| 189 |   |
| 190 |   |
| 194 |   |

**Task 9**      **Calculation of Limb Volumes**      **and comparison of differences**  
volume % changes compared to preop measurements

**Example 30**  $\Rightarrow$  new Osmis report

yellow color = >9% vol change. EE-

yellow color  
green text = >10% vol chg, confirmed LE-by CR eval

[illegible]

**Task 9** Calculation of Limb Volumes and comparison of n differences  
volume % changes compared to preop measurements

green text = >10% vol chg, confirmed LE- by CR eval

yellow color = 50% vol change LE-

orange color = new catheter report

| Site | Preop | Postop  | % Change | Notes |
|------|-------|---------|----------|-------|
| 056  | 1     | 1.13%   |          |       |
| 057  | 1     | -2.36%  |          |       |
| 058  | 1     | -1.91%  |          |       |
| 059  | 1     | 0.85%   |          |       |
| 060  | 1     | 0.65%   |          |       |
| 061  | 2     | -6.22%  |          |       |
| 062  | 2     | 1.06%   |          |       |
| 063  | 2     | 0.75%   |          |       |
| 064  | 2     | 0.42%   |          |       |
| 065  | 2     | 1.50%   |          |       |
| 066  | 2     | 4.64%   |          |       |
| 067  | 2     | -13.89% |          |       |
| 068  | 2     | 6.19%   |          |       |
| 069  | 2     | 3.20%   |          |       |
| 070  | 2     | -4.16%  |          |       |
| 071  | 2     | 4.19%   |          |       |
| 072  | 2     | -13.84% |          |       |
| 073  | 2     | -2.25%  |          |       |
| 074  | 2     | -3.84%  |          |       |
| 075  | 2     | -2.44%  |          |       |
| 076  | 2     | 3.13%   |          |       |
| 077  | 2     | 3.75%   |          |       |
| 078  | 2     | 3.75%   |          |       |
| 079  | 2     | -1.37%  |          |       |
| 080  | 2     | 5.23%   |          |       |
| 081  | 2     | -4.20%  |          |       |
| 082  | 2     | -3.64%  |          |       |
| 083  | 2     | 0.23%   |          |       |
| 084  | 2     | -10.93% |          |       |

## Appendix Item 4- Task 9 weekly volume report, Compare\_Arm\_Volumes

**Task 9** Calculation of Limb Volumes and comparison of differences  
volume % changes compared to prep measurements

green text = >10% vol chg, confirmed LE; by CR eval  
yellow color = >9% vol change, LE  
orange color = new CR report

|      |   |         |        |        |        |        |  |  |  |
|------|---|---------|--------|--------|--------|--------|--|--|--|
| 149  | 1 |         |        | 3.49%  | 2.39%  | -5.55% |  |  |  |
| 150  | 1 | -4.88%  | -5.52% | 2.25%  |        | -1.58% |  |  |  |
| 151  | 1 |         |        |        |        |        |  |  |  |
| 152  | 1 |         |        |        |        |        |  |  |  |
| 153  | 1 |         | 3.52%  |        | 0.59%  |        |  |  |  |
| 154  | 1 |         |        |        |        |        |  |  |  |
| 155  | 1 |         | -3.21% | -5.83% | -9.13% |        |  |  |  |
| 156  | 2 | 5.49%   |        |        |        |        |  |  |  |
| 157  | 1 | -14.35% |        |        |        |        |  |  |  |
| 158L | 1 | 0.20%   |        |        | -5.20% |        |  |  |  |
| 158R | 1 |         |        |        | -2.49% |        |  |  |  |
| 159  | 2 |         | -2.30% |        | -2.12% |        |  |  |  |
| 160  | 1 |         | -6.88% |        |        |        |  |  |  |
| 161  | 1 | 2.62%   | 0.20%  |        |        |        |  |  |  |
| 162  | 1 |         |        |        |        |        |  |  |  |
| 163  | 1 |         |        |        |        |        |  |  |  |
| 164  | 1 |         |        |        |        |        |  |  |  |
| 165  | 1 |         |        |        |        |        |  |  |  |
| 166  | 1 |         |        |        |        |        |  |  |  |
| 167  | 2 |         |        |        | 14.32% |        |  |  |  |
| 168  | 1 |         |        |        |        |        |  |  |  |
| 169  | 2 |         |        | -0.71% |        |        |  |  |  |
| 170  | 1 |         |        |        |        |        |  |  |  |
| 171  | 1 |         |        |        |        |        |  |  |  |
| 172  | 1 |         |        |        |        |        |  |  |  |
| 173  | 1 | -2.61%  | 3.79%  |        |        |        |  |  |  |
| 174  | 1 | 3.04%   |        |        | -7.32% |        |  |  |  |
| 175  | 1 |         |        |        |        |        |  |  |  |
| 176  | 1 |         |        |        |        |        |  |  |  |
| 177  | 1 |         |        |        |        |        |  |  |  |
| 178  | 1 |         |        |        |        |        |  |  |  |
| 179  | 1 |         |        |        |        |        |  |  |  |
| 180  | 1 |         |        |        |        |        |  |  |  |
| 181  | 1 |         |        |        |        |        |  |  |  |
| 182  | 2 |         | 0.79%  |        |        |        |  |  |  |
| 183  | 1 |         |        |        |        |        |  |  |  |
| 184  | 1 |         |        |        |        |        |  |  |  |
| 185  | 2 | -0.35%  | -1.92% |        |        |        |  |  |  |
| 186  | 1 |         |        |        |        |        |  |  |  |
| 187  | 1 |         |        |        |        |        |  |  |  |
| 188  | 1 |         |        |        |        |        |  |  |  |
| 189  | 1 | -2.72%  |        |        |        |        |  |  |  |
| 190  | 1 |         |        |        |        |        |  |  |  |
| 191  | 1 |         |        |        |        |        |  |  |  |
| 192  | 1 |         |        |        |        |        |  |  |  |
| 193  | 1 |         |        |        |        |        |  |  |  |
| 194  | 1 | -3.28%  |        |        |        |        |  |  |  |