CLINICAL TRIAL PROTOCOL

DATE: 5th March 2015

SPONSOR:
University Hospital of South Manchester
Southmoor Road
Wythenshawe
Manchester
M23 9LT

Multi-frequency Bioimpedance in the Early Detection of Lymphoedema after Axillary Surgery

Protocol no: 2010/NJB/1201.cm
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National Institute for Health Research and Cancer Research UK

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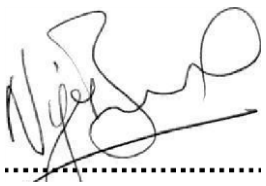
Clinical enquiries: To the Research Nurse at site, and in consultation with the local Principal Investigator when appropriate or necessary.

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP) guidelines and regulatory requirements.



N J U DRED MD FRCS
Professor of Surgical Oncology
1st August 2013

Summary of Trial

Aim

The purpose of this multi-centre study is to test whether there is concordance between bioimpedance and perometer arm measurements and in particular, whether bioimpedance identifies patients who are developing lymphoedema at an earlier stage, before arm volume measurement by perometry shows significant increases in arm volume.

Trial Design:

Endpoints

Primary endpoint:-

1) Incidence of lymphoedema (>10% arm volume increase compared to contralateral arm) at 2 and 5 years after axillary node clearance *(assessed by perometer scanning).*

Secondary endpoints:-

1) Comparison of multi-frequency BEA with perometer measurement.
2) Prediction of lymphoedema by multi-frequency BEA at 24 months.
3) Quality of life in each group (T01 and FACT B+4).
4) Multivariate model assessment of factors predicting lymphoedema at 24 months.
5) Lymphoedema symptoms related to changes in arm volume and bioimpedance readings.

Trial Intervention

First cohort; patients consented before January 2015

1100 women undergoing axillary node clearance for breast cancer will be invited to take part in preoperative baseline and 1,3,6, 9, 12,18, 24 month and then annual monitoring of arm volume by perometry and multi-frequency bioimpedance measurement.

These 1100 initial recruits will have 3 monthly reviews with arm assessments by perometer and bioimpedance, lymphoedema questionnaire and FACT B4 QoL will be assessed at 6, 9, 12, 18 months and then 2 years; they will be assessed annually thereafter.

Second Cohort; patients consented after January 2015, on version 3 (or later) of the patient information leaflet

A further 300 patients will then be recruited; these women, who are also undergoing axillary node clearance for breast cancer, will be invited to take part in preoperative baseline, 1, 3, 6, and 9month monitoring of arm volume by perometry. At all of these timepoints, apart from one month, participants will be asked to complete a lymphoedema questionnaire. FACT B4 and EQ-5D QoL will be assessed at baseline only.

Sample Size

1100 women undergoing axillary node clearance for breast cancer will be invited to take part in the five year study. A further 300 patients will take part in the nine month study, which will commence recruitment from March 2015.

1.0 INTRODUCTION

1.1 Lymphoedema

Lymphoedema is a swelling of the arm (>10% arm volume increase) after surgery or radiotherapy to the axilla. Lymphoedema occurs when the lymphatic system is unable to keep up with the normal demands of tissue homeostasis, resulting in fluid accumulating in the interstitial spaces of subcutaneous tissue.i[1,21] It is a progressive condition and has the following components: excess protein in interstitial fluid, oedema, chronic inflammation and, if untreated, can lead to fibrotic, thickened skin and tissues.[131]Lymphoedema after breast cancer treatment is affected by the extent of axillary surgery and the exposure of the axilla to radiotherapy.

Around 30% - 40% of women develop lymphoedema after axillary node clearance (ANC), 80-90% will develop this complication within two years and the remainder over a period of years post surgery. Lymphoedema still occurs after sentinel node biopsy or axillary sampling although the incidence is much less. However, 30-40% of the breast cancer patients will be node positive and require axillary clearance with its subsequent morbidity. Consequently the management of lymphoedema is an important cost item in the NHS annual budget. The cost of managing chronic arm lymphoedema has been calculated as £220/patient/yearm and at least £7m per annum to the NHS.

The affected arm is uncomfortable, unsightly and prone to episodes of superficial infection. Lymphoedema causes significant psycho-social morbidity and a poorer quality of life in breast cancer patients[15,61] and there is an extensive 'backlog' of patients that will require treatment for a considerable number of years. Lesser degrees of arm swelling (greater than 1cm) occurs in up to 40% of cases after surgery, often leading to reduced arm movement and having a major negative impact on quality of life after breast cancer surgery.[1191]

1.2 Diagnosis and measurement

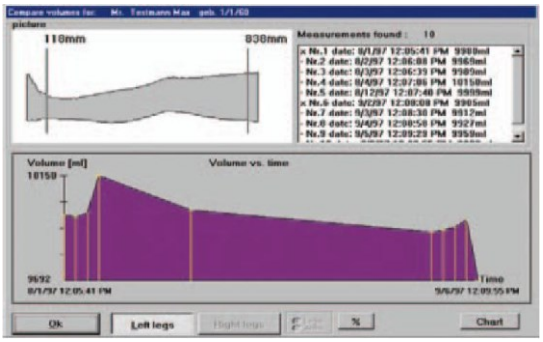
Diagnosis of lymphoedema is frequently based on clinical criteria alone. Some clinicians consider that lymphoedema exists once limb circumference at any given point is at least 1.5 cm larger than the same point on the unaffected side,[171] whilst others have made a 2cm change their defining criterion.[181] Limb swelling is generally determined by repeated measurement of arm circumference at 4cm intervals from wrist to the shoulder. The volume is then estimated with the use of a cylindrical model. There are inherent difficulties with this method of measurement: variability; and possible inaccuracies between observers and repeated measurements. Swelling may be limited to one particular area of the limb and excess fluid may move from one part of the limb to the other.[191]

True volume measurement has been seen as a solution to these problems and has been carried out by water displacement techniques, but these are considered to be too cumbersome and inconvenient for routine usei[w]and are not available in most breast or lymphoedema clinics.

Measurement of arm volume is performed in a reliable and operator-independent manner by use of a Perometer (Pero-System GmbH, Germany), a machine which calculates limb volume in cubic centimetres from optical measurements made by two sets of infra-red light sources directed at the limb at right angles [(11,121)].

1.3 Quantification of Arm Swelling and Physical Functioning

Figure 1 ± Perometer



Reliable quantitative measures of therapeutic response are needed to monitor the effects of any therapeutic intervention on lymphoedema.

1.4 Perometer Measurement

Current methods of assessing arm volume include volume measurement using repeated tape measurement at predefined intervals along the limb, with the volume being calculated assuming a circular or elliptical truncated cone geometry. This method is tedious and time-consuming to perform. There is no standardisation of the number of circumferential measurements that are required to provide a reasonably accurate measurement of volume and it is thus not considered sufficiently validated to use in the study.

Perometry volume determined from the 3D silhouette cast by the limb when passed though a ray of opto-electronic sensors(133) is rapid, accurate and precise, but requires expensive equipment which is not very portable. The total volume of the arm may change for various reasons. The most common is weight gain but work or exercise induced muscle hypertrophy are cases in point where a simple total volume measurement is not immediately related to the parameter of interest i.e lymphatic volume. Additionally, there is dispute about the definition of lymphoedema. Many people have used the definition of greater than 10% arm volume increase compared to the contralateral arm, but others have claimed that a 200m1 volume difference between the arms can be used to define unilateral lymphoedema following breast cancer treatment (143). For the purposes of this study, we are using a greater than 10% arm volume increase measured by perometer on at least two occasions to identify women with lymphoedema secondary to axillary node clearancei[l]q.

The Perometer is a sensitive and standardised device that uses infrared optoelectronic technology to detect and quantify limb volume changes.[11,26,27] Goltner at al reported that changes in interstitial tissue congestion up to 150m1 may occur before limb swelling is visible and they quantified this volume change by using optometric perometry.[283] They hypothesised that subclinical interstitial congestion is the basis for patient-reported sensory changes in the limb and is a precursor to the onset of lymphoedema.[293]

Arms will be measured on 2 occasions, 5-10 minutes apart using a Perometer. The average of the 2 measurements will be used to exclude intra-observer variability.

Cerniak et al found that perometer compared to bioimpedance spectrometry had a high concordance with bioimpedance r=0.92.

Physical functioning in this clinical context can be measured using a specific quality of life scale in upper limb lymphoedema, together with the FACT-B+4 Health Survey Questionnaire. Sentinel lymph node biopsy staging reduces the need for axillary node clearance (ANC), but 30% of breast cancer patients are node positive and require ANC to remove diseased nodes.[116,17,191] A clinical endpoint of >10% increase in ipsilateral arm volume (versus contralateral arm) is an accepted criteria for a diagnosis of lymphoedema.[8,20,21,22] Up to 40% of women develop lymphoedema by 18 months post ANC.[191] Intervention before arm swelling becomes chronic may prevent the complications of lymphoedema after ANC.

In women undergoing axillary node clearance for node positive breast cancer in the ALMANAC Trial, 40% developed arm volume increases >10% (compared to baseline and contralateral arm) by 18 months post-surgery.

Arm measurements are not routine practice prior to axillary clearance but our data from an ongoing prospective study and the ALMANAC Trial [191] data prospectively collected indicates that 40- 45% of patients develop arm volume increases between 4-8% by 3 or 6 months after surgery and 5% already have a 10% increase (i.e. Lymphoedema). The 45% of women with arm volume increases between 4-8% at 3 or 6 months post clearance account for the majority (50-60%) of patients who subsequently develop lymphoedema. [231] Counter-intuitively the absolute level of increase between 4 and 9% does not clearly define risk of later lymphoedema because despite no compression sleeve application up to 40% of women do not progress to develop lymphoedema by 2 years.

Conventional advice is that early arm swelling at 3 months does not portend chronic swelling and should be treated conservatively.[24] In the ALMANAC Trial[191] prospective arm measurements identified early arm swelling (4-5%) in patients and predicted 53% of cases would subsequently develop lymphoedema (arm swelling 10%) by 18 months, whereas for 6% arm swelling, the specificity for subsequent lymphoedema was 80% (sensitivity 56%) and this degree of arm swelling at 3 or 6 months predicted 60% of lymphoedema cases at 18 months follow-up. Arm swelling of 4-8% is usually not clinically apparent unless arm measurements have been made preoperatively and only 3% of women in the axillary clearance arm of the ALMANAC Trial complained of significant swelling at 6 months[19,251]

A recent prospective observational study identified women who developed 3% or greater arm volume increases after pre-surgery, baseline and 3 monthly measurements using a perometer. Forty three (out of 196) women then wore graduated compression garments for a mean duration of 4.4 (±2.9) weeks, followed by continued use of the garments during strenuous exercise, or if swelling appeared. Arm reductions of 4.1% were observed ($p<0.001$) which was maintained after an average follow up of 4.8 months.[291] Although the follow up and intervention period was limited, they argued for routine baseline measurement and early intervention with compression garments to prevent lymphoedema.

1.5 Multi-frequency Bioimpedance Electrical Analysis (BEA)

Multi-frequency bioimpedance electrical analysis (BEA) is a non-invasive technique to measure total water content, which involves passing an extremely small electrical current through the body and measuring the impedance (or resistance) to the flow of this current. In recent years the BEA technique has been refined to measure the impedance over a range of frequencies from 4 to 1000kHz. By mathematically modelling the measured data, the impedance at zero frequency (i.e. the impedance of the extracellular fluid alone) can be determinedr*[311]. Multiple frequency BEA is used to compare quantitatively the degree of fluid accumulation in the arms using a leg as the reference limb and a 3sd change in BEA accurately diagnoses lymphoedema. Small single centre prospective studies in Australia have claimed that multiple BEA predicts lymphoedema development up to 10 months ahead of arm volume changes with a sensitivity of 98% and a specificity of 100%.[321] BEA can be measured with a handheld device and is marketed as safe,

accurate and diagnostic for lymphoedema (even in the absence of confirmed arm swelling >10%) to justify early treatment intervention in women after axillary surgery. BEA correlates with arm measurement but is reported to be more sensitive and equally specific as arm circumference measures particularly in women whose ANC involved the non-dominant arm lymphaticsi[333].

On the basis of known disease progression, 90% of lymphoedema will have developed by 3 years after ANC surgery. At least 50% of breast cancer patients gain weight in the first year after diagnosis, and this is associated with increased risk of lymphoedema. Nonetheless, if careful contralateral arm measurements are not performed, weight gain, rather than true lymphoedema, can lead to inappropriate fitting of compression sleeves. Bioimpedance results (BEA) are unaltered by weight gain and we will test whether the bioimpedance results are similar to, more sensitive and/or more specific than, perometer measurements in detecting arm lymphoedema. Since bioimpedance is a non-invasive technique which can be measured with a mobile, hand-held device, if it is equivalent in sensitivity/specificity, it will be simpler to use in breast and lymphoedema clinics (for patients and clinicians alike), rather than a large, immobile, fixed perometer.

1.6 The Multi-frequency Bioimpedance in the Early Detection of Lymphoedema Trial

We will assess multi-frequency bioimpedance monitoring compared to perometer arm measurements in women after axillary node clearance (ANC) in 9 centres for the first 1100 patients enrolled in the 5 year study. We will use bioimpedance monitoring during the study to determine its value in predicting response to compression garment therapy. Within the study we will assess reproducibility of both methods across centres and robustly establish both intra and interobserver error rates for both methods in the study population. Subsequent recruits, as part of the 9 month study, will not undergo this as enough data will be gathered from the original cohort.

All women undergoing ANC in the UHSM Breast Unit have been invited to have preoperative 1,3,6,12 and 18 monthly bilateral arm measurements with a perometer (Pero-Systems 350S) and circumferential arm tape measurements. Of the last 270 women approached undergoing ANC within the last 11 months, 183 (67%) agreed to participate. We will use 9 centres who will monitor women undergoing ANC from pre-surgery baseline with perometer measurements and BEA to compare the sensitivity and specificity of both techniques for predicting chronic lymphoedema development. Identifying the most sensitive and specific method for detecting chronic lymphoedema would enhance selection of patients for intervention with arm sleeves should the intervention prove cost effective. Please note, this assessment will only be carried out in the initial 1100 recruits, as part of the 5 year study.

We have negotiated agreement with the manufacturers for provision and training in the use of L-DEX U400 bioimpedance spectroscopy devices for all centres taking part in the 5 year study with the appropriate software and electrodes to carry out a health technology assessment.

2.0 TRIAL DESIGN

1100 women undergoing ANC for breast cancer in 9 centres across the UK will be approached to undergo baseline (pre-operative) and subsequent BEA monitoring, along with perometer arm measurements (see flow diagram). A comparison of the sensitivity and specificity of BEA versus perometer measurement will be made firstly in women who develop arm swelling >10% by 6 months (estimated at 231/1100 (21%) of the initial group). Percentages are estimated from ALMANAC Trial (see Annex 4d). Secondly women with an arm volume increase 4-8.9% at 1, 3, 6 months where effectively the BEA 6 months readings will be compared with final 18 month perometer scores to assess the prediction of lymphoedema at 18 months by BEA. Thirdly, women with a <4% Perometer arm volume increase up to 6 months (estimated n=363/1100 with estimated lymphoedema at 18 months of 46 (14% of 264)) will be used to determine the sensitivity and

specificity of BEA 6 month measures compared to the perometer 6 month measurement in predicting the 18 month outcome.

We originally estimated we would need to screen over 1000 patients to enrol sufficient women into the PLACE Trial using perometer measurements, we will determine if BEA has a >80% sensitive and a >80% specific accuracy and currently the specificity of arm swelling measured by perometer is 87% specific for subsequent lymphoedema at 18 months with a sensitivity of 54% (assessed from ALMANAC trial data). We will recruit 1100 women before ANC into the five year study to allow for 10% drop-out over the course of the study.

The Perometer sensitivity is reported as 85% +/-3.6% (95% CI 81.4% to 88.6%) and we will be able to detect a greater or equal to 7% improvement in sensitivity with BEA to 92+/-2.5% (95%CI: 89.5-94.5%) and the Perometer specificity is 55% +1-4.1% (95% CI 50.9% to 59.1%) thus we will be able to detect a >9% improvement in specificity with BEA to 64%+/-3.9% (95%C1:60.1 to 67.9%) with this sample size, since the confidence intervals do not overlap.

Gold standard at 18 months	Test P+	Test P-	Total
	+168+138	46	352
	-168+71	284	523
Total	336+209	330	875

sensitivity = 307/352 = 87%
specificity = 284/523 = 54%

Arm volume measurement at 1 month will not be used to implement treatment outside of the trial. In women who develop lymphoedema >10% at 3 months, sleeves will be applied and the 3 month BEA value compared to the perometer used in the analysis. For all others, the 6 month value will be used.

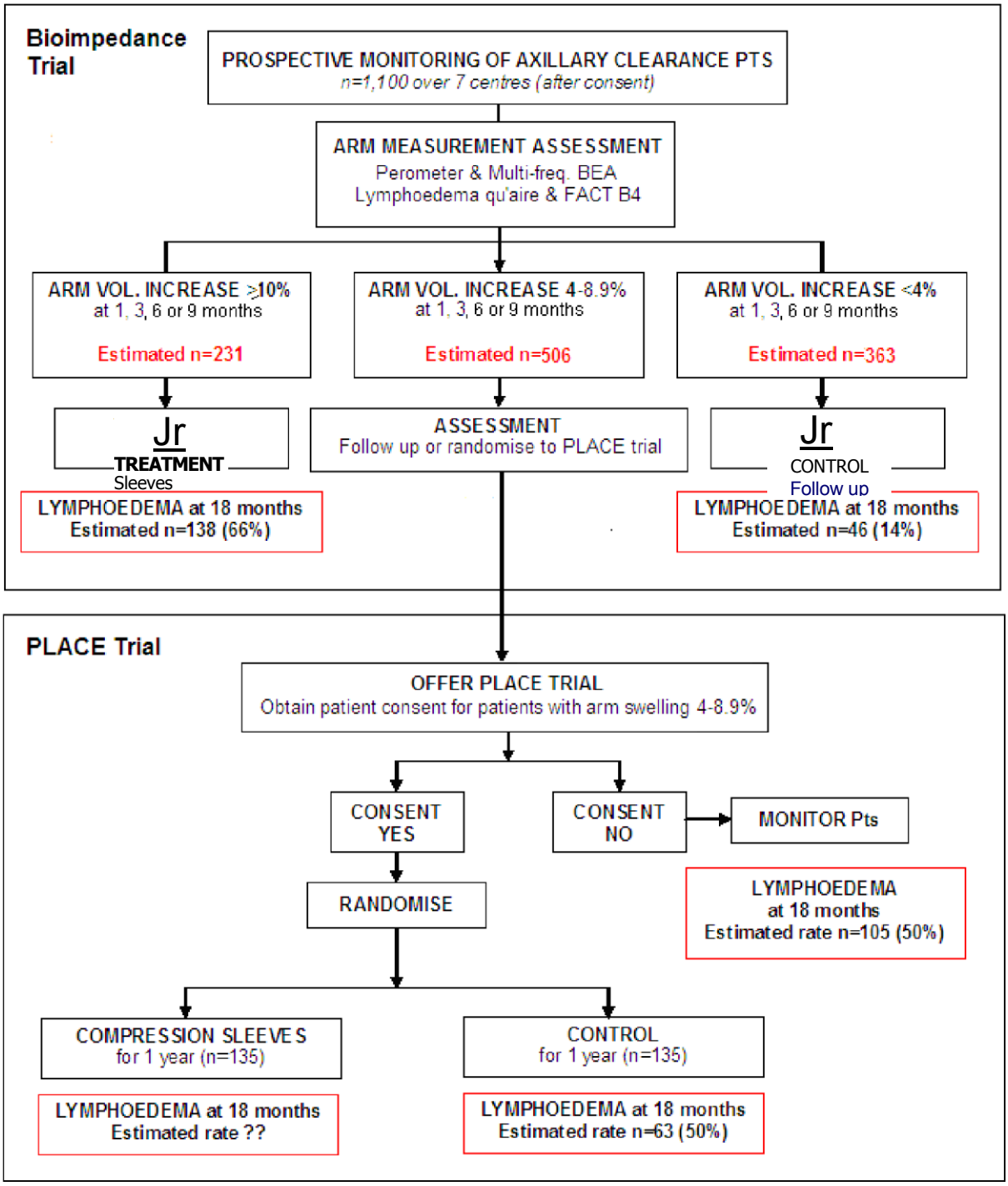
Please note, the BEA assessment will only be carried out on the initial 1100 recruits, as part of the 5 year study. Subsequent recruits, as part of the 9 month study, will not undergo this as enough data will be gathered from the original cohort.

Multivariate Model for Lymphoedema Development

Older age, increases in body mass index and postoperative radiotherapy are claimed to increase lymphoedema developmentL[8,363]. We will build a multivariate model predicting lymphoedema and will enter the following potential predictor variables: Body Mass Index, dominant limb, postoperative radiotherapy, previous sentinel node biopsy, cigarette smoking, weight gain and age. Follow up will allow us to identify what factors, as well as early arm volume changes or BEA, predict subsequent development of lymphoedema. We anticipate 1100 patients recruited by 24 months of the programme to allow us to build a multivariate model. Multiple logistic regression modelling techniques will be used to identify significant predictors of lymphoedema at early (18 months) and late time points (36 months).

An economic model will be developed, combining the economic data obtained from the planned lymphoedema prevention trial (PLACE Trial) with the multivariate prediction model to assess the cost-effectiveness of BEA in the context of either conventional management or proactive prevention of lymphoedema.

Figure 2 - BEA Trial Schema



Please note, the BEA assessment will only be carried out on the initial 1100 recruits, as part of the 5 year study. Subsequent recruits, as part of the 9 month, will not undergo this as enough data will be gathered from the original cohort.

Five year study (first 1100 patients)

	Baseline	1 month post ANC	3 months post ANC	6 months ANC	9 months post ANC	12 months post ANC	18 months post ANC	24 months post ANC	36 months post ANC	48 months post ANC	60 month s post ANC
Informed Consent	X										
Height	X										
bioimpedance measurements *	X	X	X	X	X	X	X	X	X	X	X
Blood sample **											
Perometer measurements	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X
EQ-5D questionnaire	X			X	X	X	X	X			
FACT-B+4 questionnaire	X		X	X	X	X	X	X	X	X	X
lymphoedema symptom questionnaire	X		X	X	X	X	X	X	X	X	X

	Baseline	1 month post ANC	3 months post ANC	6 months post ANC	9 months post ANC
Informed Consent	X				
Height	X				
Perometer measurements	X	X	X	X	X
Weight	X	X	X	X	X
EQ-5D questionnaire	X				
FACT-B+4 questionnaire	X				
lymphoedema symptom questionnaire	X		X	X	X

NB. PaxGene sample does not appear on the schedule as it can be taken at any visit whilst the patient is on the study, as long as they have consented.

* use the form at the back of the protocol for guidance
** Patient needs to give additional informed consent on Consent Form B before these can be taken
NB. PaxGene sample does not appear on the schedule as it can be taken at any visit whilst the patient is on the study, as long as they have consented

Nine month study (final 300 patients, recruited from February 2015)

3.0 PATIENTS

3.1 Trial Entry

Women undergoing ANC will be monitored from pre-surgery baseline, with perometer measurements and BEA (please note, only the initial 1100 recruits will have BEA measurements) to compare the sensitivity and specificity of both techniques for predicting chronic lymphoedema development. Identifying the most sensitive and specific method for detecting chronic lymphoedema would enhance selection of patients for intervention with arm sleeves should the intervention prove cost effective.

Approximately 1400 patients will be enrolled over a 5 year period over 9 investigative sites; North Manchester, South Manchester, London, Derby, North Staffordshire, Poole, Bournemouth and Wolverhampton.

Patients will be registered by a telephone call to the MAHSC Clinical Trials Co-ordination Unit (0161 446 3311).

3.2 Inclusion Criteria

- **Women aged 18-90 years.**
- **Early breast cancer (no evidence of metastatic disease by local screening procedures), scheduled to undergo axillary node clearance.**
- **Willing to consent to pre-surgical arm measurements by perometry and BEA.**
- **Agreeable to follow-up for up to five years.**
- **Written informed consent to enter bioimpedance study.**

3.3 Exclusion Criteria

- **Any patients unwilling to consent to pre-surgical baseline measurements.**
- **Known distant metastasis.**
- **Inoperable breast cancer (T4 category or distant metastasis).**
- **Node negative not undergoing axillary clearance.**
- **Previous axillary radiotherapy or clearance.**
- **Past history of breast/chest wall radiotherapy.**
- **Previous axillary clearance; either unilateral or bilateral.**
- **Pregnancy.**
- **External pacemaker/defibrillator.**

3.4 Treatment Measurements

For the first 1100 recruits (recruited before January 2015), arm volume will be measured at baseline, 1, 3, 6, 9 and 12 months then 6 monthly thereafter to 2 years, followed by annual measurements to 5 years using perometer arm scanning (and circumferential tape measurement of arm girth with anatomic landmarks (e.g. lateral epicondyle) as reference points). The contralateral arm will act as a control. *For the additional 300 patients (recruited from February 2015, on version 3.1 or higher of the patient information leaflet), these measurements will take place at baseline, 1, 3, 6, and 9months only.*

Patients developing a 4-8.9% increase in arm volume within 9 months of arm surgery will be offered randomisation. Within the same visit, patients will undergo multi-frequency bioimpedance measurements, comparing the affected arm with the contralateral arm and the leg. Bioimpedance measurements will not lead to change of treatment but will be recorded and performed according to the trial Standard Operating Procedures (please note, Bioimpedance will only be measured in

the 1100 patients who are part of the 5 year study. Subsequent patients, who will only be followed up for 9 months, will not undergo this assessment).

Perometer measurements demonstrating an increase in arm volume >10% (on two occasions) will be utilised to commence treatment for lymphoedema.

For the first 1100 participants, FACT B+4 questionnaires will be administered at all visits apart from the 1 month visit to permit calculation of Trial Outcome Index (FACT B TOD following the ATAC Trial methodology. [PG 60] A lymphoedema symptom questionnaire will be admistered at the same time points. EQ5D questionnaires will be administered at all time points apart from months 3, 36, 48 and 60.

Please note, quality of life questionnaires will only be administered at baseline for the final 300 participants.

3.5 Sample Collection

A 20m1 PaxGene sample is to be collected on one occasion from all patients who have given their informed consent to provide blood samples. PaxGene, samples will be collected during any scheduled study visit as these samples are not time critical. The analysis of these blood samples has not yet been finalised, but we would like to perform some tests that will give us additional information on the effects of surgery and the effects of treatment following surgery on the lymphatic system. We are also interested in finding out through DNA and RNA analysis whether there are any genes that may cause lymphoedema after surgery, or increase the chance of side effects from radiotherapy.

Breast tumour specimens will be collected and, where patients have given their informed consent, these tissue samples may be used for future research.

3.6 Data Management

CRFs will be provided for recording of all data. Each one will be printed on a single sheet. Data will be recorded directly and legibly on the CRFs in black ballpoint pen. Entries should be made legibly and initialled and dated by approved personnel. The reasons for significant changes must be provided. Correction fluid or covering labels must not be used. The MAHSC Clinical Trials Co-ordination Unit (CTU), Manchester will provide data management for all centres and a copy of the CRF will be sent to the Data Manager at The MAHSC CTU in Manchester.

4 STUDY OBJECTIVES

4.2 Primary Objective

1) Incidence of lymphoedema at 2 and 5 years after axillary node clearance *(assessed by perometer scanning).*

4.3 Secondary Objectives

1) **Comparison of multi-frequency BEA with perometer measurement.**
2) **Prediction of lymphoedema by multi-frequency BEA at 24 months.**
3) **Quality of life in each group (T01 and FACT B+4).**
4) **Multivariate model assessment of factors predicting lymphoedema at 24 months.**
5) **Lymphoedema symptoms related to changes in arm volume and bioimpedance readings.**

5 STATISTICAL ANALYSIS

Analysis 1 and 2 will directly compare BEA and perometer assessment at a given time point (6 and 18 months). The reported concordance/correlation in small series is 0.93[1341]. Thus, even if a sleeve has been applied in patients before 6 months' measurements and the arm circumference has been reduced, the reduction in fluid in the arm should have reduced both the perometer and BEA scores concomitantly.

Sample Size Calculation

We estimate 1100 women are needed for screening by perometer to recruit 270 women to the PLACE trial and this sample size of 1100 (derived from having approached 1500 women to take part in the study) allows us to assess equivalence for sensitivity and specificity for BEA compared to perometer measurement with tight confidence intervals. Previous reported correlation between the techniques is very high [115], and this sample size allows us to have a 95% Confidence Interval (CI) around our sensitivity and specificity estimates such that they are ±5% or less. Thus if perometer and BEA are equivalent in sensitivity and specificity to within 5% of each other, we would expect that the BEA would become the preferred option as it would be mobile, non-invasive and simpler to use in any outpatient setting compared to a fixed, large instrument, such as the perometer. There will be less patients with lymphoedema at 6 months but nonetheless if BEA sensitivity is 95% of the perometer sensitivity, we can demonstrate this with a 95% CI of 91.42% to 97.49%. If the BEA sensitivity rate was as low as 90%, we would have a 95% CI of 85.12% to 93.49%. All subsequent analyses will use sample sizes based on larger numbers as there will be more lymphoedema events at 18 months and again at 36 months but their confidence intervals are within ±5%. We have used the exact method for calculating confidence intervals for a binomial proportion (Documenta Geigy Scientific tables page 185 equation 769); the actual calculation was done using the www.measuringusability.com/wald.htm website calculator.

The sample will allow us to measure accurately, inter- and intra-technique variability at different time points.

Analyses 1 to 3 will assess whether BEA can be used instead of perometer in defining lymphoedema status. The second group of analyses is to look for any variables collected at operation or in the first 6 months post operation that singly or in combination can be used to predict lymphoedema status at or beyond 18 months.

Analysis 1

Sensitivity and specificity analysis of the BEA assessment (lymphoedema or not) against the 'gold standard' perometer assessment (lymphoedema or not) using data available by 6 months.

Analysis 2

Analysis of the sensitivity and specificity of the 18 month BEA assessment status (lymphoedema or not) against the 'gold standard' 18 month perometer assessment status (lymphoedema or not) using all data available at 18 months.

Analysis 3

Assessment of the relationship between perometer measurement and BEA measurement.

Analysis 4

Cox regression multivariate analysis of the time to Lymphoedema (as defined by perometer) to find out which combination of variables gives the best prediction of this complication.

Analysis details:

Analysis 1: Sensitivity and specificity analysis of the BEA assessment (lymphoedema or not) against the 'gold standard' perometer assessment (lymphoedema or not) using data available by 6 months. Can BEA be used instead of perometer in predicting lymphoedema status?

All cases with a 6 month BEA and perometer measurement will be used. This is acceptable even if some cases are treated as what we are asking is do cases measured at the same time (and therefore under the same circumstances whatever they are) agree in their assessment of lymphoedema status.

The two methods will not agree on their actual scores as perometer measurements are in percentage differences and BEA measures are ratios. However we will assess the relationship between all the pairs of values using statistical techniques recommended by Bland and Altman for assessing agreement between methods of measurements with multiple observations per individuall[36,311] (see also analysis 3).

With 1100 cases consented to having measurements taken and followed-up, we would expect 231 to have developed lymphoedema (positive) using perometer assessment and 869 to be negative at 6 months. If we accept that BEA status has at least 95% sensitivity and 95% specificity against the perometer status then the 95% CI for sensitivity based on 231 cases is 91.42% to 97.49% and for specificity based on 869 cases is 93.31% to 96.47% (CI's calculated by 'exact' method). Consequently if sensitivity is <91 % or specificity is <93% we can conclude that the true BEA rates are not as high as 95%. This analysis can be done 6 months after the last case has their 6 months measurements taken. The perometer is deemed to be the gold standard.

A further assessment of the BEA value cut off level will be made to see if a change in the standard definition is worth recommending (ROC analysis). This will be done at 18m from the start of the study (using cases accrued in the first year) and repeated on the new cases post 1 year recruitment to see if a new cut off level works on the second data group. The final sensitivity and specificity analysis will take place 6 months after the last case is recruited.

Analysis 2: Analysis of the sensitivity and specificity of the 18 month BEA assessment status (lymphoedema or not) against the 'gold standard' 18 month perometer assessment status (lymphoedema or not) using all data available at 18 months.

This analysis uses all the data available at 18 months, following the same logic and procedures as Analysis 1. Assuming at least 1,000 women are followed-up to 18 months after surgery, there will be more lymphoedema cases, this is estimated to be 35% of the total group (i.e. 350 cases). The sensitivity calculations produce a 95% CI for a 95% BEA sensitivity rate (333/350) against the perometer status at 18 months of 92.34 to 97.15 (again using the `exact' method). The other 650 cases are used for the specificity calculation, here the 95% CI for 95% BEA specificity (618/650) has a 95% CI of 93.12 to 96.61. Consequently if sensitivity is <92% or specificity is <93% we can conclude that the true BEA rates are not as high as 95%.

Analysis 3: Assessment of the relationship between perometer measurement and BEA measurement. Any changes will be measured by both systems at different time points (1m, 3m, 6m, 12m and 18m and later on out to 5 years) and all results will be used as the modelling will be based on the paired perometer and BEA values. This will be used to define the relationship between the two methods (we will use Bland-Altman methods[136,371] at individual time points and generalized estimating equations (GEE) regression models across time points). The relationship established may lead to a clearer definition of `true' lymphoedema status when using either system.

Analysis 4: Cox regression multivariate analysis of the time to Lymphoedema (as defined by perometer) to find out what combination of variables gives the best prediction of these events.

For this 'modelling' analysis we will use 'time to the first lymphoedema event per case' as the measure (cases not becoming lymphoedema will be censored at their last assessment time) and apply a Cox regression multivariate analysis to see what variables (if any) predict the long term outcome. The variables lis ted below are candidates. Concerns about the treatment paradox affecting this analysis will be dealt with by excluding cases who develop lymphoedema before 6 months and using a factor 'sleeve' v 'no sleeve' in the model to adjust for the cases treated in PLACE.

BMI, dominant limb, postoperative radiotherapy, previous sentinel node biopsy, cigarette smoking, weight gain, and age. As we will be measuring the patient's assessment of their own status using FACT-B and the Lymphoedema Symptom Checklist we will also use individual question responses and the overall scores for these questionnaires out to 6 months. The BEA values and perometer values are available at baseline, 3 months and 6 months. The 3 months and 6 months values will be used as distinct time points or as summary scores over the 3 measurements. It may well be possible to have a factor that represents 'early treatment' or 'lymphoedema status before 6 months', in which case all the information will be used. These variables will be assessed univariately and then as part of a multivariate model to see if any predict lymphoedema status by 18 months follow up.

As routine clinical data on lymphoedema status will be available in due course with 5 year follow up, a subsequent analysis will be possible to build a predictive model of outcomes up to 5 years.

This analysis will take place 18 months after the last case is entered. For the multivariate regression analyses, it is typically recommended that between 10 and 30 cases per variable are used. The higher number of cases per variable are required when the relationships are weaker. With approximately 1000 cases this should allow us to examine around 30 variables with at least sufficient power to pick up moderately weak relationships. See analysis 4 for the type of variables we will be assessing.

All percentages for the 3 groups (A-C) are estimated from ALMANAC Trial data (see Annex 4d). None of the analyses outlined will use cases where a treatment for lymphoedema has been given prior to 6 months as explained above. A "treatment paradox" will not affect analyses 1 to 3 and treatment will be a variable in analysis. Potentially, the predictive value of a measurement at 6months by perometry of the arm may be altered by treatment when assessing lymphoedema at 18 or 36 months. We do not believe this will occur for the majority of patients but in any case we will take account of this in the Cox multivariate regression analysis based on perometer measurements at 18 and 36 months and by looking at variables which include treatment with a compression sleeve. As we indicated in the flow diagram of this study, 3 possibilities may arise:

- Group A: Women in whom the arm volume increase is less than 4% at all time points up to 6 months (approximately 33% of the population; 330 individuals). None of these patients will undergo treatment within the first 6 months and therefore the measurement at 6 months will not be subject to "treatment paradox" and should they subsequently develop lymphoedema before 18 months, they will be registered as having developed the lymphoedema event in a time-dependant manner for the multivariate analysis and subsequent treatment will not affect this analysis.

- Group B: Women who will have developed a 4-10% arm volume increase by 6 months (estimated as 46% of the total group; 460 patients). Around 135 women from this group (with a 4-8.9% volume increase) will go into the PLACE trial and have a sleeve applied and a similar number will go into the PLACE trial and will not have an arm sleeve applied.

  Thus, in this group there will be 325 patients (460 minus 135) who are not treated until they develop lymphoedema and will not have a "treatment paradox" for the same reason as previously described. Out of the 135 cases allocated to the sleeve arm within the PLACE trial, who are chosen at random, we will use their data in a multivariate analysis as we will incorporate it as a factor, sleeve versus no sleeve in building the model.

- Group C: Women who develop greater than 10% arm swelling by 6 months (approximately 210 patients). Arm swelling of greater than 10% at 1 month will need confirmation but in current practice, we would review these patients at 3 months, before deciding to put on an arm sleeve as some women do observe amelioration of swelling over this period following the operation. Thus we will have 3 month perometer readings on all patients in this group to compare with 3 month BEA measurements. All other patients will provide 6 month perometer and BEA measurements and will therefore be eligible for the analysis of the prediction of arm swelling at 18 and 36 months. The data for patients who have undergone treatment before 6 months in this group will not be included in our multivariate analysis, although we expect few cases to be excluded in this way.

6 SAFETY REPORTING PROCEDURES

6.2 Adverse Events

An **Adverse Event (AE)** is defined as any untoward medical occurrence in a participant to whom a research procedure has been administered, including occurrences which are not necessarily caused by or related to that procedure.

In research involving medical devices, a **Serious Adverse Event (SAE)** is an untoward occurrence that:

- Results in death;
- Is life-threatening*;
- Requires in-patient hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity, or;
- Consists of a congenital anomaly or birth defect;
- Other important medical events***.

*life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Adverse events can be either:

- **'related' or `unrelated'i.e.** resulted from administration of the medical device, or;
- **'expected' or `unexpected'** i.e. a type of event that is not listed in the protocol as an expected occurrence.

6.3 Adverse Event Reporting

Only adverse events/reactions **specifically related to the device** should be reported.

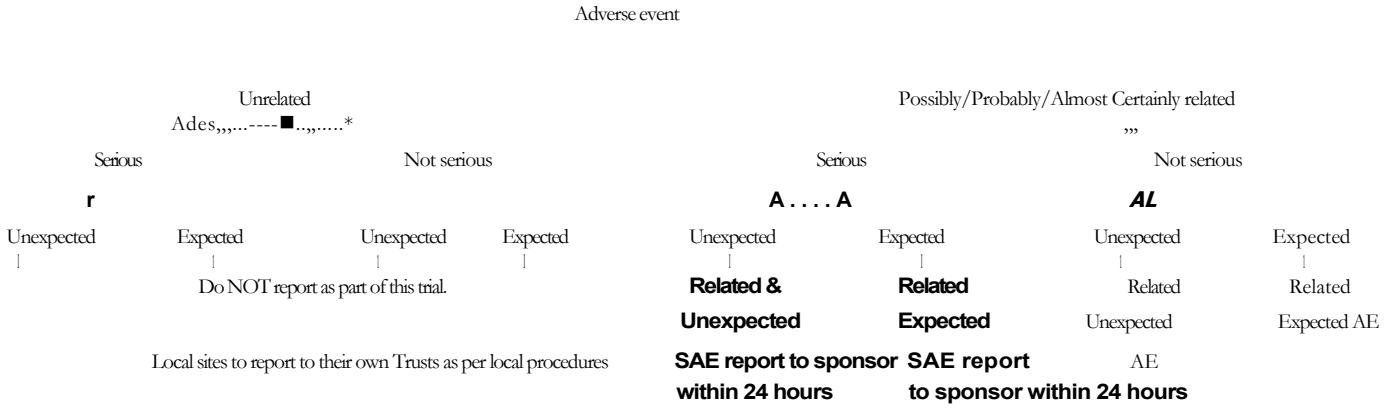
Do not report any complications or side effects commonly associated with cancer and/or chemotherapy e.g. septicaemia, neutropenia, deep vein thrombosis and hospitalisation due to viral illness.

All device-related SAEs must be reported immediately by the local Investigator to the Chief Investigator. The site should:

- Either, complete the SAE case report form, signed and dated and send immediately (within 24 hours or the next working day, preferably by fax on 0161 291 5771) to the sponsor together with relevant treatment forms and anonymised copies of all relevant investigations.
- Or, contact the sponsor by telephone and then send the completed SAE form to the sponsor within the following 24 hours as above.

The form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely and not assessable). The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

The sponsor will provide the Main REC with an annual report of all SAEs. Investigators should report any SAEs as required by their Main Research Ethics Committee and/or Research & Development Office.



NB. Only adverse events e.g. illness, injury and accident <u>specifically related to the device</u> should be reported.

Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

To report an SAE, an SAE form must be completed and returned within 24 hours of the clinician becoming aware of the event.

Fax: 0161 291 5771 for the attention of Sian Hanison

7 METHODS

Current methods of assessing arm volume include volume measurement using repeated tape measurement at predefined intervals along the limb, with the volume being calculated assuming a circular or elliptical truncated cone geometry. This method is tedious and time-consuming to perform. There is no standardisation of the number of circumferential measurements that are required to provide a reasonably accurate measurement of volume and it is thus not considered sufficiently validated to use in the study. Perometry volume determined from the 3D silhouette cast by the limb when passed through a ray of opto-electronic sensorsi[1]i is rapid, accurate and precise, but requires expensive equipment which is not very portable. The total volume of the arm may change for various reasons. The most common is weight gain but work or exercise induced muscle hypertrophy are cases in point where a simple total volume measurement is not immediately related to the parameter of interest i.e lymphatic volume. Additionally, there is dispute about the definition of lymphoedema. Many people have used the definition of greater than 10% arm volume increase compared to the contralateral arm, but others have claimed that a 200m1 volume difference between the arms can be used to define unilateral lymphoedema following breast cancer [11'11]. For the purposes of this study, we are using a greater than 10% arm volume increase measured by perometer on at least two occasions to identify women with lymphoedema secondary to axillary node clearance[1151] Czerniec et al found that perometer compared to bioimpedance spectrometry had a high concordance with bioimpedance r=0.92.

<u>Perometer Measurement</u>

The perometer is a standard arm volume measurement device that uses infra-red optoelectronic technology to detect and quantify limb changes. Perometer software then calculates the entire limb

volume and the % difference between the limbs and since a hard copy of each patient's data is retained on the database, it can be used to compare limb volume changes over time. Pre-surgical limb volume measurement accounts for pre-existing normal inter-limb variation which may range from 3-10% depending on arm dominance and activity leve1[1291], hence the need for pre-surgical measurements. The upper limb volume and circumference are calculated by the perometer software (rather than the operator) and a comparison made between the previous reading from the same patient.

A standard operating procedure for the use of a perometer has been developed across all centres for this study and the PLACE trial. At least 2 readings at each visit by the same perometer operator (lymphoedema, research nurse or CTA depending on centre) will be required in the study, to minimise any variability in the measurements. Additionally, before the patient is randomised or considered to have failed intervention, a lymphoedema nurse will be required to repeat the duplicate measurements to confirm the findings.

With regard to the variability of perometer measurements using a standard operating procedure, which involves duplicate bilateral arm measurement of each individual patient produces an inter-observer (day to day) variability of measurements with a 1.2% standard deviation. Given entry to, and exit from, the PLACE trial requires a further confirmatory duplicate measurement by the lymphoedema nursing sister, the likelihood of "migration" across "category" purely due to inter-observer variability will be under 2%. Review of the ALMANAC trial data revealed the mean percentage increase in the volume of operated arms was 4.0% and 5.14% at 3 and 6 months respectively. Thus, the majority of patients who will be eligible will require a near doubling of arms volume before developing lymphoedema (>10% AVI).

Multifrequency Bioimpedance Monitoring

Multi-frequency bioimpedance electrical analysis (BEA) is a non-invasive technique to measure total water content, which involves passing an extremely small electrical current through the body and measuring the impedance (or resistance) to the flow of this current. In recent years the BEA technique has been refined to measure the impedance over a range of frequencies from 4 to 1000kHz. By mathematically modelling the measured data, the impedance at zero frequency (i.e. the impedance of the extracellular fluid alone) can be determinedi[3"11]. The use of BEA as a measurement tool for the presence of lymphoedema has been previously well-describedi[3"3,351]. Briefly, two measurement electrodes will be placed at either end of a 40 cm long segment of the limb with current drive electrodes placed approximately 10 cm distally. Identical electrode positions will be used on both arms. BEA measurement on each arm will be performed using a U400 multiple frequency BEA (ImpediMed) and will be performed to a standardised method (see SOP in Appendix B). Two results will be recorded:

The ratio of these values comparing the treated and untreated sides of these women with unilateral breast cancer (unaffected arm:affected arm) will be calculated. A patient will be classified as having lymphoedema when the impedance ratio is more than 3 standard deviations above normative data, with the normative data taking into account the significant effect of limb dominance.

1) Absolute BEA score (with a greater than 3sd level compared to the contralateral arm and reference leg equalling lymphoedema status);
2) Change in BEA score from baseline. Changes from preoperative baseline of >10% increase in BEA would represent a value score identifying lymphoedema using BEA.

All treatment decisions in the study will be based on Perometer measurements as this currently represents the standard of care internationally.

We will assess multi-frequency bioimpedance monitoring compared to perometer arm measurements in women after axillary node clearance (ANC) in 9 centres. We will use

bioimpedance monitoring during the study to determine its value in predicting response to compression garment therapy. Within the study we will assess reproducibility of both methods across centres and robustly establish both intra and interobserver error rates for both methods in the study population.

Please note, this assessment will only be carried out on the initial 1100 recruits, as part of the 5 year study. Subsequent recruits, as part of the 9 month study, will not undergo this as enough data will be gathered from the original cohort.

8 QUALITY OF LIFE

The research nurses will ensure each patient completes the quality of life questionnaires at baseline.

Subsequently, questionnaires will be given to patients by the research team at study follow-up visits at 3, 6, 9, 12, 18, 24, 36, 48 and 60 months for the initial cohort of patients.

The FACT-B+4 is a validated forty item arm cancer specific instrument which has 4 additional arm morbidity questions relevant to axillary surgery[1381]. The TOI health survey questionnaire will also be used. In accordance with NICE technology assessment guidance the EQ-5D generic utility instrument will be administered at baseline, 6, 9, 12, 18 and 24 months by the research team for the initial cohort of patients. Subsequent patients will not complete any further questionnaires as part of this study. .

9 PATIENT SATISFACTION AND LYMPHOEDEMA QUESTIONNAIRE

Study specific patient satisfaction questionnaires will be developed (with input from patient representatives) and reviewed to assess level of utility for each mode of delivery. Also, the preference in patients prior to, and following treatment, will be compared to identify the proportion of patients likely to choose early intervention rather than the conventional approach. Compliance will be assessed by means of patient diaries.

10 DEFINITION OF CELLULITIS

Cellulitis of the arm after axillary node clearance is a recognised complication and will be recorded in the study. Hospital admission with cellulitis for intravenous antibiotics should be recorded in the Case Record Form (CRF). Entry criteria have therefore been based on a confirmed diagnosis of cellulitis by a general physician, dermatologist or dermatology nurse, along with a checklist of presenting features that will be used to describe the study population.

To confirm diagnosis of the recent (index) episode of cellulitis lymphangitis„ evidence that the following 4 signs and symptoms were present must be obtained from the patient's notes or through discussion with the patient:

- Presence or history of local warmth and tenderness or acute pain.
- Unilateral erythema, or asymmetrical erythema with the more severe side having a temporal relationship to symptoms.
- New or increased swelling of the arm.
- Constitutional disturbance (e.g malaise, rigors, fever).

11 ECONOMIC EVALUATION

Early intervention for arm swelling could result in resource savings to the NHS. If we establish that early detection and intervention is successful, cost effectiveness analysis will be carried out to compare any utility benefits to cost differences between the two strategies. Two analyses will be presented: NHS direct costs only, and NHS plus patient/carer direct costs (including lost income but excluding estimated productivity losses). To facilitate this, comprehensive comparison of the costs of the two groups will be undertaken.

For each patient group the following resource data will be collected using hospital records for resource use and patient diary cards for care in the community:-

1) Number of outpatient visits (planned and unplanned).
2) Resources used in therapy (compression garments).
3) Patient/carer trips associated with hospital care (mode of transport and costs).
4) Time off work/loss of income associated with chronic lymphoedema care.

Resource data will be validated using the unit costs of the UHSM finance data using appropriate and explicit assumptions regarding staff time and equipment use. Extensive sensitivity analysis will be carried out where assumptions are made. This data should enable a comprehensive comparison of total costs to the NHS in the two groups to be made. Any savings to the NHS will be identified.

In addition to a cost effectiveness analysis, we will estimate the budget and service impact of early intervention (for arm swelling) to the NHS based on the experience of the study and will include the possibility of extending this treatment service to non-specialist centres.

Health Economics Modelling

The additional factor introduced into the modelling described is the comparison of a new diagnostic technology (BEA) with conventional measurement to predict / determine the development of lymphoedema. It is necessary to model the costs and health consequences of the four potential outcomes of a diagnostic test (true or false positive, true or false negative), and to then compare overall costs and benefits of using BEA with conventional measurement in the context of either early preventive intervention or of conventional management of emergent lymphoedema. In practice this will require multiple applications of the long-term model developed for the PLACE Trial with appropriate parameter values and assumptions, combined with the performance characteristics of the diagnostic tests, as a basis for determining whether BEA is a cost-effective technology with or without early preventive intervention.

This is a good example of the economic evaluation of a diagnostic technology, which is a developing field of study in which the economics team already have an interest and are developing experience in the context of the new NICE diagnostics programme.

12 INFORMED CONSENT, ETHICAL AND REGULATORY CONSIDERATIONS

12.2 Ethical Approval

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, GCP, the Data Protection Act and other regulatory requirements, as appropriate.

Multicentre Research Ethics Committee (MREC) approval has been obtained for this trial, and Site Specific Assessments (SSAs) will be performed at participating centres. The trials centre will maintain contact with NRES and will submit any protocol amendments. The trials centre will forward any resulting documentation to local centres.

12.3 Patient Informed Consent

The local investigator is required to explain the nature and purpose of the trial to the patient prior to trial entry. A detailed patient information sheet and consent form will be given to the patient and written informed consent obtained before entry to the study.

12.4 Protocol Compliance

Christie CTU office staff will be in regular contact with local centre personnel to check on progress and to help with any queries that may arise. Incoming forms will be checked for completeness, consistency, timeliness and compliance with the protocol. Centres may be withdrawn from further recruitment in the event of serious and persistent non-compliance.

12.5 Indemnity and Compensation

The multi-frequency BEA study was investigator-initiated but internationally peer-reviewed and is funded by the National Institute for Health Research, but approved by the Cancer Research UK CTAAC Committee. The trial will be co-ordinated by the University Hospital of South Manchester, through an NIHR Programme Grant.

The principal investigator, local investigators and co-ordinating centres do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial. Therefore compensation is available in the event of clinical negligence being proven.

12.6 Data Protection

All data will be kept strictly confidential according to Good Clinical Practice (GCP) Guidelines. At the end of the study, all study data will be stored by the University Hospital of South Manchester NHS Foundation Trust in a secure fashion for 20 years in accordance with the ICH GCP. During the study period, the Case Report Forms will be stored at the Christie Clinical Trials Co-ordination Unit. Source data will be stored at the relevant clinical sites in line with respective Trust policies. The trials centre will act to preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and our trials are registered in accordance with the Data Protection Act 1998 with the Data Protection Officer at the relevant NHS Trusts.

12.7 Publication Policy

Data from all centres will be analysed together and published as soon as possible. Individual participants may not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications.

All publications shall include a list of participants, and if there are named authors, these should include the principal investigator, clinical trial coordinator(s), and statistician(s) involved in the trial and contributors of more than 10% of participants. If there are no named authors then a writing committee will be identified.

13 TRIAL GOVERNANCE

13.2 Independent Data Monitoring and Ethics Committee (IDMC), Independent Trial Steering Committee (TSC) and Trial Management Group (TMG)

The data will be reviewed (at least annually) by an IDMC, consisting of at least two clinicians not entering patients into the trial and an independent statistician. The IDMC will be asked to recommend whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDMC will make confidential recommendations to the TSC.

The role of the TSC is to act on behalf of the funder, to provide overall supervision for the trial, to ensure that it is conducted in accordance with GCP, and to provide advice through its independent Chairman. This independent committee will review the recommendations from the IDMC and will decide on continuing or stopping the trial, or modifying the protocol.

The Trial Management Group under the chairmanship of the Chief Investigator will coordinate and manage the trial's day-to-day activities.

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APPENDIX A— STANDARD OPERATING PROCEDURE: BIOIMPEDANCE MEASUREMENT OF THE ARMS USING THE U400

To calibrate the U400:

- Calibration of the device should be undertaken once per day prior to measurement of a limb.
- Turn on the device and select calibration check.
- Insert the leads into the matching coloured points on the test cell.
- Run the calibration check.
- Continue with the bioimpedance measurement if PASS is displayed.
- If a FAILURE measure is displayed record the failure number and report this to Impedimed. Use the replacement leads and/or test cell to rerun the calibration.

Contraindications:

- *Impedance measurements should not be undertaken on patients with active implanted medical devices (such as pacemakers, defibrillators) or patients undergoing external defibrillation.*
- *The U400 has not been clinically validated for use in pregnant women.*

To undertake Impedance measurements:

Impedance measurements can be variable and certain situations that affect body water composition can influence the results produced. It is suggested that the measurements are undertaken under similar conditions, e.g time of day, activity levels, food and fluid intake, to improve reliability.

- Ask the patient to empty their bladder, if needed.
- Ask the patient to remove jewellery (rings and earrings may be left).
- Ask the patient to remove their shoes, socks / tights.
- If applicable, ask the patient to remove their compression garment.
- The patient is required to lie on their back in a fully supine position and rest for at least 3 minutes prior to undertaking the measurements.

- The patient needs to be hydrated — check for and note on the CRF;
  - Alcohol within the last 12 hours,
  - Exercise within the last 12 hours,
  - Medical history of renal or heart failure including medications,
  - Medications including hormones treatments,
  - Caffeine within the last 2 hours,

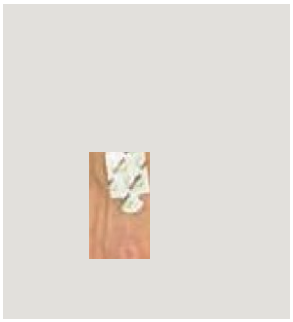
- Determine at what part of the menstrual cycle the patient is currently in (just prior, during and just after).

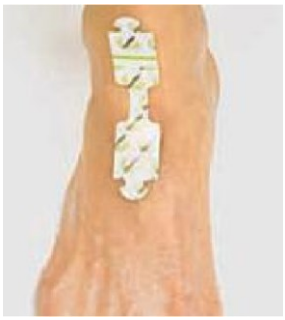
- Record if the patient has a metal implant insitu in their arm or shoulder.
- Enter / identify the participants name and study ID number onto the U400.
- Before placing the electrodes, clean the skin sites with an alcohol wipe (to remove any excess oil or lotion) and allow the skin to dry.
  - Avoid placing electrodes on irritated skin or wound sites. If the electrode position needs to be adapted for one arm, adapt it also for the other arm and future measurements. Ensure that electrode position is recorded if they have been changed from the standard positions.
  - If the patient has heavy or curly hair that cannot be parted this may need to be shaved.
- Position the patient with their arms by their side, hands resting next to (but not touching) their body and palms down. Legs need to be apart with the feet at shoulder distance (if the patient cannot separate their inner thighs, it may be necessary to place insulating material, such as a towel, between them).

Electrode position:

- To ensure good electrode contact, start from the outer edge and run your finger around the electrode several times, working towards the centre.

Right and Left Arm: Place the proximal end, with the green line on the midline of the ulnar styloid process, on the wrist, and run the distal end down towards the fingers.





Right Foot: Place the proximal end, with the green line between the medial and lateral malleolus bones, on the ankle, and run the distal tab down towards the toes.

Taking the impedance measurements:

- Select which arm is the dominant limb and which is the affected limb.
- **Measure the right arm first.** Connect the coloured alligator clips to the electrodes.
  - The **yellow clip** is attached to the wrist electrode on the right arm and the **red clip** to the hand electrode of the right arm.
  - The **blue clip** is attached to the left arm at the wrist.

    - **The black clip is attached to the right foot electrode.**
- Once these are attached press select ACCEPT and then MEASURE. The device will perform the measurement of the right limb.
- If the electrodes have been placed incorrectly or the clips not connected correctly "out of range check leads and electrodes" will be displayed.
- If the electrodes are placed correctly "Attach electrodes to patient for LEFT arm" will be displayed.
    - The **yellow clip** is attached to the wrist electrode on the left arm and the red clip to the hand electrode of the left arm.
    - The **blue clip** is attached to the right arm at the wrist.
    - The **black clip** stays on the right foot electrode.
- The device will perform the measurement of the left limb.
- When all the measurements have been taken the L-Dex will be displayed on the screen and whether this is within the normal limit. Record the L-Dex on the CRF. Save the data to the U400.

Transferring the data onto the computer software:

- At the end of each clinic / day, transfer the data from the U400 onto the software.
- Ensure the device is turned off.
- Plug the USB device into a USB port on the computer.
- Connect the red lead to the device and USB device.
- With the U400 turned on, select STATUS and then GET RECORDS to transfer the data to the software.

Measurements may be affected by:

- Placing a mobile phone in close proximity to the device during operation.
- Metal implants, clips or other types of artificial limbs or implants in the patient.
- Patients touching a metal surface during the measurement process.
- Using the device when the patient is connected to other medical devices.
- Incorrect electrode placement.
- Using electrodes that are past their use by date.
- Re-using disposable electrodes.
- Using a part of the full electrode tab.

PLACE / BEA CRF Page XX

Study ID ..... **Date** ..... **Time** .....

Data Collection Point: Baseline, 1, 3, 6, 9, 12, 15, 18 months.

Contraindications: *Does the participant have / is the participant....* 。

	Yes	No
• Any active implanted medical devices? (such as a pacemaker or defibrillator)		
• Undergoing external defibrillation?		
• Pregnant?		

If the answer to any of the above questions is YES DO NOT undertake bioimpedance measurements

Please identify if the participant is / has:	**Yes**	**No**
• Currently menstruating, just finished or just prior to menstruation: Details:		
• Currently taking Hormone treatments: Drug name, dose and frequency		
• Caffeine within the last 2 hours: Details		
• Has known renal impairment: Details		
• Has known cardiac failure: Details		
• Currently taking diuretics: Drug name, dose and frequency		
• Has artificial limbs: Details		
• Completed excessive exercise within the last two hours: Details		
• Consumed alcohol within the last 12 hours: Details:		
• A metal implant insitu in their arm or shoulder: Details		

• **Dominant Arm**	**Left** ☐	**Right** ☐
• **Affected Arm**	**Left** ☐	**Right** ☐
• **L-Dex Score***		
• **Baseline L-Dex**		
• **Change from baseline**		
• **L-Dex > 10**	**Yes** ☐	**No** ☐

** Please note, this assessment will only be carried out on for recruits who are taking part in the 5 year study. For subsequent recruits, as part of the 2 year study, you will not need to take Bioimpedance measurements.*

Protocols - PLACE – Qualitative Study

PLACE Qualitative study research plan

PLACE is clearly testing a complex intervention as defined by MRC.[1,2] We have had difficulty recruiting to PLACE and even with recruited patients we need to understand more fully their adherence to the intervention programme if it is to be successful. We thus propose to undertake qualitative work alongside the PLACE RCT as recommended by MRC. The embedded qualitative study will investigate motivators and barriers to recruitment, aspects of acceptability of the intervention to patients and clinicians, which can be used to enhance adherence, and effect mechanisms of the RCT.

Overall qualitative work will involve interviews using topic guides based on literature review, previous consultations with service users and insights from clinical observations. We will be guided by recent recommendations for mixed method research design to synthesis with RCT.[3] Interviews will be 30-60 minutes to allow enough time for in-depth discussion.

Methods
The qualitative research will involve interviews with purposively sampled patients, and clinicians.

For aim 1 (recruitment) we need to sample purposively, and interview patients who were successfully recruited to the study and those that declined. We also need to interview staff in the recruitment centres to explore what differs between successful recruiting centres and less successful centres (see slide 1 page 5 stakeholder meeting report). We estimate data saturation will occur within 2x15 patient interviews and 10 clinician interviews.

For aim 2 (acceptability) we need to sample purposively, and interview patients who were adhere to wearing compression bandages and those that struggle or do no adhere. We also need to interview staff to explore their views of what differs between success and failure to adhere. Again we estimate data saturation should occur within 2x15 patient interviews and 10 clinician interviews.

For aim 3 (RCT effect) we need to sample purposively, and interview patients allocated to each of the different arms of the study. We also need to interview staff in the study sites to explore their perceptions of the trial. We estimate data saturation should occur within 3x15 patient interviews and 20 clinician interviews.

Approach to data analysis

Interview data will be entered into NVivo 9.0 and analysed using the five stages of Framework Analysis[4]: familiarisation, developing a thematic framework, indexing, charting, and mapping & interpretation. The qualitative study is embedded within the PLACE RCT, and thus our approach to combining quantitative and qualitative data needs to be informed by mixed methods.[3,5] The aims of the qualitative study are (1) to determine the facilitators and barriers to recruitment and (2) to investigate how to maximise the acceptability of the intervention to patients and clinicians so as to enhance adherence, and (3) to gain insight into the mechanisms of effect of the trial.[5] The qualitative data will be collected and analysed separately but interpreted alongside the RCT.[6] Data will be presented on a mixed methods matrix and synthesised for publication. Publications will include at least one mixed methods paper presenting qualitative data alongside quantitative data, and further qualitative

publications presenting prominent themes in the data. Data analysis with aim 3 will in part depend on the success or otherwise of the RCT in demonstrating a significant effect of the intervention.

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Costs

RA 12 months	£41,227
C Todd 1% for 12months	£1,218
Transcription, travel, etc.	£13,900
Total	£56,345