The reliability, validity and sensitivity to change over time of the figure of eight method measuring hand size in patients with breast cancer related lymphoedema

Yolande Grace Borthwick
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College of Medical, Veterinary and Life Sciences

University of Glasgow

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Summary

Breast cancer related lymphoedema (BCRL) affects approximately 21% of patients following treatment for breast cancer. The current gold standard method of measuring hand swelling associated with BCRL is to use water displacement (volumeter). However, this is not always possible in the clinical setting. The circumferential tape measurement method is often used clinically but this does not include the area on the dorsum of the hand where the oedema is most commonly situated. The figure of eight method, which involves wrapping a simple measuring tape around the hand in a specific way, may be an alternative method to measure BCRL.

The aim of this study was to determine whether the figure of eight tape method was a valid and reliable method of measuring hand size in patients with hand oedema associated with BCRL. This was investigated by comparing the figure of eight tape method of measurement against the “gold standard” method of water displacement. The aim was also to establish whether the figure of eight tape method of measurement was reliable and valid for novice practitioners to ensure that the method could be used by any practitioner assessing a patient with BCRL. It was also investigated whether the figure of eight method of measurement was sensitive enough to detect change in hand size over time.

In study 1, 24 patients with hand swelling associated with BCRL participated. Two novice testers performed three “blinded” figure of eight measurements and three volumetric measurements of the affected hand. In terms of inter-tester and intra-tester reliability, the intraclass correlation coefficients were all greater than 0.8 indicating high intra- and inter-tester reliability for the figure of eight method. For validity, a Pearson moment correlation was used to compare the figure of eight and volumetric methods. The results demonstrated a statistically significant correlation of 0.7 for both testers.

The results from this study, therefore, found the figure of eight method to be a valid and reliable method of measuring hand swelling in this population, even when measurements were made by novice practitioners.

Ten subjects, with hand oedema associated with BCRL, participated in study 2. One tester, who was an experienced lymphoedema practitioner, performed three "blinded" sets of figure of eight measurements, circumferential measurements and volumetric measurements of each hand. These measurements were taken at the start of a course of treatment for lymphoedema management and then again at the end of this treatment course. In terms intra-tester reliability, the intraclass correlation coefficients (3.1) were all greater than 0.9 for each of the measurement methods indicating high intra-tester reliability. For validity, a Pearson moment correlation was used to compare the results from the figure of eight and volumetric methods, and showed a statistically significant and strong correlation of 0.7 between these methods. The Pearson moment correlation between volumeter and circumferential measurement was 0.6 which indicated a good correlation, suggesting this method was also valid. In this study, sensitivity to change in hand size was also considered using the Wilcoxon signed rank confidence interval and, of the three measurement methods, only the figure of eight method indicated a difference in the pre and post treatment measurements. This may suggest this method is sensitive enough to detect change in hand size over time. It was recognized, however, that this study was carried out on a small sample.

Further studies are required to investigate the sensitivity to change in hand size of this method on a larger sample. The study also highlighted the natural variability that occurred in the unaffected hand over the course of the treatment time and therefore, future work to establish the extent of this variability would enable the identification of a clinically significant change in hand size with treatment.

The studies would support the use of the figure of eight method for monitoring hand oedema in patients presenting with BCRL. The early results, albeit on a small sample, indicate that the figure of eight method may be valid, reliable and responsive to change over time. The figure of eight tape measurement method is suitable for all patients, is inexpensive, quick and does not require specialist training.

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Publications and presentations from this work

Borthwick Y., Paul L., Sneddon M., McAlpine L., Miller C. Reliability and validity of the figure-of-eight method of measuring hand size in patients with breast cancer-related lymphoedema *European Journal of Cancer Care* (2013)

Oral presentation - Reliability and validity of the figure-of-eight method of measuring hand size in patients with breast cancer related lymphoedema (BCRL) BLS Annual Conference Manchester October 2010

Oral presentation - Reliability and validity of the figure-of-eight method of measuring hand size in patients with breast cancer related lymphoedema (BCRL) Chartered Society of Physiotherapy Congress Liverpool October 2011

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Author's declaration

I declare that this thesis is my own work. It is being submitted for the degree of M.Sc. (Med) Nursing and Health Care (Research) at University of Glasgow. It has not been submitted for any other degree or examination in any other University.

Definitions/abbreviations

ALA – Australian Lymphology Association

ANC – axillary node clearance

BCRL – breast cancer related lymphoedema

BIS – bioimpedence spectroscopy

BLS – British Lymphology Society

BMI – body mass index

CI – confidence interval

CREST - Clinical Resource Efficiency Support Team

CTEC – Clinical Trials Executive Committee

DoH – Department of Health

DLT –decongestive lymphoedema therapy

DNA - Deoxyribonucleic acid

EBCTCG - Early Breast Cancer Trialists' Collaborative Group

ECF – extracellular fluid

GP – General Practitioner

HCP – health care professional

ICC – intraclass coefficient correlation

ILF – International Lymphoedema Framework

IHTAB – In House Trials Advisory Committee

ISD – Information Services Division

ISL – International Society of Lymphology

IPCP – intermittent pneumatic compression pump

KT – kinesiotape

LF – Lymphoedema Framework

LLLT – low level laser treatment

MCP – metacarpal phalangeal

MLD – manual lymphatic drainage

NHS – National Health Service

NICE - National Institute for Health and Care Excellence

NLN – National Lymphedema Network

RCT – randomised controlled trial

SD – standard deviation

SEM – standard error of measurement

SIGN - Scottish Intercollegiate Guidelines Network

SLD – simple lymphatic drainage

SNB – sentinel node biopsy

SPSS – Statistical Package for the Social Sciences

SRD – smallest real difference

SRM – standardised response mean

SSI – static stiffness index

UK – United Kingdom

YB – Yolande Borthwick

Chapter 1

Introduction

Breast cancer is the most common cancer affecting women in Scotland, accounting for 28% of all cancers in the Scottish female population (World Cancer Research Fund 2013). Breast cancer in Scotland has increased by 13.7% since 2001 to a level that 29.4% of all women diagnosed with cancer in 2011 had breast cancer (ISD Scotland 2013). Although there has been an increase in the number of patients being diagnosed with breast cancer, the mortality rates have fallen by 19.3% over the same period. This means there are a larger number of breast cancer survivors in the population.

One of the side effects of the treatment for breast cancer is lymphoedema. Lymphoedema is a progressive chronic condition resulting in swelling due to an imbalance in fluid homeostasis caused by insufficient lymph drainage which allows lymphatic fluid to collect in the extracellular space (Rockson 2001, Ng and Munnoch 2010). Patients who have received treatment for breast cancer may have lymphoedema of the arm, hand, breast or trunk. The literature varies on the prevalence of lymphoedema resulting from treatment for breast cancer. This is mainly due to there being no standardised methods for collecting the data or making the diagnosis of lymphoedema (Bulley et al 2013 (a), O'Toole et al 2013, Lee et al 2008). However it is estimated that approximately 21% of women who undergo treatment for breast cancer will develop lymphoedema (Bell et al 2013, DiSipio et al 2013, Hayes et al 2012).

Recent research has concluded that by identifying and treating lymphoedema early the management will be more effective (Hayes et al 2012, ALA position statement 2012, NLN position statement 2011, Bernas et al 2010, Morais et al 2009, Stout Gergich et al 2008). Clinicians working with breast cancer patients need to be able to identify patients who are at risk of developing lymphoedema and to have a method of taking accurate measurements to both detect these early changes and to monitor the progression of the lymphoedema.

1.1 Hand measurement

It is common clinically to measure the size of the limb as a method of monitoring the lymphoedema as well as an objective measurement of clinical outcomes from treatment (Lymphoedema Framework 2006). Current clinical practice involves taking circumferential measurements of the arm which can then be used to calculate the volume of the limb by considering the limb as a cylinder. The hand, however, cannot be measured in this way as its shape is not cylindrical. The "gold" standard method of measuring hand size is by water displacement which has been found to be reliable and valid. However, this is not currently used in the clinical setting due to various difficulties associated with this technique, such as the water temperature needs to be kept constant, the tank needs to be filled and calibrated correctly between each measurement, the equipment needs to be cleaned correctly between each patient to ensure no risk of cross infection and also to restrictions for using with patients with wounds. Therefore a simple circumferential measurement is taken. For the circumferential technique, there is no research published to indicate the validity or reliability of this method.

The figure of eight method of measurement of hand size has the potential to be a valuable alternative to water displacement. It requires only a tape measure, therefore no expensive equipment is needed, and it crosses the area of the hand which is most frequently oedematous. The figure of eight method has been proven to be reliable and valid for patients both with and without hand pathology (Maihafer et al 2003, Pellecchia 2003, Leard et al 2004, Dewey et al 2007).

1.2 Aims of this study

The primary aim of this study was to determine whether the figure of eight tape method of measurement was a valid and reliable method of measuring hand size in patients with hand oedema secondary to breast cancer related lymphoedema (BCRL). This was to be investigated by comparing the figure of eight tape method of measurement against the "gold" standard method of water displacement. The secondary aim was to establish whether the figure of eight tape method of measurement would be reliable and valid for novice

practitioners to ensure that the method could be used by any practitioner assessing a patient with BCRL.

If the figure of eight method was found to be valid and reliable for measuring hand volume in this patient group then a further aim was to investigate whether the method was sensitive to change in hand size over time and whether it was as sensitive as the clinically used circumferential method.

1.3 Contents of thesis

Chapter two contains the literature review of the background to breast cancer and its treatment, the link to breast cancer related lymphoedema, along with the current methods of management of lymphoedema.

This thesis describes the two studies which were undertaken.

The first study which investigated the reliability and validity of the figure of eight tape method of measurement compared to the "gold" standard method of water displacement is discussed in chapter three.

Chapter four describes the second study which aimed to establish whether the figure of eight method was sensitive to change in hand size over time and to assess the intra-tester reliability and validity of the circumferential measurement of measuring hand size by comparing it with the "gold standard" approach of water displacement. It also aimed to re –examine the reliability and validity of both the figure of eight method and volumeter method of measuring hand size when used by an experienced lymphoedema practitioner and to validate the results of reliability and validity of the phase one study.

Chapter five concludes the study and reports the clinical implications as well as the areas for future research.

Chapter 2 – Literature review

2.1 Background

2.1.1 Breast Cancer

Breast cancer is by far the cancer with the highest prevalence among women worldwide, with an estimated 1.38 million new cancer cases diagnosed in 2008; 23% of all cancers diagnosed at this time (Cancer Research UK 2013). It is now the most common cancer both in developed and developing regions with incident rates shown to be high (greater than 80 per 100,000) in developed regions of the world and ranks second in all of the cancers reported (10.9% of all cancer) (Cancer Research UK 2013).

Breast cancer ranks as the fifth cause of death from cancer. It is still the most frequent cause of cancer death in women in both developing and developed regions, where the estimated 189,000 deaths worldwide is almost equal to the estimated number of deaths from lung cancer (188,000 deaths) (http://globocan.iarc.fr/factsheets/cancers/breast.asp). Global incidence of breast cancer continues to increase (WHO 2008) and breast cancer survival rates are reported as varying between 40% in low income countries and 80% in high income countries (Khan et al 2012).

In the UK, it is estimated that there are 550,000 people who have had a diagnosis of breast cancer (Breast Cancer Care 2012*)*. There are nearly 50,000 people diagnosed with breast cancer every year in the UK with around 4,000 of these living in Scotland or approximately 1.6% of the population (Breast Cancer Care 2012, ISD Scotland 2013). There was an increase of 13.7% in the incidence of breast cancer in females in Scotland between 2001 and 2011 but also a decrease of mortality in this group of 19.3% over this time period. The five year relative survival of females with breast cancer within the latest data period of 2003 and 2007 is 85.9% (ISD Scotland 2013).

2.1.2 Treatment for breast cancer

Treatment for breast cancer includes surgery, radiotherapy and chemotherapy or a combination of these treatments.

2.1.2.1 Surgery

Surgical intervention is either breast conservation surgery or mastectomy with the surgery depending on the extent and presentation of the tumour as well as being tailored to the patient (SIGN 134). Axillary surgery is required to adequately stage the spread of any metastatic spread and also for the treatment of invasive breast carcinoma. This can be carried out by sentinel node biopsy (SNB) or axillary node clearance (ANC).

In patients diagnosed with breast cancer, metastatic spread to the axillary lymph nodes occurs in approximately 30% of patients. Lymph node status has been used as the strongest predictor of survival for this patient group (Woodward et al 2003). It can also be used to provide the information necessary to determine further treatment. However, the surgery used to investigate the lymph nodes traditionally required an axillary lymph node dissection which is associated with significant morbidity, for example, numbness, pain and lymphoedema. At present other surgical techniques such as SNB and lymphatic mapping are being investigated and performed more widely to avoid these potential problems (Morrell et al 2005, SIGN 134). Sentinel node biopsy attempts to decrease the risk of post treatment complications by minimising the damage to the axilla. The aim is to identify and remove the first tumour draining node in the axilla (SIGN 134). Sentinel node biopsy is the recommended surgical approach to the axilla in the NICE clinical guidelines for early and locally advanced breast cancer (NICE 80).

2.1.2.2. Radiotherapy

Radiotherapy acts by using high energy radiation to damage the DNA of cancer cells. However, radiotherapy can damage normal cells as well as cancerous cells and therefore treatment is planned to minimise side effects (National Cancer Institute 2010, Westbury and Yarnold 2012). Radiotherapy has been shown to reduce the risk of breast cancer recurrence. In a meta analysis of 17 randomised trials, it was shown that the risk of any first recurrence in 10 years was reduced from 35% to 19.3% when radiotherapy was included as treatment (EBCTCG 2011). Radiotherapy would be required if breast conservation surgery is chosen. The morbidity caused after radiation therapy has been attributed to radiation

fibrosis and its effect on normal tissue (Stone et al 2003, Westbury and Yarnold 2012). This fibrosis reduces tissue elasticity as well as hardening and distortion of soft tissues which may result in pain. Radiotherapy has been shown to increase the risk of developing lymphoedema following treatment for breast cancer (Tsai et al 2009) (see section 2.6.2). Due to the changes associated with radiotherapy, the function of the superficial lymphatic system will be affected due to its proximity to the skin surface and its reliance on skin mobility to allow it to operate effectively (see section 2.2.2).

2.1.2.3 Chemotherapy

Chemotherapy uses cytostatic drugs which stop cancer cells from continuing to divide uncontrollably (National Library of Medicine 2012). It has been recommended that adjuvant chemotherapy should be considered for all patients with breast cancer where benefit outweighs risks (SIGN 134).

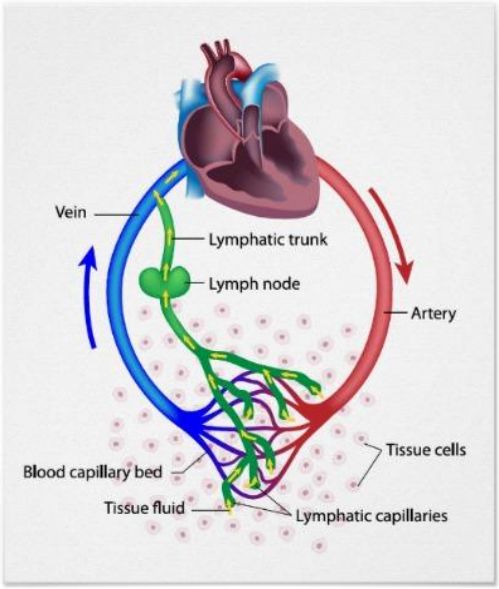
2.2.1 Physiology of the lymphatic system

There are two closely linked circulatory systems in the human body, the vascular system and the lymphatic system (Rovenska and Rovensky 2011, Choi et al 2012).

The primary role of the lymphatic system is the maintenance of fluid homeostasis in the body; it enables the uptake of dietary lipids and vitamins from the intestine and provides the transport route for distribution of immune cells (Schultze – Merker et al 2011, Pal and Ramsey 2011). It drains lymph fluid which contains water, protein, cellular debris, toxins and other macromolecules from the interstitial spaces and returns this to the intravascular circulation (Morrell et al 2005, Warren et al 2007). There is evidence that the lymphatic vessels are not only passive conductors for the immune system but play an active role in adjusting the immune responses (Choi et al 2012).

The lymphatic system is made up of a highly branched network of capillaries and ducts which are present in all organs other than avascular tissue or the central nervous system (Schultze – Merker et al 2011). Differing from the blood vascular system, which is a circular system with the blood leaving and returning to the heart (see Figure 1), the lymphatic system is a linear system which collects

lymph from the interstitial spaces of the tissues and organs and returns this fluid eventually to the blood circulation (Choi et al 2012) .



http://www.shutterstock.com/pic-147789437/stock-photo-fluid-exchange-between-the-circulatory-and-the-lymphatic-systems.html

Figure 1: Relationship between the vascular and lymphatic circulatory systems

If the lymphatic system, composed of superficial and deep lymphatic vessels which collect the lymph fluid (see below), is compromised then drainage of the interstitial spaces will be affected leading to an accumulation of this fluid and swelling resulting in lymphoedema.

2.2.2 Lymph Capillaries

Unlike the blood circulation the lymphatic system, is a one way system which starts with blind ended capillaries, which are the first collection point for lymph fluid, commencing in the interstitial spaces of the tissues and organs (Rovenska and Rovensky 2011). The single layer endothelial cells have overlapping flaps which allow fluid to flow unidirectionally along pressure gradients from the interstitium into the capillary lumen. Unlike blood capillaries, these lymphatic capillaries are not round but are irregularly shaped and are usually collapsed (Alitalo and Carmeliet 2002). There are anchoring filaments which are

connected to the extracellular membrane (see Figure 2) (Negrini and Moriondo 2011). When there is an increase in interstitial pressure these filaments open up the overlapping flaps and allow the lymph fluid to drain into the lymphatic capillaries (Lawenda et al 2009, Rovenska and Rovensky 2011, Schultze – Merker et al 2011, Choi et al 2012).

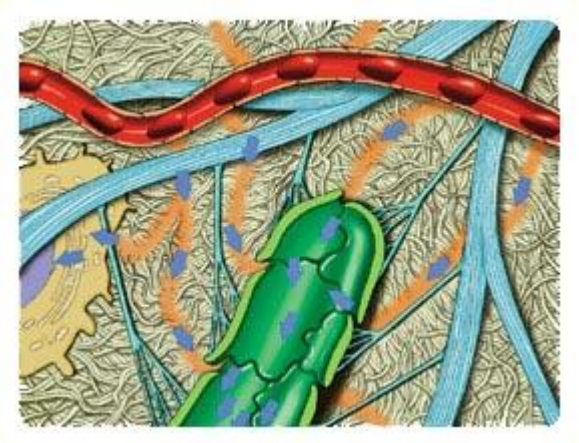


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Figure 2: A lymphatic capillary (green) depicted in the interstitium with the anchoring filaments shown and the single layer of endothelial cells

These small capillaries, which are designed for drainage of lymph, then channel lymph into precollecting and then larger, collecting vessels. As there are no valves in this part of the system the lymph flows from higher to lower pressure (Lawenda et al 2009).

2.2.3. Precollectors and Collectors

Lymph from the capillaries is drained into the precollecting lymphatic vessels which have elements of both the lymphatic capillaries and the collector vessels in that they have lymphatic endothelial cells as well as valves. These lymphatic vessels are designed to transport fluid and the precollectors link the lymphatic capillaries with the collectors (Lawenda et al 2009). Collecting vessels consist of a series of functional units named lymphangions (Witte et al 2006) which are separated by bileaflet valves, similar to those found in veins, which ensure that the flow of lymph is unidirectional. These collecting vessels are covered by a

continuous basement membrane and also by smooth muscle cells (Choi et al 2012). The valves are constructed so that the high pressure pushing the fluid upstream in the lymphatic collector will cause them to open and allow the lymph to flow but any reverse flow will cause the leaves of the valve to close over and prohibit backflow. This flow of lymph therefore requires periodic changes in fluid pressure within the lymphangions. The lymph flow depends on cyclical compression and expansion of the lymphatic vessels by the surrounding tissues as well as the intrinsic pump forces generated by the spontaneous phasic contraction of the smooth muscle within the vessel (Zawieja 2009, Schultze – Merker et al 2011). The sympathetic nervous system, which innervates lymphangions, causes them to contract at a rate of 10 to 12 contractions per minute although there is capacity to increase this if there is increased lymphatic load (Zuther 2005 cited in Lawenda et al 2009).There are also anastomoses between adjacent collectors and these connections allow collateral routes to be utilised when required in cases of increased lymph load (Kubik and Kertz 2006).

2.2.4 Lymph Nodes

There are hundreds of different sized lymph nodes situated around the body (Ellis 2006) and lymph fluid is said to pass through at least one lymph node on its return to the venous circulation (Witte et al 2006). Lymph nodes play an essential role in the immune system. As the lymph enters the lymph node it passes through the connective tissue within the node. This acts to clean the lymph of any bacteria or viruses as the lymph nodes contain specialised white blood cells such as lymphocytes which are a vital component of the immune system (Ellis 2006). The protein content of the lymph may also be modified as it passes through the lymph node with the lymph node acting as a fluid exchange chamber (Witte et al 2006). It appears that the protein concentration can either be diluted or further increased as it passes through the lymph node depending on the relative concentration of the protein content of the lymph prior to it entering the lymph node (Witte et al 2006). After passing though the lymph node, the lymph is collected in new collecting vessels and transported into the larger lymphatic trunks.

2.2.5. Lymph Trunks

Lymphatic trunks transport the lymph to the final vessels in the system, which are the largest ones known as ducts. These trunks also contain valves and a layer of smooth muscle innervated by the sympathetic nervous system (Lawenda et al 2009).

2.2.6 Lymphatic Ducts

There are two main ducts in the body; the right lymphatic duct and the thoracic duct.

The right lymphatic duct transports lymph from the right side of the head and neck, the right arm, the right side of the chest (including the right lung and the right side of the heart) and a small part of the liver. This right lymphatic duct then drains the lymph into the right venous angle which comprises of the right subclavian and the right internal jugular veins (Lawenda et al 2009).

The thoracic duct is the largest of the lymphatic trunks and drains the lymph from all other areas of the body including both lower limbs. This lymph then drains into the left venous angle which comprises of the left internal jugular and left subclavian vein to return it back to the venous blood stream (Ellis 2006). The thoracic duct will drain approximately three litres of lymph in one day (Lawenda et al 2009).

2.3.1 Mechanisms of transport throughout the lymphatic system

The massaging effects of muscle contractions and arterial pulsation, acting as an extrinsic pump, causes an increase in the uptake of the interstitial fluid into the lymphatic capillaries (Witte et al 2006). However, the propulsion of lymph beyond this relies on the intrinsic pump of the larger lymph ducts, carried out by the smooth muscle in the walls of these vessels. As the control mechanism of this is auto regulation, the increased force and frequency of the contraction of the lymphatic vessels occurs in response to the amount of dilatation of the vessels (Witte et al 2006).

The process of fluid movement across the blood capillary walls is explained by principles described by Starling (1896).The blood hydrostatic pressure, the pressure in the circulatory system exerted by the volume of blood when it is confined in a blood vessel, forces fluid into the tissues from the capillary. The colloid osmotic pressure of the blood, which is the pressure exerted by proteins in a blood vessel's plasma that usually pull water into the circulatory system and acts as an opposing to hydrostatic pressure, attracts fluid back into the capillary. Previously it was felt that there was a balance in these forces which meant that as the hydrostatic pressure decreased along the capillary, the forces would change from filtration to reabsorption (Dennis 2008). However, it has now been recognised that the forces do not balance and so there is a net excess fluid flow into the tissues which would normally be drained by the lymphatic system (Levick 2004, Carati et al 2010) (see Figure 3).

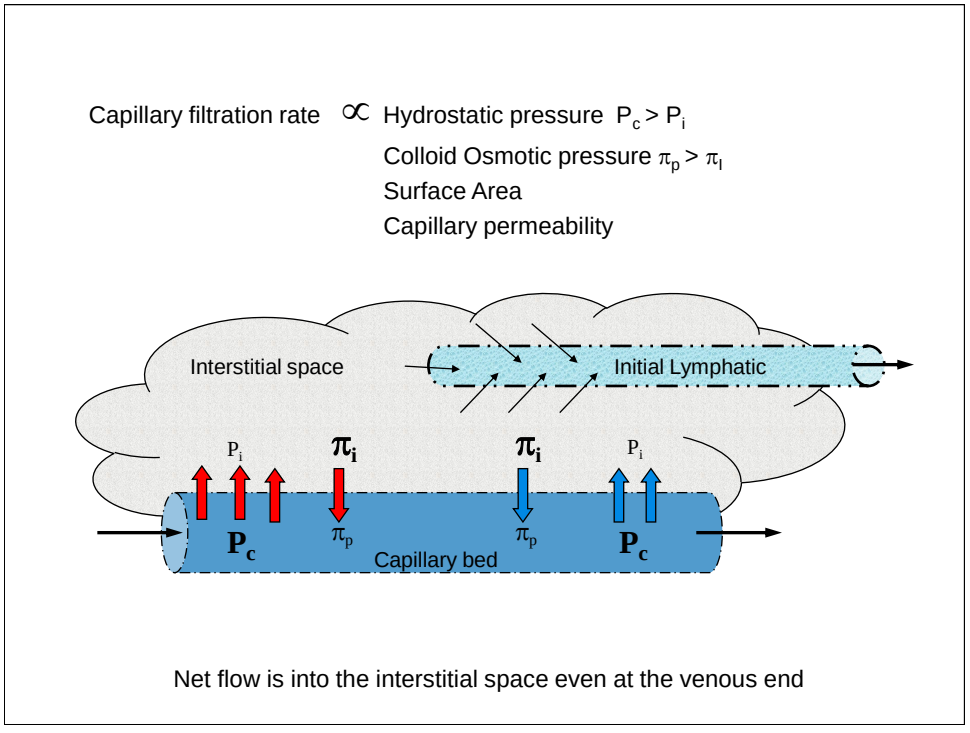

Figure 3: Starling's Hypothesis of Homeostasis P_c=capillary hydrostatic pressure, P_i=interstitial hydrostatic pressure, π_p = plasma colloid osmotic pressure, π_i = interstitial colloid osmotic pressure

One of the largest influences on fluid balance is the venous haemodynamics as these forces will affect the capillary hydrostatic pressure. An increase in venous pressure will cause an increase in capillary hydrostatic pressure and so result in increased capillary filtration which may cause oedema (Dennis 2008).

As the plasma proteins of the blood do not cross the capillary membrane in most cases, they are mainly retained within the vascular system. At present it is considered that there is a complex luminal layer of anionic polysaccharides and glycoproteins which is attached to, and secreted by, probably all endothelial cells of capillaries which is called the glycocalyx. This acts as a fine fibre filter for the larger molecules and influences the colloid osmotic forces which are established across the microvessel endothelium (Weinbaum et al 2003). There are, however, small breaks in the junctional membrane strands at the inter-endothelial cell junctions which would allow fluid leakage. These junctional membrane strands can also act to seal these junctions tightly. Thus it is very unlikely that there is capillary reabsorption in normal circumstances although this may be altered when inflammation is present and there are larger breaks in the endothelium. Therefore the fluid flux through the lymphatic system is much greater than previously thought (Carati et al 2010).

Lymphoedema most commonly presents in the skin and subcutaneous tissues, therefore understanding lymphatic drainage of the skin is important. The skin has a system of initial lymphatic capillaries located in the superficial fatty tissues, which connect with the vertical precollectors (Lawenda et al 2009). The skin is divided into zones which drain into a common lymphatic collector (Carati et al 2010). These adjacent zones, which all drain into a common lymphatic bundle, form territories or lymphotomes. Between these lymphotomes, there are few anastomoses and so these lymphotomes have linear boundaries at the skin which are referred to as “watersheds”. However, the anastomoses between these lymphotomes allow for the flow of lymph across these watersheds in times of increased intra-lymphatic pressure. This is utilised in simple lymphatic drainage and manual lymphatic drainage to encourage movement of fluid from one congested lymphotome to another with less congestion (Mortimer 1995, Lawanda et al 2009) (see section 2.7.6).

The lymphatic system, therefore, utilises two separate systems to provide drainage – the superficial system which drains the skin and subcutaneous tissues and the deep system, which follows the blood vessels, which drains tissues deeper to the fascia (Lawenda et al 2009).

2.3.2 Lymphatic Drainage within the Upper Limb

The superficial lymphatic system for the upper limb is situated within the skin of the upper limb (see Figure 4). The main drainage of the hand is along the palmar surface leading through larger vessels towards the basilica vein. The lymphatic vessels draining the antero – lateral aspect of the arm drain across the upper part of the arm and into the apical lymph nodes in the axilla. The lymph from the posterior – medial aspect of the forearm drains through the nodes at the medial cubital fossa and then into the lateral lymph nodes at the axilla.

The deeper lymphatic system commences at the deeper soft tissue and travels close to the deep veins of the arms arriving at the lateral axillary lymph nodes (Carati et al 2010).

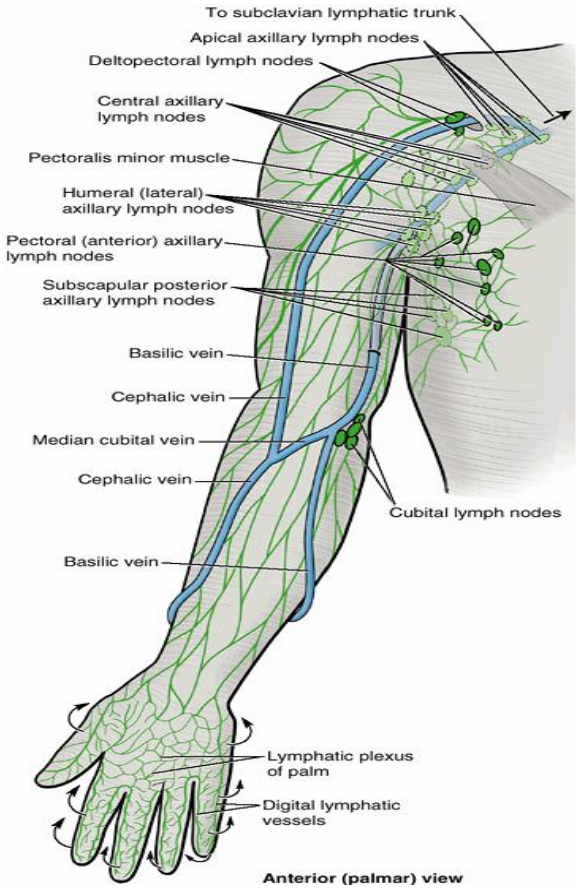

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Figure 4: Venous and lymphatic systems of the hand and arm

2.4.1 What is lymphoedema?

Lymphoedema is a progressive chronic condition characterised by swelling. It usually affects the limbs but can affect any area of the body such as the trunk, head and neck or genitals. Lymphoedema can affect just one area or can result in swelling in many segments. Lymphoedema develops as a result of an imbalance in fluid homeostasis caused by insufficient lymph drainage which therefore allows lymphatic fluid to collect in the extracellular space (Rockson 2001, Ng and Munnoch 2010). Within this lymph fluid there may be plasma proteins, excess water, extra vascular blood cells, parenchymal products and substances (ISL consensus document 2003, Schulte – Merker et al 2011).

This chronic condition affects a significant number of the population, with an estimated prevalence of between 1.33 and 3.99 in 1000 people of all ages in the UK affected by lymphoedema with prevalence increasing in people over the age of 65 (Moffatt 2003, Moffatt 2012). Lymphoedema often has detrimental effects on both physical and psychosocial well being (Lymphoedema Framework 2006).

There is a clinical classification system for lymphoedema defined by the International Society of Lymphology (ISL). Within this system there are 4 classifications, see Table 1, with stage 0 becoming increasingly recognised as assessment techniques are being developed to allow identification of these "at risk" individuals and management strategies commenced much earlier (Lawenda et al 2009, Bernas et al 2010). If the individual at risk can be provided with information about the condition, risk reductions strategies and treated prophylactically it may slow or stop the progression to a more severe condition.

International Society of Lymphology (ISL) lymphoedema staging
ISL stage 0 Latent or subclinical condition. No oedema is evident despite an impaired lymph transport system. May exist for months or years before any oedema becomes evident.
ISL stage 1 An early accumulation of fluid which subsides when the limb is elevated. May have pitting oedema.
ISL stage 2 Pitting oedema is manifest. Unlikely to reduce with elevation.
ISL stage 2 (late) Pitting oedema may or may not occur as there is more fat and fibrosis
ISL stage 3 Pitting is likely to be absent due to the fibrotic tissues and there are skin changes such as thickening, hyperpigmentation and increased skin folds

Table 1. ISL lymphoedema staging (2009 consensus document of the International Society of Lymphology)

Current adopted clinical terminology also describes lymphoedema as complicated or uncomplicated. Complicated oedema refers to any lymphoedema which affects the digits, involves shape distortion of the limb which is calculated using the ratio between the upper segment and lower segment of the limb and any midline oedema or extension of the swelling beyond the root of the limb. Uncomplicated lymphoedema would mean the absence of any of these complications (BLS 2013).

In patients with lymphoedema there is an increase in the density of the lymphatic vessels in the lymphatic cutaneous network. When Mellor et al (2000) examined the upper limbs of women with BCRL with fluoroscopy, it was noted that the density of the superficial lymphatics and the total length of the

capillaries was greater in the oedematous limb compared to the “unaffected limb”. There was no evidence of increased lymphatic dilatation in the swollen limb however and there was a greater distance for the lymph fluid to travel in the affected limb when compared to the unaffected limb. Carati et al (2010) suggest that this is caused by the local re-routing of the lymph and also the increased number of lymphatic capillaries results in a longer length of travel would help to maintain the drainage capacity to filter capacity ratio (Mellor et al 2000). This may impact on clinical treatment in that it may be of importance to assist the drainage, by establishing a pressure gradient along the limb, when the lymphatic fluid is travelling a greater distance (Carati et al 2010).

2.4.2 Differential diagnosis

When there is oedema present, it is important to establish the differential diagnosis of lymphoedema as there may be other causes of oedema. Oedema will occur if there is an increase in fluid in the interstitial tissues whether the cause of this imbalance is due to an outflow problem, such as decreased lymphatic function or due to an inflow problem such as increased hydrostatic pressure. A complete assessment is required to exclude any other potential causes of oedema such as tumour recurrence, deep venous thrombosis or post –thrombotic syndrome (Bernas et al 2010).

Causes of lymphoedema will be discussed further (see section 2.4.3.) but it is important to consider other conditions which will result in oedema formation. Chronic venous insufficiency results in damage to the vessels in the vascular system resulting in increased pressure and increased production of interstitial fluid. Hypoalbuminemia, which decreases the amount of protein within the plasma, alters the relationship between the hydrostatic pressure and the colloid osmotic pressure which causes an increase of fluid in the interstitium resulting in oedema formation (Simonian et al 2008). Some medication will result in the formation of peripheral oedema (see section 2.7.10) due to its action on the hydrostatic pressure within the capillaries or by causing peripheral arteriol vasodilation (Keeley 2008).

It is therefore important to ensure a full and comprehensive assessment is carried out prior to reaching the diagnosis.

2.4.3 Causes of Lymphoedema

Lymphoedema can be categorized as primary or secondary depending on the cause of the abnormal function of the lymphatic system.

In primary oedema, the lymphatic system does not form properly due to a genetic dysfunction (Choi et al 2012) and this may present as swelling at birth or be undetected until later in life when some trigger, often hormonal, will cause the lymphatic system to become unable to carry out its normal function and result in swelling occurring.

There has been progress made in identifying specific genes, such as VEGFR3 and FOXC2, which are associated with congenital lymphoedema for some of the subgroups. Continued efforts are being made to establish new classifications for primary lymphoedema based on various factors including clinical phenotypes, family history, associated abnormalities and underlying genetics (Connell et al 2010).

Secondary lymphoedema is due to some extrinsic cause of damage to what was a normally developed lymphatic system. This could be for example, cancer and/ or its treatment, infection, trauma, venous insufficiency, obesity or immobility (Mortimer 1995).

Lymphatic filariasis is a specific form of secondary lymphoedema and affects more than 120 million individuals with more than one billion individuals in 80 countries at risk of infection (Whitworth and Hewitt 2005). A wide range of mosquitoes can transmit the parasites which then inhabit the lymph vessels, particularly the extremities and male genitalia, and produce microfilarial larvae which circulate in the blood (Taylor et al 2010). The damage to the lymphatic system caused by a combination of obstruction and dilatation of the lymphatic vessels caused by the adult worms, along with the immune response, causes manifestations of chronic infection. The thickening of the skin can lead to secondary infections and elephantitis which at the later stage are irreversible. There are various mechanisms to diagnose the condition through blood results and medication is available to prevent progression to chronic disease. Mass subsidised drug administration programmes are being undertaken which aim to

eliminate filariasis (Hoeraul et al 2011) and the first eight years of these have already reported enormous health and also economic benefits (Chu et al 2010).

In Western Europe, the most common cause of lymphoedema is secondary to cancer treatment following the removal or obliteration of lymph nodes due to treatment such as radiotherapy or surgery (CREST 2008) (see section 2.6.1).

2.5.1 Oedema formation

When the lymphatic load exceeds the maximum amount of transport capacity within the lymphatic system, the lymphatic system becomes overwhelmed and this leads to lymphatic insufficiency or failure (Lawenda et al 2009). If the lymphatic system is compromised then drainage of the interstitium will be affected and the result of this functional overload of the lymphatic system becomes an accumulation of fluid, causing swelling. In experimental models using animals, lymphoedema is produced after a period of months or years if there is disruption of the lymph vessels in the limb (Rockson 2001). There is a theory that a build up of macromolecules in the interstitium causes an increase in oncotic pressure in the tissues which, in turn, causes more oedema (Petrek et al 2000). However, research showed that the protein level in the interstitial fluid in oedematous limbs was lower than non oedematous limbs. This could be explained by the theory that there is an increase in capillary filtration rate due to altered haemodynamics within the limb (Bates et al 1993).

The swelling and build up of protein leads to fibrosis and increases the risk of cellulitis. The valves in the lymphatics also become incompetent due to the dilatation of the lymphatics and this causes further stasis (Rockson 2001). It has been shown through histopathology that, with chronic lymphoedema, there are many changes such as thickening of the basement membrane of the lymphatic vessels, degeneration of the elastic fibres, increased numbers of fibroblasts and inflammatory cells and increased collagen fibres (Ryan and de Berker 1995). All these changes result in progressive subcutaneous fibrosis (Rockson 2001) as well as an increase in the risk of cellulitis. There is an increase in collagen deposition with increased adipose and connective tissue in the oedematous skin and subcutaneous tissues of most patients (Rockson 2001).

Due to the clinical presentation of uneven oedema throughout the affected limb, which is apparent in many cases of lymphoedema, Stanton et al (2006) carried out a study to investigate the lymph flow in women with and without hand oedema. The study was carried out on a small sample of women (n=8) presenting with unilateral moderate to severe hand oedema associated with BCRL. The study showed that the lymph flow was reduced by 34% in the affected hand when compared to the contralateral hand. There was also dermal backflow in the affected hand. This study, when it compared its results with previous similar studies on participants with no hand swelling, suggested that hand swelling results from the failure of the peripheral lymphatics in the forearm or the wrist rather than as a result of decreased lymphatic function at the axilla. It led the authors of this study to suggest that there might be two groups of BCRL patients – hand swollen or hand spared - and furthermore that these symptoms are related to other risk factors such as extent of cancer treatment or age. However, these studies have been carried out on small numbers only. It does, nevertheless, offer an explanation of the clinical presentation seen at lymphoedema clinic where the oedema in the hand does not appear to relate to the treatment approach undertaken for the treatment of the patient's breast cancer.

2.5.2 Skin Changes

Although oedema mainly occurs in the subcutaneous layer, the changes in the skin are more apparent. There are many changes visible on the skin when a patient has lymphoedema. The chronic inflammation within the tissues causes fibrin and collagen to be laid down which make the skin thicker and the skin creases become deeper. This thickening causes the tissues to be less compliant and so the lymphatic system becomes compromised causing the risk of infection to increase (Lymphoedema Framework 2006, International Lymphoedema Framework 2012). The over proliferation of the keratin layer causes hyperkeratosis, scaly brown or grey patches. Papillamatosa, firm raised vessels on the skin, occur as there is dilatation and fibrosis of the upper dermal lymphatics. If this continues untreated then the dermal lymph stasis progresses allowing further changes towards elaphantiasis to occur (Mortimer 1995). Secondary infections, both bacterial and fungal become more common. Lymphangectasia are softer filled projections onto the skin which are also caused

by dilatation of the lymph vessels. These may also produce lymphorrhea, leakage of lymph fluid, and again increase the risk of infection (Lymphoedema Framework 2006).

2.5.3 Increased Risk of Cellulitis

There is an indication that impaired lymphatic function results in poorer local immune responses (Mallon et al 1997). Both blood vessels and lymphatic vessels undergo significant remodelling during chronic inflammation (Wang and Oliver 2010). With each recurrent episode of cellulitis the lymphatic system undergoes further damage causing additional injury to the skin and resulting in increased oedema. With this damage to the lymphatic system there is more "leakage" of proteins into the tissues contributing to the imbalance in the fluid homeostasis. This increase in protein in the interstitial fluid will affect the colloid osmotic gradient and allow more fluid to be attracted into the tissues while, conversely, there is less colloid osmotic plasma pressure - all resulting in further oedema (Carati et al 2010).

2.6 Breast Cancer Related Lymphoedema (BCRL)

2.6.1 Overview

The swelling which occurs in BCRL is the result of excessive accumulation of interstitial fluid due to impairment in lymphatic drainage (Kocak and Overgaard 2000). This impairment could be related to pressure on the lymphatic system from the tumour itself or as a result of the management of the disease. Surgery may disrupt the lymphatic system causing the main drainage routes to be compromised. The oedema associated with treatment for breast cancer is a chronic swelling which may occur in the arm and/or hand, trunk or breast of these patients.

Lymphoedema may develop from the first few months, or up to 20 years, after receiving axillary lymph node surgery and/or radiation therapy (Petrek et al 2001). The incidence of BCRL is not certain but it is suggested that 3-15% of women who have undergone a sentinel lymph node biopsy (increasing up to 49% following axillary dissection) may develop lymphoedema (Sener et al 2001, Ronka et al 2005, Norman et al 2009). A prospective study by Norman et al

(2009) demonstrated a five year cumulative incidence of lymphoedema in 42% of women with the majority of these women (89%) developing their lymphoedema within the first three years. Bevilacqua et al (2012) also found that the incidence of lymphoedema following treatment for breast cancer increased in a linear manner for the first three years and then reduced after this time, but they reported a five year cumulative incidence of 30.3%. In a 20 year longitudinal study 77% of those that developed lymphoedema reported that the onset occurred within the first 3 years and then BCRL appeared to present at a rate of 1% each year after this (Petrek et al 2001). A shorter prospective study carried out by Clark et al (2005) on a sample of 188 women, actually found that 80% of the women who developed lymphoedema post surgery did so within the first year post surgery. However, the exact incidence is difficult to determine due to different diagnostic criteria for lymphoedema, different study populations, and different methods used to measure lymphoedema (National Cancer Institute 2007, Park et al 2008, Megens and Harris 1998).

Breast cancer related lymphoedema may cause reduced range of movement in the affected limb, impaired functional ability, physical disfigurement, pain and skin problems, as well as anxiety, depression and overall poorer quality of life (Park et al 2008, Ahmed et al 2008, Ridner 2005, Thomas –McLean et al 2005, Thomas – MacLean and Miedema 2005, Clough – Gorr et al 2010). In some cases it predisposes to severe cellulitis which may require hospitalisation (BLS consensus document 2013, Halpern et al 2008). The evidence base for the management of BCRL is limited however the consensus document 'Best Practice for Management of Lymphoedema' published in 2006 recommends complex decongestive physiotherapy which involves a combination of manual lymphatic drainage, compression, advice on skin care and exercise (Lymphoedema Framework 2006)(see section 2.7.1).

Often patient with BCRL will report symptoms of heaviness and mild discomfort in the limb or hand. They may have noticed tightness in clothing or jewellery. Patients may be able to report or recognize changes occurring before there is a measurable difference in limb volume to assist in a diagnosis (Norman et al 2009, Czerniec et al 2010). This latent stage of lymphoedema may exist for years before measurable oedema is present (ISL 2003).

In order to establish a diagnosis of lymphoedema a thorough assessment should be undertaken (Lymphoedema Framework 2006). Diagnosis of any other causes of swelling should be excluded or investigations undertaken to clarify the cause (Warren et al 2007).

Often however, BCRL is not identified or addressed by the health care professional (HCP). In the study by Ahmed et al (2008), of the patients who had signs and symptoms, 92% had not been identified with BCRL and were receiving no treatment.

Over 80% of breast cancer patients are predicted to survive 5 years (ISD Scotland 2013). As there is a continued increase in survivorship following breast cancer this will have an impact on the importance of addressing the associated morbidities following treatment and the impact these have on the quality of life and function for this patient group.

There is some debate within the literature surrounding the changes which occur with both the vascular and the lymphatic system following treatment for breast cancer. There is discussion as to whether there is an increase in the arterial inflow to the lymphoedematous arm and whether this will result in an increased fluid filtration which would increase the risk of developing lymphoedema. This is not conclusive as some studies have reported as much as a 42-68% increase (Carati et al 2010) but Stanton et al (1998) found no increase in blood flow. In cases where no increase was detected, this would indicate a decreased flow in reality as there is a larger relative arm volume (Stanton et al 1998). Kuhl and Molls (1995) suggest this change in arterial flow could be a result of damage to the innervation of the autonomic nervous system of the limb resulting from the surgery or perhaps consequence of radiotherapy.

There is some evidence that the venous outflow in a lymphoedematous limb may be decreased demonstrating venous obstruction (Carati et al 2010). This would influence the lymphatic load as any venous obstruction would cause an increase in capillary hydrostatic pressure which would result in increased fluid filtration into the tissues.

2.6.2 Risk factors associated with BCRL

It has been identified that mastectomy, extent of the axillary node clearance, radiation, and presence of positive nodes all increase the risk of developing lymphoedema (Tsai et al 2009,Card et al 2012). However, these risk factors associated with treatment may be unavoidable.

It is has not been established what radiation related pathophysiological changes occur to cause lymphoedema, but it may be related to fibrosis of the soft tissues and also depletion of the lymphatic vessels (Senkus-Konefka and Jassem 2006, Avraham et al 2010). It is unclear whether this fibrosis is triggered or exacerbated by repeated infections that are difficult to eliminate due to the lymph stasis and also the impaired lymphatic proliferation response which appears to be precipitated by the radiotherapy (Meek 1998). A systematic review, which aimed to identify the upper limb morbidities experienced after surgery and radiation in the treatment of early breast cancer, found that lymphoedema was reported more frequently following radiotherapy then when there had been no radiation (Lee et al 2008). However, there were varying definitions, including self report, used to report lymphoedema across the published work included in the review. The systematic review highlighted that although there are a number of studies which contribute lymphoedema to post radiation affects, the measurements and treatment protocols are not consistent which makes it difficult to draw definite conclusions. Lee et al (2008) identified evidence that if radiation excludes the axilla there may be less morbidity affecting the upper limb post radiotherapy. In a recent study, Johansen et al (2014) investigated the relationship between arm and shoulder morbidity after surgery and radiotherapy in 183 breast cancer patients. The results demonstrated that there was swelling in the arm along with other morbidities but the association between radiotherapy related parameters and these clinical findings were not strong, suggesting that the morbidities may be due to the combination of surgery, chemotherapy and radiotherapy as multiple treatments.

Radiotherapy appears to increase the risk for the development of lymphoedema but this may also be due to radiation therapy being given to patients with a higher number of positive nodes (Tsai et al 2009). Increased involvement of lymph nodes has been recognised as an increased risk for developing

lymphoedema (Morcos et al 2014) so it is difficult to distinguish between these factors with the research currently available.

There are however, other risks factors which could be controlled or avoided such as obesity (Swenson et al 2009, Ridner et al 2011, Card et al 2012, Di Sipio et al 2013) or weight gain after diagnosis, upper extremity infection, injury or trauma, overuse of the arm and air travel (Clark et al 2005). In a study investigating the risk of developing breast cancer related lymphoedema (BCRL) following breast reconstruction after surgery for breast cancer management, a comparison was carried out between patients receiving an immediate reconstruction and those having mastectomy only. It was shown that patients following reconstruction had a statistically significant reduced incidence of BCRL and also a delayed time for those who did develop BCRL, compared to the mastectomy only group (Card et al 2012). The study presented the possibility that the reduced incidence of BCRL was due to the transferred vascular tissue bridging the damaged lymphatics which is also linked to lymphatic regeneration and spontaneous anastomosis (Card et al 2012). However, due to the difficulty in defining risk factors and the complexity of the lymphatic system, it is difficult to predict which breast cancer patients will develop BCRL (Fu and Rosedale 2009).

A systematic review and meta – analysis of the incidence of BCRL (DiSipio et al 2013) aimed to update the evidence on treatment related risk factors and identify the impact of non treatment related risk factors. This systematic review recognised there was evidence that having an axillary lymph node clearance made the possibility of developing BCRL four times greater than after sentinel lymph node biopsy. There was also substantial evidence of increased risk with extensive surgery, high BMI, adjuvant therapy and low physical activity. The study recognised that preventative strategies should be targeted at these areas and effective management should aim to decrease these factors.

A further factor contributing to the increased risk of lymphoedema following treatment for breast cancer may be an alteration in lymph outflow. Stanton et al (2009) investigated the lymph drainage in the muscle compared to that in the subcutis and reported that patients who had higher subcutis drainage went on to develop lymphoedema. This study investigated 36 women who had recently had axillary surgery for treatment of breast cancer, with no lymphoedema, and

measured lymph flow in the forearms and subcutis. This was then repeated two and a half years later when some of the participants had developed BCRL. The conclusion was that some patients who had received axillary surgery, as part of their treatment for breast cancer, had increased filtration rates and so had increased rate of lymph flow at the axilla. This would increase the risk of developing lymphoedema as they would have less lymphatic reserve following surgery to cope with this increased lymphatic load.

Recent research has questioned whether there are physiological changes which occur after treatment for breast cancer which may result in increased risk of developing lymphoedema (Carati et al 2010). Arterial flow has been shown to be increased in some patients who have developed lymphoedema in their upper limbs subsequent to treatment for breast cancer (Carati et al 2010), although this was disputed by Stanton et al (1998) who felt that there could be a reduction in blood flow in the affected arm when the larger volume of this limb was considered. It is not clear why there may be a change in the arterial flow after breast cancer treatment but an increased arterial flow may result in increased fluid filtration to a compromised system and may increase the risk of developing lymphoedema (Dennis 2008, Carati et al 2010). Compromised venous flow has been shown in lymphoedematous upper limbs and this may also result in increased capillary hydrostatic pressure which in turn causes an increased risk of lymphoedema (Svensson et al 1994, Dennis 2008).

2.6.3 Prevalence

Obtaining accurate figures for prevalence of lymphoedema is difficult as there is a wide variation in the literature with lymphoedema developing in 10-56% of patients who have had surgery and radiotherapy and in 0-23% of patients following sentinel node biopsy (Kwan et al 2010). This wide range of results is due to the many different methods of defining and diagnosing lymphoedema within the various studies. A recent study by Bulley et al (2013a) examined different methods of measuring and classifying lymphoedema in order to estimate prevalence of lymphoedema after treatment for breast cancer. The study found poor agreement between subjective and objective methods of measurement with the highest prevalence estimated when using an objective measurement method, but it recognised that lymphoedema is multifaceted and

so requires measurement methods that recognise this. It was concluded that between 20-25% of women developed BCRL but recommended that further research is required to establish which measures would enable comparisons to be made between different studies of prevalence.

A systematic review and meta – analysis of the incidence of BCRL (DiSipio et al 2013), which included research articles published between 2000 and 2012, aimed to provide evidence of the incidence of BCRL as well as identify the impact of non treatment related risk factors and update the evidence on treatment related risk factors. All published English, and non-English with translation, research studies related to incidence, prevalence and risk factors for BCRL were considered but only studies on female patients with unilateral breast cancer and no metastatic disease were included in the systematic review. Studies were included if the participants had a clinical diagnosis of lymphoedema or self reported swelling but not if they reported multiple symptoms, such as heaviness which may have indicated lymphoedema, but no swelling. Studies with measurements taken at three months post treatment were not included in case any oedema detected at this time was post surgical oedema. 398 potential articles were identified but only 79 met the inclusion criteria. From this the incidence for development of BCRL following treatment for breast cancer was determined to be 21%. The studies which reported the highest incidence of lymphoedema were those which used more than one method of measurement whereas the lowest reported incidence was in the one study which had used lymphoscintigraphy. There was increased incidence in the first two years after treatment but this rate then slowed after this time period. However, it was also recognised that the data may not be complete due to the difficulty in recording BCRL as it moves from an acute to chronic condition, and so it may make the estimated incidence low.

2.6.4 Diagnosis

The diagnosis of lymphoedema relies on a comprehensive assessment which includes clinical presentation, past medical history and familial history as well as objective findings. Often it is the patient who first identifies signs of lymphoedema, whether this be through noticing changes in clothing or jewellery as it becomes tighter due to the increase in size of the part affected or changes

in their skin with it becoming tighter or harder. There may also be change in the range of movement or dexterity of the fingers (Gerber 1998). These early changes may be an indication of a change in the pressure in the interstitium even though at this early stage this is not measurable (Kosir et al 2001). Armer et al (2003) suggested that self reported instances of "heaviness in the past year" and "swelling now" were predictive of lymphoedema. Their study used bilateral circumferential measurements and also a structured interview tool to explore the symptoms of lymphoedema. To establish which symptoms were predictive of lymphoedema, the study was carried out with a control group of healthy women and a group of patients with lymphoedema to see if the data collected could predict to which group the subject belonged (lymphoedema group n =40, control group n= 40). The symptoms which were highly reported by patients with lymphoedema were rarely reported by the control group e.g. "heaviness in the past", "swelling, now" and "numbness now". It was felt that these three symptom descriptions distinguished between healthy subjects and those with lymphoedema. The study was then carried out on a group of patients who had been treated for breast cancer (n=100) to assess whether the patients who had the self reported symptoms reported above also had larger circumferential differences. The results showed that the patients with the symptoms of "heaviness in the past year" and "swelling now" had a significantly larger difference in the measurements (p values 0.0279 and 0.0007 respectively). Armer et al (2003) have therefore suggested that these reported changes could be an early indicator of the development of lymphoedema.

Lymphoscintigraphy may be used as a diagnostic tool to identify lymphoedema and is conserved to be the "gold standard" for the diagnosis of lymphoedema (Rockson 2001). A radiopharmaceutical, linked to a filtered sulphur colloid, is used as, due to its size, it will be taken up preferentially by the lymphatic system (Bernas 2010).This radiolabelled macromolecular tracer is injected into the subdermal, interdigital region of the limb being investigated. The progress of this radiolabelled macromolecule through the lymphatic system can be monitored by a gamma camera. This allows the major lymphatic trunks and lymph nodes to be visualised and the time it takes for the lymphatic transport to be recorded. Common abnormalities detected would include absent or delayed transport of the tracer, absent or delayed visualization of the lymph nodes or

backflow (Rockson 2001). Clinically, this technique tends to be used when there is no history of trauma to the lymphatic system and so there is doubt of the cause of the oedema and the results of the lymphoscintigraphy would establish a confirmed diagnosis. In BCRL there tends to be a clear history of trauma to the lymphatic system and so lymphoscintigraphy would not generally be necessary.

Diagnosis is therefore often established by the accumulation of the information from the clinical assessment; the patient's presenting history, medical history, signs and symptoms and objective clinical measurements.

2.6.5 Signs and Symptoms

Patients may present with a feeling of heaviness or tightness in the arm or hand. There may be a feeling of restricted movement. The oedema may also affect the adjacent area of the trunk. However, severe pain should not be a symptom of lymphoedema and there should be no alteration to colour or temperature of the limb or hand. As there is a lifelong risk of developing lymphoedema following treatment for breast cancer there is no time limit on presentation. However, a thorough assessment should always be carried out to exclude any other reason for the oedema such as cancer recurrence or thrombosis (Lawenda et al 2009).

2.6.6 Functional Implications

The increase of size of the limb, or the breast to some degree, may result in various changes which will have an effect on function and quality of life (Schmitz et al 2009(a)).

Lymphoedema is associated with a lifelong increased risk of developing cellulitis (Schmitz et al 2009(a)). Further complications of developing lymphoedema include decreased range of movement, pain, fibrosis and negative body image (Mayrovitz 2009a).

There may be decreased range of movement in the upper limb or decreased muscle strength. There is some evidence to show that women treated for breast cancer develop pectoralis tightness and the risk of developing this is increased following mastectomy or radiation therapy. The possibility that patient's endeavour to protect their surgical sites by thoracic flexion and scapular

protraction may also contribute to this muscle tightness (Yang et al 2010). Any condition which affects the range of movement at the shoulder joint will potentially have a detrimental effect on the function of the limb. As the muscle pump is one of the main mechanisms for moving lymph through the body, any decrease in muscle contraction will have a detrimental impact on lymphatic function (Mortimer 1995, Swartz 2001).

Due to the size or weight of the affected limb or the breast area, patients can no longer wear the clothing which they would prefer. The increased weight may cause the patient to reduce the activity they carry out with the limb which will affect their muscle strength. Also if the limb is sufficiently oedematous, it may impact on the range of movement available. There may be changes required in the manner they carry out household tasks or in their work or leisure activities and hobbies.

2.7 Background to the management of lymphoedema

There is no relationship between the treatment methods used for the management of breast cancer and the possible measurement issues or restriction on measurement of hand volume. Also, as this study was concerned with investigating a method of measurement only, rather than considering outcomes of treatment or assessing management methods, the treatment which had caused the hand oedema was not of particular relevance. However, these sections are included as background information on lymphoedema treatment to ensure the understanding of lymphoedema management.

2.7.1 Treatment of Lymphoedema

As lymphoedema is a long term condition, it is of extreme importance to empower the patient to be able to self manage their condition and to be aware of when and how to seek advice when intervention is required.

As the aim of treatment for lymphoedema is management rather than cure, any interventions which will help reduce known risks as well as education to assist in prevention are extremely important. Early detection and intervention are

beneficial rather than waiting for the condition to progress before management is instigated.

"Gold standard" treatment for lymphoedema consists of four elements; skincare, compression, exercise and massage (Huang et al 2013, Lymphoedema Framework 2006). The aim of treatment is always to decrease the excess limb volume as much as possible and then maintain it at this volume along with empowering the patient to be self caring, as able, and to achieve maximum potential function (Lawenda et al 2009). This treatment is usually considered to be divided into two phases - intensive therapy lead treatment which is decongestive lymphoedema therapy (DLT) or phase one, and maintenance phase or phase two which is patient led and ideally involves the patient self managing (Lymphoedema Framework 2006, Lasinski et al 2012). For effective treatment and good outcomes it is important that the patient is an active participant in management and that they are involved in the goals set around management and outcomes.

DLT consists of all the elements of care including some form of multilayer short stretch compression bandaging as well as manual lymphatic drainage (MLD). This intensive phase takes place over 2-3 weeks and usually involves attendance at an outpatient clinic. The aim of this phase is to reduce the size of the limb or affected area and to achieve the maximum fluid loss (Chang and Cormier 2013).

Phase 2 or maintenance phase contains all four elements of treatment but enables the patient to self manage. Compression is in the form of a graduated compression garment or a compression wrap, which the patient can apply themselves. The MLD is replaced by simple lymphatic drainage (SLD) which the patient, or their carer, carries out independently of the therapist. The patient then performs their individualised programme of care on a daily basis. Although the evidence to support DLT is only of moderate strength due to the lack of randomised controlled trials (RCTs), trials with adequate sample sizes and follow up and well controlled interventions, a systematic review of the published evidence between 2004 and 2011 has concluded that, particularly in BCRL, DLT is effective in reducing lymphoedema (Lasinski et al 2012). The review focused on original research on DLT as well as MLD (see section 2.7.6) and compression bandaging (see section 2.7.4.1) as a separate treatment components. There

were 99 articles related to lymphoedema management reviewed but only 26 of these studies met the inclusion criteria, with 12 of these studies focusing on BCRL only. It was recognised that the level of evidence was only of moderate strength mainly due to there being few RCTs with the interventions well controlled, objective outcome measurements and control groups. Many of the studies had small sample sizes, different protocols and definitions of lymphoedema, lack of blinding across assessors and participants, and different measurement methods. This made it difficult for the reviewers to make comparisons across the studies. However, the studies investigating BCRL had the advantage that, as BCRL is often a unilateral presentation, the unaffected limb can act as a control, there is a clear aetiology and also a larger sample group. This allowed more comparisons to be made and the conclusion that DLT is effective in reducing lymphoedema in this group, although it is recognised that there is still little evidence to support the role of each component or what factors have an impact on the efficacy of treatment (Lasinski et al 2012).

2.7.2 Advantages of early detection and management

Many of the strategies for risk reduction have been derived from anecdotal evidence, expert opinion, clinical experience and theories based on pathophysiology rather than high quality research.

The importance of information provision and education for patients to improve the efficiency of self management strategies has been well recognised in coping with long term conditions. Patients require information to achieve an understanding and have knowledge regarding their condition in order to make decisions and develop coping strategies to assist with self management (Fu et al 2009).

When considering reducing risk, the patient needs to be informed in several areas. Activities and behaviours which are recognised as potentially linked to exacerbating or triggering lymphoedema, such as insect bites or suddenly increasing the exercise load, should be avoided where possible (Lymphoedema Framework 2006). The patient needs to be informed about possible signs and symptoms or changes which they could monitor as early signs of the development of lymphoedema and they should also be aware of how to facilitate

early evaluation by an appropriate health care professional if they suspect the onset of lymphoedema (Mayrovitz 2009 b).

Patients should be well informed about the signs and symptoms of infection and what they should do if an infection develops. Any risk of injury should be kept to a minimum to reduce the chance of infection. There has been some evidence that there is increased incidence of lymphoedema following infection or cellulitis. In fact, Bevilacqua et al (2012) stated that infection was an independent risk factor for the development of lymphoedema in breast cancer survivors.

Patients value and adhere to information provided by nurses rather than the information they have sourced externally by themselves (Sherman and Koelmeyer 2011). Therefore, it is important that HCPs have awareness of lymphoedema and current management of the condition to be able to provide appropriate and correct information and support.

Women with risk of developing lymphoedema following treatment for breast cancer find it difficult to adhere to the risk reduction advice that requires daily changes of lifestyle, for example, wearing gloves for household duties to avoid risk of trauma. Conversely the more sporadic changes in lifestyle, such as avoiding venepuncture in an “at risk” limb, are easier to adhere to, along with those which can be included in daily grooming such as skin care (Sherman and Koelmeyer 2011).

There are also studies which demonstrate a link between increased risk of developing BCRL and obesity. Sagen et al’s (2009) study investigated the influence of physical activity on the likelihood of developing lymphoedema following treatment for breast cancer. One of the findings was that having a BMI of over 25kg/m^2 preoperatively represented a significant risk factor for developing lymphoedema at 2 years post treatment. Swenson et al (2009) also found that being overweight was a significant predicator of developing breast cancer related lymphoedema and now other studies have identified this link (Helyer et al 2010, Swenson et al 2010, Ridner et al 2011, Bevilacqua et al 2012, DiSipio et al 2013).

Patients should be encouraged where possible to approach risk reduction from a holistic point of view. By maintaining a healthy diet and exercise regime so risks associated with obesity and other co morbidities, such as hypertension and diabetes, are well controlled with the benefits of healthy living assisting in general health and function as a positive gain.

2.7.3 Skin Care

As skin acts as a barrier to the outside world it is very important for this patient group that the skin is kept intact to help reduce the incidence of cellulitis. The skin is also subject to changes in lymphoedema which may be due to the normal physiology, including the mechanisms for delivering nutrition to the skin, being altered (International Lymphoedema Framework 2012). As a result the skin is often drier in lymphoedematous limbs than in normal limbs. Typical skin changes in lymphoedema are hyperkeratosis and papillamotosa which again result from altered functioning of the skin. There is also an increased risk of lymphorrhea which in turn increases the risk of further skin damage or cellulitis (International Lymphoedema Framework 2012).

This requires that the skin is kept intact and well moisturised. Skin care should involve meticulous hygiene and daily moisturising.

Breaks or punctures, including venepuncture, to the skin should be avoided to reduce the risk of cellulitis. Although there is little evidence to support this it is accepted that, rather than cause potential harm, it is best to avoid the risk to a patient where possible. This would be the same for blood pressure monitoring where there is a risk that the cuff when inflated could occlude superficial lymphatics. The same theory is used to discourage patient from wearing tight or constrictive clothing or jewellery. Patients are encouraged to protect their skin when carrying out activities which could potentially result in harm, such as gardening or using household cleaners. Extremes of temperature are generally discouraged as this causes changes in the vascular circulation which in turn alters the lymphatic flow. Much of this advice regarding risk reduction is anecdotal or standard clinical practice based on physiological theoretical principles rather than based on researched evidence.

2.7.4 Compression

Compression is considered to be the main stay of lymphoedema treatment and it is the most important component of treatment (International Lymphoedema Framework 2012). It may be used in all phases of management from prophylaxis, treatment and long term management (Carati et al 2010). Compression therapy utilises a wide range of techniques which include compression garments or multilayer bandages and intermittent pneumatic compression devices.

The aim of compression garments on the limb is to reduce the fluid influx into the tissues. The increased interstitial pressure resulting from the graduated compression applied by the garment causes a reduction in the pressure gradient between the capillaries and the interstitium. This, in turn, decreases the amount of fluid being forced out of the capillaries into the tissues and will reduce the amount of oedema formation (Carati et al 2010).

Compression garments are constructed with a graduated compression which is at its highest distally and reduces through the remainder of the garment. There are various options for the compression class of garment provided depending on the requirements of the patient. Various fabrics are also available to assist in the provision of a garment which is both comfortable and practical for the patient but also effective in treatment of the lymphoedema. The clinician can make a decision on the style of garment as well as the structure of the garment, all of which will affect the garments performance due to the different properties and provide benefits according to the patients' individual needs. It is important that the fit of the garment is correct to allow for the graduated compression to be applied appropriately throughout the length of the limb (Carati et al 2010). Low compression class garments for patients identified with subclinical BCRL have reduced the progression to more significant levels of BCRL (Stout Gergich et al 2008).

Along with the graduated pressure within the garment, another important factor is the stiffness index of the fabric. The most commonly used index to measure this is the Static Stiffness Index (SSI) which is the difference in the interface pressure at the medial gaiter area when standing minus the pressure in the supine position (Mosti et al 2008). This describes the ability of the compression

device whether it be a garment or bandages to counteract the effects of gravity when the user is upright. The current understanding indicates that the flexibility of the material used in garments may provide another element to the control of the oedema (International Lymphoedema Framework 2012, Mosti 2013). During exercise, muscle contraction results in a temporary increase in tissue pressure as they work against the "casing" of the garments. This increased tissue pressure will cause the adjacent dermal lymphatics to compress, cause the valved larger lymphatics to passively pump and in doing so move the lymphatic fluid proximally through the limb (Carati et al 2010). The stiffness of the fabric then allows some increased resistance to the stretch on the skin and also some counter pressure to muscle contraction may benefit the muscle pump and so result in an increased flow in the lymphatic system. This in turn, would decrease the excess fluid in the interstitium. Further research is required in this area.

2.7.4.1 Multilayer Bandaging

Multilayer bandaging may be required during the intensive phase of treatment. It may be necessary prior to fitting garments due to various factors such as poor limb shape, fragile skin, fibrotic tissues and lymphorrhea or wounds. However, the long term aim would always be for the patient to be supplied with compression garments to allow independence from the health care professional.

Multilayer bandaging traditionally acted in the same way as compression garments. Bandages were applied in a graduated compression over padding which ensured an even conical shape and created a uniform distribution of pressure around the limb (Mosti et al 2008). This was based on the theory of the Law of Laplace which considers the relationship between the transmural pressure difference, wall tension and the radius of the curvature of a concave surface (Medical Dictionary 2013).

This is expressed for a cylinder as

$$\Delta P = T/R$$

pressure difference (ΔP), wall tension (T), and radius of curvature (R) in a concave surface

This has been adapted to apply to the pressures associated with compression bandaging:

“sub-bandage pressure is directly proportional to bandage tension but inversely proportional to the radius of curvature of the limb to which it is applied” (Thomas 2003).

This adaption by Thomas (2003) shows the importance of the various elements of the bandaging materials, such as bandage width, number of layers in relation to the circumference of the limb, to provide a graduated compression throughout the limb with the highest pressure distally.

Laplace’s Equation (adapted by Thomas 2003)

$$P = (T \times N \times 4620) \div (C \times W)$$

P = sub-bandage pressure (mmHg), T = bandage tension (kilograms force – kgf), N = number of layers, C = limb circumference (cm) W =bandage width (cm)

The theory behind the graduated compression bandage is similar to the garments in that the increase in interstitial pressure would result in a change in the pressure gradients and so limit oedema formation (Lasinski 2013). However, by using short stretch inelastic bandages there is a high working pressure, when there is muscle contraction, and a low resting pressure (Lasinski 2013). This results in a more comfortable compression for the patient as during rest there is little additional pressure on the limb but when exercising there is an increase in the assistance provided to the muscle pump which would in turn increase the activity of the lymphatic system (Mayrovitz 2009b).

A newer bandaging system is now being used in treatment of lymphoedema which does not utilise the graduated system. Instead of padding to make a uniform conical shape, the bandages are applied on the limb in the shape that it presents. The padding is much thinner but it is short stretch bandages which are applied over the top of this to make a firm casing. The principal behind this system of bandaging is to apply the Pascal’s Law which states

“that when there is an increase in pressure at any point in a contained fluid, there is an equal increase at every other point in the container” (Schuren and Mohr 2010).

In this case, the fluid is considered to be a muscle or muscle group and the closed container the fascia and the compression bandaging (Schuren and Mohr 2010).

Both bandaging systems result in a firm case on the limb which results in less flow of fluid to the interstitium and more activity in the lymphatic system due to the assisted muscle pump. However, multilayer bandaging requires a significant level of commitment from the patient. It is disruptive to normal lifestyle, especially for those patients who require their hand to be bandaged as function will be impaired to some degree due to the bandaging. It is difficult, even with the newer less bulky system, to hide the bandaging so more attention is drawn to the limb and clothing will be a consideration due to the increased size of the limb with the bandaging making applying normal clothing difficult. Bandaging can have a considerable impact on the patient's lifestyle including their occupation.

2.7.4.2 Intermittent Pneumatic Compression Pumps (IPCP)

Intermittent pneumatic compression pumps (IPCPs) are used in many clinics as an adjunct to DLT. The device consists of a series of chambers which inflate and deflate sequentially to a preset pressure. Previous older models were single chamber devices but these are no longer advised as there were concerns that the fluid may be moved to areas already swollen or accumulate at the root of the limb. The IPCPs work by decreasing capillary filtration and also applying a pressure similar to the muscle pump (Chang and Cormier 2013).The aim is for the action of the IPCP to mimic the effects of MLD.

A study carried out by Szuba et al (2002) investigated the use of the IPCP in conjunction with DLT with patients with BCRL in a small randomised control trial. The first phase of this trial recruited 23 patients who were randomised to either a treatment group with DLT plus IPCP or a control group who had standard DLT only. The results showed a greater reduction in volume for the treatment group compared to the control group (mean percentage reduction 45.3% compared to 26% $P<0.05$) but the results at 40 day follow up were not statistically significant (mean percentage reduction 30.3% compared to 27.1%). The second phase of the study continued to use the IPCP independently

alongside the patients' normal self management and demonstrated a further average loss of 29mls in volume. It was concluded from the study that IPCP can be used safely and effectively in patients with BCRL. The authors also felt that as it was easy to apply, it may have wider use for this population than is currently used clinically, although it was admitted that this was a small study sample.

In the systematic review of the evidence for IPCP carried out by Chang and Cormier (2013), there were no clear guidelines regarding pressures to be used or the optimal length of treatment time. However, the evidence indicated that, as part of a lymphoedema management plan, it may be valuable but should only be prescribed by lymphoedema practitioners who have received specialist training. Monitoring was also important to ensure there was no increased oedema or fibrotic changes at the root of the limb. It was recognised, however, that it may be beneficial for patients who are unable to receive MLD or to assist in self management in conjunction with DLT.

2.7.5 Exercise

Until recently it was argued that patients with, or at risk of, developing lymphoedema should avoid any strenuous activity. This advice was based on the theory that the physiological changes which occur during exercise result in an increased blood flow, which would necessitate an increase in lymph formation and so a potential increased risk of lymphoedema (Harris 2012, Schmitz et al 2009(b), Petrek et al 2000). Although there was no evidence to substantiate this theory, it was widely adopted and caused patients to avoid activity due to concerns that this may induce or exacerbate lymphoedema (Lee et al 2009, Chang and Cormier 2013). More recent evidence, particularly for patients following treatment for breast cancer, demonstrates this is not necessarily true and strenuous activity does not need to be avoided (Harris and Niesen – Vertommen 2000, Lane et al 2005, Hayes et al 2009, McNeely et al 2009, Sagen et al 2009, Schmitz et al 2009, Schmitz et al 2009(b), Schmitz et al 2010, Kwan et al 2011). The benefits which exercise provides to the general population in terms of psychological wellbeing and the advantages of improving general fitness, which should also be encouraged with this patient group (Hayes et al 2009). There is still contradictory advice available to patients regarding exercise

and this may add to the patients fear that use of the “at risk” limb may lead them to develop or exacerbate lymphoedema (Lee et al 2010).

2.7.6 Manual Lymphatic Drainage (MLD)

Manual lymphatic drainage (MLD) is a specialised form of massage used to assist in the management of patients with lymphoedema. MLD requires a specially trained therapist to carry out the technique. This can be modified to a simpler version which the patient or their carer can carry out, this is known as simple lymphatic drainage (SLD). The principles of both these techniques are to encourage the flow of lymph to be redirected to the non – obstructed or functioning cutaneous lymphatics. The massage is carried out in a sequence which aims to move lymph from the congested area towards the non congested area along alternative pathways so that any normal pathways which have been damaged are avoided (Mayrovitz 2009b). The technique is performed with a very light hand pressure and involves skin movement only in order not to increase the vascular circulation. MLD aims to encourage improved filling of the initial lymphatics and increase the transport capacity by causing initial lymphatic dilatation and developing accessory lymph collectors (Rockson 2001).

The aim of treatment would always be to provide clearance within the trunk prior to trying to influence the lymph flow in the limb. This assists the flow of lymph fluid, ensuring the truncal pressures and volumes are reduced prior to attempting to clear any lymphoedematous areas (Mayrovitz 2009b).

A systematic review evaluated the evidence of the effectiveness of MLD in the prevention and management of BCRL (Huang et al 2013). Ten randomised controlled trials (RCT) were found to fit the criteria of the review. To be included in the review trials had to be RCTs or quasi RCTs which described the inclusion and exclusion criteria for patient selection into the trial. There also needed to be details of the MLD and compression therapy used as well as a definition of lymphoedema and an evaluation of the severity of the lymphoedema. Huang et al (2013) excluded any RCTs in which axillary node dissection had not been performed on the participants, there were no clearly stated clinical outcomes and there was duplicated reporting of patient cohorts. No significant benefit for reducing BCRL by using MLD was found by the review,

however, it was recognised that individual trials did report advantages related to MLD but the inconsistent methodology across the trials did not allow for an overall comparison. This resulted in the review concluding that it could not recommend the addition of MLD to manage BCRL but this is not generally in keeping with clinical findings. The systematic review of the evidence (2004-2011) carried out by Lasinski et al (2012) concluded that MLD improved QOL and enhanced the effects of compression.

2.7.7 Low Level Laser Treatment (LLLT)

Low level lasers (LLLT) have a wavelength within the visible infra red range. The wavelength affects the amount of penetration into the tissues, however the depth of penetration will also be affected by other factors such as skin pigmentation, haemoglobin level and the cleanliness of the skin (Tilley 2009). Promotion of lymphangiogenesis, stimulation of lymphatic mobility as well as improved overall lymphatic flow are the mechanisms which are proposed to assist in limb volume reduction (Carati et al 2003, Dirican et al 2011, e Lima et al 2012). It has been reported that LLLT appears to stimulate cell metabolism when the tissue state requires boosting but has little effect on normal tissue (Tilley 2009). There is limited evidence as yet on the efficiency of low level laser treatment (LLT) for patients with BCRL. Tilley (2009) provided a summary of the evidence supporting the use of LLT and the physiology behind its effect. A systematic review carried out by Omar et al (2012) reviewed the literature available between 1990 and 2011 and revealed 10 articles in this area. These studies did not compare the effectiveness of different modes of treatment with the LLT or collective dose for lymphoedema management. The research collated indicated that there is a cumulative effect of treatment but due to study errors it was difficult to assess whether the results for laser effectiveness may be masked. However, the conclusion from the systematic review was that there was moderate to strong evidence from five small studies to support the effectiveness of low level laser treatment as a management option in BCRL, however further research is required. E Lima et al (2012) raised concerns that as the LLLT can also cause a decrease in the extracellular matrix proteins which are responsible for the adhesion of cells, this may increase metastasis. Their systematic review which included four studies (41 studies were found which matched their keyword search but only four of these matched the inclusion criteria for the systematic

review) with 75 patients and 74 controls over these studies. In all of these studies, a decrease in limb volume was shown compared to the control group and none of the studies included reported any increase in cancer spread in the included patients after treatment but this was not part of the scope of any of the studies selected. It was therefore their conclusion that LLLT did result in reduced limb volumes but this was when compared to placebo, no intervention or IPCP (see section 2.7.4.2) and that the hypotheses of whether LLLT could increase metastasis or recurrence had not been considered. E Lima et al (2012) therefore suggested LLLT should be used cautiously in patients with cancer.

Carati et al (2003) carried out a randomised control trial using LLLT to treat patients with post mastectomy lymphoedema. 28 patients were included in the placebo group and 33 in the active group. Although the group were matched for age and weight, the patient's in the active group had a larger excess limb volume and a longer time with lymphoedema. This study measured the limb volume post treatment by circumferential measurement (see section 2.10.2) and then over a three month period, it also measured extracellular fluid by bioimpedance (see section 2.10.5) and tissue "hardness" using tonometry (see section 2.10.6). The findings showed there was a continued reduction in limb volume in the treatment group at the subsequent review appointments with 31% of the subjects having a clinically significant (when compared to the placebo group) reduction in the affected limb volume two-three months after having two cycles of laser therapy. There was also a sustained reduction in the affected arm for 52% of the participants at the three month follow up appointment in the group which had two cycles of laser therapy compared either to one cycle or the placebo. Although significant hardening of the affected arm was reported immediately after the treatment with two cycles of LLLT, by 3 months after treatment there was a significant softening of the tissues measured ($p=0.025$). The study concluded that further work needed to be undertaken to understand the mechanisms of action of LLLT for treatment of lymphoedema and also to improve the efficiency of treatment. However, it was felt that it may have clinical benefit in the treatment of lymphoedema.

2.7.8 Kinesiotape

Kinesiotape (KT) is a specialist tape which is applied to the skin in a specific direction. Although, at present, the mechanisms for the effectiveness of KT is unclear (Kaya et al 2012), it is thought that the KT may have many physiological effects including facilitating circulation of lymph by increasing the space between the skin and muscles and therefore improving the subcutaneous lymphatic drainage. It has been claimed that it can change the pressure in the initial lymphatics and help to open and improve pathways and uptake (Kase and Stockheimer 2006). The tape can be left in place for several days and patients or their carers can be taught how to apply the tape which promotes self management. Although there is limited research available to explain the mechanisms of its effectiveness, clinically KT is being used as a valuable addition to the management of lymphoedema especially when treating truncal oedema or oedema affecting the extremities i.e. the hands and feet (Tsai et al 2009b).

2.7.9 Surgical intervention

At present surgical intervention for lymphoedema tends to be recommended for patients who no longer respond to DLT. Chang and Cormier (2013) carried out a systematic review of the literature between 2004 and 2013 regarding surgical intervention in lymphoedema. From this literature review, there were three types of surgical intervention available in the management of lymphoedema – excisional, lymphatic reconstruction and tissue transfer (Cormier et al 2012).

Excisional procedures include debulking, liposuction and amputation. Liposuction has been the more favoured surgical options from these recently.

Lymphatic reconstruction involves microsurgery and supramicrosurgical techniques and aims to reconstruct or bypass the obstruction areas to increase the lymphatic drainage.

Tissue transfer procedures consist of transferring lymph tissue into the congested region with anastamoses of the lymphatic vessels to aim to establish new pathways of lymph flow and so remove the excess fluid for the interstitium.

All surgical techniques carry risks and are therefore not considered first line treatment (Chang and Cormier 2013). At present these surgical techniques are not curative and continued management is required. Compression garments are required lifelong as part of the post operative management along with follow up assessment and high levels of concordance from the patient. A systematic review (2004-2010) relating to surgical management of lymphoedema included 20 studies (Cormier et al 2012). Most of the studies were on small numbers of less than 100 subjects with no control groups or long term follow up. The systematic review also commented that the majority of the included studies did not comment on post operative complications. The conclusion from this review was that, although there are some promising results from the surgical interventions, they do not negate the need for postoperative use of conventional therapy such as DLT which should continue to be the standard care for this patient group.

2.7.10 Pharmacological Management

Some drugs, such as calcium channel blockers, combined oral contraceptive pill and corticosteroids have known side effects of peripheral oedema. These may cause an exacerbation of any existing chronic oedema, for example, lymphoedema, when they are used to treat co-existing conditions (Keeley 2008). Often these drugs will cause increased oedema when there is already a deficiency in the lymphatic system due to either increasing hydrostatic pressure in the capillaries, and so increasing fluid retention and blood volume, or by causing peripheral arterial vasodilation (Keeley 2008). Although the co-existing conditions require treatment it may be possible to alter the medication to a different drug without this side effect.

Benzopyrones have been suggested to be beneficial for lymphoedema patients but at present are not clinically used in UK. A Cochrane review of published trials concluded that there was not enough evidence to support their use in lymphoedema (Badger et al 2003). Selenium, which has anti –inflammatory properties, is another drug which has been used in lymphoedema management but again a Cochrane systematic review suggested there is not enough evidence to support this use (Dennert and Horneber 2006). Loop diuretics have also been recommended for short periods only with specific patients who have had an

exacerbation of their oedema due to a complex cause such as advanced disease or when a drug causing fluid retention has been taken. Long term use of these drugs is not recommended as there may be an increase in interstitial protein concentration due to the decreased capillary filtration causing lower fluid re-entry. This increased protein concentration would cause an increase in oncotic pressure and result in more oedema (Keeley 2008).

There may also be short term benefit from the use of corticosteroids in advanced cancer to reduce the peri tumour oedema which may in turn reduce the pressure on the lymphatic or venous system and decrease oedema. Care needs to be taken however, as there is a risk of increased peripheral oedema production with corticosteroid use.

2.7.11 Self Management

Self management is the goal of any management strategy in long term conditions. Self management incorporates the four cornerstones of treatment; skin care, SLD, exercise and compression. Often patient compliance with their entire management plan is poor. Carrying out self management is emotionally challenging as well as physically demanding (Mayrovitz 2009b). Time is required to be set aside daily for the completion of the management plan and, as this is a chronic condition, this will be a lifelong commitment. In order to enhance the commitment to the self management component of treatment individualised support as well as education is required. Armer et al (2011) investigated the difficulties which breast cancer survivors found in continuing with their risk reduction programme for lymphoedema. It was apparent that it was not always a lack of education which was the main issue but the level of personal support and the idea of result which would help with continued engagement by the patients (Armer et al 2011).

2.8. Psychosocial Impact

Lymphoedema can be devastating, especially for patients who have undergone treatment for cancer and then develop limb swelling (Ng and Munnoch 2010). In a qualitative study using a descriptive phenonomelogical method carried out by Fu and Rosedale (2009), one of the themes which emerged was “living with

perpetual discomfort". The study reported that anxiety was caused by the fact that these symptoms were chronic and would be present on a daily basis. There was an awareness expressed that health care professionals did not always show an understanding of lymphoedema or the symptoms which would be involved and even when the patients had had this explained there was no offer of counselling or support to deal with these lifelong symptoms. Due to the lack of public and health professional awareness a feeling of social isolation has been reported, Hayes et al (2009) stated lymphoedema is a condition that is

"difficult to explain but visible to all".

The swelling can act as a constant reminder to the patient of their cancer history as well as a more visual symptom which the patient feels draws unwanted attention to themselves (Petrek et al 2000, Fu and Rosedal 2009, Hayes et al 2009). In the qualitative study carried out by Thomas-MacLean and Miedema (2005) patients reported that they were able to disguise the fact that they had undergone a mastectomy but they were less able to hide their BCRL. Patients with lymphoedema have a lower quality of life score than breast cancer survivors without lymphoedema (Fu and Kang 2013, Ridner 2005, Pyszel et al 2006).

Pyszel et al (2006) investigated the quality of life among Polish breast cancer survivors with lymphoedema by sending 1000 sets of questionnaires. There was a response rate of 28.3% of which 31.7% had lymphoedema. The patients with lymphoedema showed a lower score on physical, emotional, social cognitive and role functioning than subjects without lymphoedema.

Ridner (2005) compared the quality of life and symptoms between breast cancer survivors with and without lymphoedema using a mixed methods, cross sectional study design. Quantitative and qualitative data were collected. Each group contained 64 subjects and the data was collected at a single time point. Women with lymphoedema had statistically significant lower scores on all the QOL measurements.

Disruption to normal working patterns is also a common complaint from lymphoedema sufferers. Too much repeated activity or too heavy a work load

may cause the limb to tire or the oedema to increase (Thomas – MacLean and Miedema 2005).

In a systematic review carried out by Fu and Kang (2013), publications from 2004-2011 were examined. The aim of the review was to summarise and evaluate the evidence, identify risk factors and consider strategies to target the psychosocial impact of lymphoedema. 18 out of the 23 studies which fitted the inclusion criteria for the review were focused on BCRL. In all of the quantitative studies (11 out of 23), poorer overall quality of life was reported in cancers survivors with lymphoedema. Poorer social well being, negative body image, appearance, sexuality and social barriers were all statistically significant in those cancer survivors with lymphoedema compared to cancer survivors without lymphoedema. From the qualitative studies (12 out of 23), negative emotional feelings were reported. These studies also reported the negative social impact and included feeling of lack of support from HCPs, negative impact on their working life and the visible sign of lymphoedema causing unwanted social reactions. There were reports of the negative impact on body image, sexuality and relationships in these qualitative studies. Hand lymphoedema in BCRL, along with pain in the affected breast, had a statistically significant association with higher psychosocial distress.

The treatment or management of lymphoedema can have a detrimental effect on quality of life and lifestyle. During the intensive phase when multilayer bandaging is being carried out, there is an impact on lifestyle and activities of daily living (Radina and Armer 2001, King et al 2012). Many patients find wearing garments during the self management phase difficult to cope with and intrusive to their daily life. Depending on the patient's role at work this may be further compounded by uniform requirements or infection control directives. Although there has been much improvement in the range of garments and hosiery choice available to patients, many patients find garments are not optimal in both effectiveness and comfort/acceptability and this can have an impact on psychosocial standing as well as quality of life.

Lymphoedema also has significant effects on body image, this is further compounded by the difficulties often faced by patients in choosing clothing and the restrictions the differing size of their limbs puts on this (Woods et al 1995,

Thomas – MacLean et al 2005, Ahmed et al 2008, Stamatakos et al 2011). The psychosocial maladjustment to their disease and its residual effects do not appear to be related to the size of the swollen limb (Woods et al 1995). Chachaj et al (2010) investigated the factors which predict disability and emotional disturbances in breast cancer survivors who developed lymphoedema. Oedema affecting the hand increased the disability scores and also the psychological distress measures using a general health questionnaire. Only lymphoedema within the breast and the hand was associated with a poorer function score. There was little correlation between the severity of the oedema and the disability scores. Function and psychological distress are higher in patients with hand oedema as the oedema restricts fine movements and hand swelling is difficult to disguise or conceal, which may have an even greater negative effect on body image.

2.9. Prognosis

A study by Johansson and Branje (2010) considered the progression of BCRL in a group of 98 women who were identified as having BCRL and were followed up over a period of 10 years. In this group the importance of early diagnosis or diagnosis when the limb volume difference was small was of significance and with treatment this low level of lymphoedema could be maintained over the 10 year period.

2.10.1 Assessment of Lymphoedema and Monitoring Progress

In order to evaluate lymphoedema it is essential that measurements of the limb or hand size are taken as accurately as possible. These act as a baseline and assist in the detection of lymphoedema as well as enabling an evaluation of the response to any management plan to be monitored (Park et al 2008). There are various methods of measuring limb size and to detect any change in volume from normal to assess whether lymphoedema is present. For use in clinic the measurement system needs to provide reliable and valid results but be easy to use and easy to calibrate due to the variety of different health care professionals (HCP) who will use it, some who may have very little training in lymphoedema management. It must be portable to allow for use in a clinic but

also at other settings such as the patients home or on a ward and must be inexpensive to allow access for different HCPs.

2.10.2 Circumferential Measurements

Circumferential measurements are the most common method of measuring limb size and volume in clinical practice. Circumferential measurements are measured with a standard tape measure. The limb is marked at defined intervals from a documented start point or from an anatomical landmark and then the tape passes around the limb, maintaining the horizontal alignment of the tape, and this value documented. However there is no standardised method for use of this technique. Measurements can be taken at bony or anatomical landmarks such as the ulnar styloid or olecranon or at designated intervals along the limb.

To establish the volume of the limb, circumferential measurements are taken at defined intervals from the styloid process, for example in 4cm sections, with each section representing a cylinder or a truncated cone. The sum of all the volumes of each of these sections is then calculated to provide a volume for the limb.

There have been some studies into the recommended “height” of each of these segments which can vary between 4cm and 10cm and also the recommended formula to define the volume. This final volume is either calculated as a cylinder or as truncated cone (frustum). There is no agreement in the literature or between clinicians as to preferred methods to be used or to standardise the distance between measurements (Rinehart – Ayres 1998).

In these circumferential measurements the hand is not included as part of the volume measurement as it is not a cylinder. The hand volume is measured as a simple circumferential measurement by placing the tape around the hand using the base of the metacarpal phalangeal joint as the bony landmark to promote consistency.

This method however is low in cost, simple to perform and easily available. It is easy to carry out and provides some quantitative data although it is recognised that there are inaccuracies within this system (Shah et al 2012). Chen et al

(2008) carried out a small study on a sample of 14 patients who all had BCRL. Their study was to investigate the reliability and consider the indicators of clinical improvement by three methods of measurement; water displacement (see section 2.10.4), tonometry (see section 2.10.6) and circumferential measurements. The hand was not included in the circumferential measurements as the measurements were only taken at three points on the upper limb. Although intra-rater and inter-rater reliability was high for the circumferential measurements (ICCs >0.99), there were some errors found in this measurement technique. This was particularly related to the consistency of the tension applied to the tape and also standardising the measurement sites. Circumferential measurement, however, allows individual measurements to be monitored so that there is an appreciation of what is happening segmentally in the limb and so the shape variations of the limb can be scrutinised.

There was no evidence found in the literature of the reliability and validity of this method of measurement for the hand being tested. There does not appear to have been any studies published regarding the testing of circumferential hand measurements or its responsiveness to change.

2.10.3 Perometry

The technique of optoelectronic perometry calculates limb volumes by using infrared beams at fixed increments which creates a two dimensional silhouette of the limb. It has been designed specifically for measuring limb volume, circumference, contour and cross sectional area (Lee et al 2011). The perometer scans the limb by moving a frame along the length of the limb with the patient in a documented standardised position at each time of measuring. Measurements are taken at intervals of 5mm, recording the limb volume at each of these points which allows more measurements than those taken by circumferential measurements (Stanton et al 2000).The measurement takes seconds and there are no contraindications for patients with wounds or skin infections which is not always the case with other forms of measurement (see section2.10.4) (Lee et al 2011). Perometry has been found to have increased reliability and increased sensitivity in detecting BCRL compared to more traditional methods (Jain et al 2010) because it eliminates the errors associated with discrepancies in tape tension or in variations in marking anatomical points (Bernas 2010). More than

one measurement should be taken at each time of measuring to ensure accuracy and it is better to use the mean of two sets of measures (Ancukiewicz et al 2011).

The perometer, however, is an expensive device and so not commonly available in clinics.

2.10.4 Volumeter or Water Displacement

Water displacement or volumetry can be used to measure limb volume. This technique is based on Archimedes principle which states the water volume displaced is equal to the volume of the object immersed in the water (DeVore and Hamilton 1968). This method of measurement has been shown to be highly reliable (Sander et al 2002) with little error incurred. It is also able to determine changes in volume in irregular shaped areas which is necessary when trying to measure the hand or foot (Chen et al 2008).

The volumeter is a specifically designed tank with an out flow spout at a set distance along the wall of the tank and also a dowel placed near the bottom of the tank (see Figure 6 section 3.1.5.2.). The volumeter is filled with water at a consistent temperature and then calibrated by allowing any excess water to drain from the spout until there is more than 5 seconds between each drip.

The patient is asked to lower their limb into the tank in a standardised manner until again there is longer than 5 seconds between any drips of water at the out flow spout. The displaced water is collected in a jug and then measured in a calibrated container. This volume of water is then recorded.

It has been reported that the water displacement methods can detect a change of 10 ml and so it has been considered to be the “gold standard” for measuring limb volume (Boland and Adams 1996). Karges et al (2003) examined test – retest reliability of volumeter measurements and carried out three tests in eleven arms over a 30-40 minute time frame. Within this study reliability was high (ICC (2.1) = 0.99) and there was a SEM of only 11.46mls. They concluded that one measurement was acceptable rather than repeat measures, however Farrell et al

(2003) recommended that the average of three measurements should be taken to provide greater reliability and decrease any variability.

However, there are limitations to its use in clinical practice. The water needs to be maintained at the correct temperature as variations in temperature have been shown to affect the results. In the literature which uses water displacement as a method of measurement there is a range of temperatures used from 20°C (Deltombe et al 2007) to 38°C (Damstra et al 2006). Although extreme temperature differences will alter results, temperatures between 20° C and 35°C demonstrated no significant difference in the amount of water displaced by the hand (King 1993). Ng and Munnoch (2010) also discussed that the different density of water at different times will also have some effect on the measurements taken and so there should be an effort to standardise this as far as possible. As the water temperature needs to be kept constant and the tank needs to be filled and calibrated correctly between each measurement, it can be time consuming to use in a clinical environment. Due to infection risk it is not appropriate for use with any patients with broken skin which in many lymphoedema patients is a common problem. Also the equipment needs to be cleaned correctly between each patient to ensure no risk of cross infection. As the tank needs to be kept on a level surface and water collected and replaced it is impractical to take out with the clinic setting to measure limbs in any other setting, for example, the patient's home. The tank also needs to be large enough to accommodate the often large limbs of lymphoedema patients, thus holding several litres of water – this would take significant time to fill and empty the tank and also make it difficult to move once filled (Karges et al 2003). Due to the positioning of the spout it is also difficult to measure entire limbs as there needs to be a space above the spout in the tank and so the entire limb will never be submersed. This is not such a problem when measuring hand volume however, the position can be standardised so that it is repeatable for each individual patient, as the dowel is always placed at the same web space to ensure repeatability for that individual. However, there will be a discrepancy between patients as to how much of their forearm is measured due to the variation in finger size so making the arm deeper into the water with smaller hands and although this would be consistent each time the limb is measured, many patients who have hand lymphoedema will also have arm lymphoedema. This means that

if treatment is carried out for the whole limb and the size of the forearm changes with this treatment, there will no longer be an accurate measurement of the hand as the amount of water displaced will also reflect the change in forearm size.

Palmada et al (1998) reviewed the literature to assess whether the clinical measurements used for monitoring oedema, especially hand oedema, were accurate, reliable and valid. When Palmada et al (1998) summarised the literature available at this time, they concluded that there were discrepancies in what is considered a standard protocol for volumeter use and the results could be made inaccurate by many variables. These included the position of the patient, the amount of pressure applied to the dowel within the tank and the height and surface levels. A difference in water displacement of approximately 5mls can be made with small variations in hand position within the volumeter or the amount of pressure which is applied to the dowel (Waylett – Rendall and Seilby 1991). There have been some efforts to address this which include external trunk supports and an adjustable height table to aim to make the pressure more consistent and reduce this error (Farrell et al 2003, Dodds et al 2004).

There has also been an attempt to establish a method using inverse water displacement. In this instance the limb is placed in an empty tank and then the tank is filled to a predetermined level. The limb is then removed and the volume of the limb calculated as the difference between the level of the water remaining in the tank and the predetermined level (Sagen et al 2005, Damstra et al 2006). Although this may eliminate some of the difficulties of ensuring the limb is submerged to the same place each measurement time – most other disadvantages to this method would still be applicable.

The water displacement method also only gives a single volume measurement for that limb and so there is no way of detecting changes in different segments of the limb to monitor any alterations in the shape (Shah et al 2012).

2.10.5 Bioimpedence Spectroscopy (BIS)

BIS uses resistance to low frequency electrical current to allow the measurement of volume in the extracellular fluid (ECF) compartment of the limb (Shah et al 2012). The extracellular volume is then reported as a ratio relative to the intracellular volume and can be used to provide information as to whether this is within a normal or abnormal range (Cornish et al 2002). A standardised protocol has been established using an increase of three standard deviations to assist clinicians in the detection of early lymphoedema (Shah et al 2012). This figure has been established based on prospective data. A study by Ward et al (2009) showed a strong correlation between the bioimpedence index scores and the volume measurements from perometry. BIS has also been shown to have increased sensitivity when compared to more traditional methods of measuring and so can detect any early signs of lymphoedema and also any physiological changes resulting from treatment (Bernas et al 2010, Cornish et al 2001).

There is caution to be used when interpreting the results of BIS however as the device cannot distinguish between lymphatic and venous oedema as both result in extracellular fluid. Ng and Munnoch (2010) question its validity in non-pitting oedema when there is fibrotic and adipose tissue. This is because non pitting oedema may cause increased volume but it may actually result in a normal BIS ratio as this type of oedema will have less extracellular fluid than newly developed lymphoedema. They also suggest caution in interpreting the results when aiming to detect early lymphoedema formation following breast cancer treatment as if the lymphoedema is assessed for too early post surgery then normal post surgical oedema may be presumed to be lymphoedema (Piller 2009).

Ward et al (2012) examined the use of BIS compared to perometry in assessing hand volume. This study did not measure the thumb and the other digits were also excluded from the measurement so that the values were for hand volume only. This is comparable with clinical measurement as hand volume would refer to the volume around the palmar and dorsal aspect of the hand but would exclude digits. 50 subjects were recruited but none of these subjects had hand oedema. However, the values from the BIS readings correlated to the perometer volumes. There was different responsiveness depending on the position of the limb. The study detected different BIS readings after elevating the hand for a

period of time so reducing the amount of vascular volume. This may have implications for establishing a clinical protocol for measurement to ensure that the same position is established for each set of measurements. It also implies that this method measurement would be sensitive to measure change as even positional changes affected the results.

BIS is relatively expensive technology and is not available in most clinics as yet.

2.10.6 Skin Tonometry

Most of the measurement methods used in lymphoedema aim to assess the changes in limb volume or, in the case of bioimpedance, the electrical properties of the limb. This is useful to provide a baseline and measure of how limb size is changing but will not give an indication of the actual physical properties of the lymphoedematous tissues. Tonometry is based on the amount of pressure necessary to depress the skin a specified amount (Gerber 1998). A tonometer device was developed by Clodius and Piller to measure the resistance of tissue to compression (Clodius et al 1976, Piller and Clodius 1976). The principal behind this device is that if the tissue is loaded by a fixed weight then there will be a greater depth of indentation caused by this weight in softer tissues than in harder tissue (Mayrovitz 2009). This depth of indentation can be recorded and used to give an objective measurement of the tissue resistance which would then give an indication of the subcutaneous tissue changes. As skin tissue tonicity can vary within healthy individuals at various times, it is important that both limbs are measured at the same level each time measurements are taken (Chen et al 1988). As limb volume may not increase even though there is an increase in tissue fibrosis caused by protein accumulation, change in the subcutaneous tissues may be an appropriate method of measuring the progress of the lymphoedema (Chen et al 2008). The disadvantage with this device is that the tonometer depends on gravity and it is necessary that is applied vertically to the area being assessed and also to a surface which is sufficiently flat to allow the device to be almost free standing. Not all patients will be able to be positioned to meet these requirements and the anatomical considerations may also make it difficult to ensure the surface is flat. The device itself is however simple and portable and further research is being carried out to develop a device which is not reliant on this vertical placement (Mayrovitz 2009). Tsai et al

(2005) carried out a study to examine the reliability of this method of measurement and found that the variability depended on the area of the upper limb being assessed. The intra-rater reliability was less strong than the inter-tester reliability but Tsai et al's study (2005) was based on healthy subjects rather than those with lymphoedema. In Chen et al's studies (2008), carried out on a sample of lymphoedema patients, intra-rater and inter-rater intraclass correlation coefficients showed fair to good reliability but were lower than those for water displacement or circumferential measurements. This study was on a small sample of only 17 patients but there were difficulties in ensuring the device was positioned correctly and there was also difficulty in establishing the amount of pressure that was being applied to the device.

Chen et al (1988) noted that this device is not useful for measuring dorsal hand oedema as the unaffected hand will record a higher score. This is because there will be very little indentation recorded as there is little soft tissue overlying the bone, so less tissue to compress. Any affected hand with oedema present will record a lower score as the oedema is likely to indent more easily.

2.11.1 The Importance of Measurement in Clinical Practice

Limb volume measurement provides an objective measure to establish the level of severity at time of diagnosis or to assist in monitoring to establish whether there is clinical evidence of lymphoedema as well as to allow the response to treatment or progression of the condition to be recorded. It allows a quantitative measure for establishing and monitoring achievement of goals as well as to provide one method of measuring clinical outcomes.

It is important in clinical practice to assess not only the "affected" limb but also the "unaffected". It cannot be assumed that the volume of the "unaffected" limb will not change over time. There is often a discrepancy between any individual's limbs which may be affected by dominance, activity levels and general lifestyle (Armer 2000 cited in Armer et al 2003). To establish a baseline and to be able to review changes accurately it is important that both limbs are measured by whatever method especially if relying on a system which calculates limb volume. This allows a comparison between the affected and "unaffected" limbs to assist in recognition of apparent changes. For example, weight loss or

gain or exercise involvement, would affect the size of the limbs and, without the comparison between the two limbs, lead to a misinterpretation of the results (Ancukiewicz et al 2011).

It has been identified that the most effective method of monitoring whether there is development or progression of limb lymphoedema relies on, not only the comparison between limbs but also, limb volume changes monitored over time (Armer et al 2003).

Ideally for patients who undergo treatment for breast cancer, a pre intervention or pre operative measurement should be obtained to provide a baseline measurement. If there is no pre treatment measure it is difficult to accurately identify the formation and severity of lymphoedema as early as possible and thus allow post treatment management to be undertaken (Stout Gergich et al 2008).

In clinical practice, any method of measurement requires to be reliable and valid but also sensitive to any changes in size. It also needs to be practical and realistic for practice. This means that any method used is preferably inexpensive and uses equipment readily available both to specialist clinics and generalist practitioners. Lymphoedema patients are often first assessed, and many continue to be managed, out with specialist clinics. Therefore, a measurement technique needs to be such that a non specialist practitioner can be taught to do it easily as the skills will need to be disseminated widely. As many clinicians may also see patients out with a clinical setting, for example, in the patients' homes, the measurement technique should ideally require equipment which is portable and minimal with little "setup" required.

2.11.2 Reliability

Reliability is the reproducibility of measurement (Lexell and Downham 2005). For measurements to be of use in both clinical practice and for research it is necessary for any measurements that are taken to be reliable, that is the measurement procedure would provide the same value if repeated on the same subject under the same conditions (Lachin 2004, Downing 2004). Reliability, therefore, reflects the internal consistency and the amount of variability in the measurement procedure being tested (Karras 1997).

Various statistical tests can be used to test the reliability of a series of measurements. In order to ascertain reliability, it is necessary to calculate the extent to which the measurement is free from error. Statistically this is calculated by examining the difference or the agreement within a range of scores (Portney and Watkins 2009). This agreement can be reported as the kappa statistic (Viera and Garrett 2005) which provides a quantitative measure of the agreement between observers. The basis of the calculation is establishing how much of the agreement has actually occurred compared to how much agreement may have happened by chance alone.

The kappa statistic has been further developed and Cohen's Kappa is the measurement of agreement between two raters or two methods of measurement. This system however, is best suited to an ordinal scale, such as the five point Likert scale, rather than continuous data which was collected in this study (Portney and Watkins 2009, Cohen's and Fleiss's Kappa Explained accessed 20.8.14). Fleiss's Kappa is an extension of Cohen's Kappa which evaluates concordance or agreement between multiple raters but there is no weighting applied and again it is less suited to continuous data.

Bland - Altman analysis also calculates the agreement between two measurement methods. This method was developed for use with independent data that are collected as two sets of data taken on the same occasion. However, this method is generally used to compare a new measurement method with an existing one to determine if the agreement is strong enough to allow these methods to be interchangeable or to replace the pre-existing method (Myles 2007, Bland and Altman 1990). This was not appropriate for this study as the figure of eight method which measures hand size was being compared against a "gold" standard method of measuring hand volume. There was no expectation that these methods would be interchangeable.

Correlation coefficients provide information about the degree of association between two data sets (Bruton et al 2000).

Intraclass correlation coefficients (ICC) are commonly used as a measure of reliability when considering continuous data (Lexell and Downham 2005, Sim and Wright 2005, Shourki and Asyall 2004). They supply information on the degree of

consistency and agreement between the measurements and can be used to compare different measurement procedures that use different units of measurement (Bruton et al 2000).There are various types of ICC depending on the study design. In this instance ICC (3.1) was used to determine intra-rater reliability and ICC (2.1) for inter-tester reliability. Intra-rater reliability determines the repeatability of the measurement when undertaken by one tester whereas inter-rater reliability investigates the degree in which the measurements are repeatable with more than one tester.

ICC (2.1), which was used to investigate the inter-rater reliability, is based on a two-way random effects model (McGraw and Wong 1996). This model considers the testers and patients to be random effects with the trials as irrelevant. The aim is to identify whether the measurements are interchangeable between the testers.

ICC (3.1) is based on a mixed model ANOVA model with consistency agreement and was used to assess the intra-rater reliability (McGraw and Wong 1996, Nichols 1998). In this instance the trials were the fixed effect, the patients were considered as a random effect and the testers were irrelevant.

Intraclass correlation coefficients were used to determine reliability in previous published research which had the same methodology and measurement method as the studies presented here. This therefore allowed a comparison of the results from the present study with this previously published literature (see chapter 3) (Maihafer et al 2003).

In clinical practice, the measurements recorded on the same patient by the same therapist using the same method on repeated attendances to clinic are required to be consistent, as are measurements which are recorded on the same patient on the same attendance date using the same method by different health care professionals. Therefore, it was important to establish that there was strong intra and inter – tester reliability with the figure of eight tape method of measurement.

As the ICC uses an equation which calculates the ratio between a calculated subject variability and that variability plus the error involved, the ratio can

range from negative one to positive one (Guyatt et al 1995). Therefore if the ICC was zero there would be no reliability whereas if the value was one it would indicate perfect reliability (Weir 2005). A correlation coefficient of negative one would indicate a perfect negative relationship in that the lowest values on one test have the highest in the other. In Fleiss (1986), it is indicated that an ICC of between 0.4 and 0.75 represents fair to good reliability whereas an ICC greater than 0.75 indicates excellent reliability. Chin (1991) also stated that in order for the measurement to be useful, there should be an ICC of at least 0.6.

2.11.3 Validity

Validity refers to whether the specific measure may or may not measure the characteristic or quantity being examined (Lachin 2004).

There are different types of validity which can be examined depending on the needs of the research.

Construct validity is examined in situations where there is no established standard or method with which to test the measure against. Construct validity investigates the correlation between the test/measure being studied and other measures of similar qualities.

Content validity, is a weak form of validity which explores whether the test being carried out is designed in such a way that it can measure what it intends to measure (Scott and Mazhindu 2005). This would be a subjective measure of validity as there are no statistical tests which can be used to establish content validity and it is therefore usually determined by expert opinion (Portney and Watkins 2009).

Face validity is also considered a weak form of validity and would not be considered scientifically strong enough to prove validity of a measurement method as there is no standard or scale to measure it against. Again, it is a subjective form of validity. Face validity requires that the test being considered is a plausible method of testing and also that it appears to test the quality it sets out to test. It may require the end users of the measurement method being tested to affirm the face validity of the test (Portney and Watkins 2009).

Criterion – related validity or concurrent validity, a strong form of validity, assesses the correlation between the new test method being researched and an established "gold standard" method. Concurrent validity assesses the measurement method's consistency with this external criteria. It also measures the systematic error which would be inherent in the method being tested (Karras 1997). This was the aim in this study as the volumeter has been established as the "gold standard" method of measuring hand size in patients with lymphoedema. Previous research had established the validity of the volumeter (see 2.10.4) in measuring hand size and it was therefore an appropriate "criterion" to use.

Pearson correlation coefficient is used to quantify validity. In this context the correlation coefficient quantifies the strength of the relationship between the new test and the 'gold standard'. This statistical test is used to assess whether or not the linear relationship is statistically significant. In this test a value of 1 would represent perfect agreement between two measures and 0 would represent no agreement. This statistical test was chosen as this was in keeping with previous published literature of studies with similar methodology and investigating the same method of measurement (Maihafer et al 2003, Pellecchia 2003, Leard et al 2004, Dewey et al 2007). This would enable the statistical analysis of any data produced from the current study to be compared with previously published work (see chapter 3).

Validity needs to be considered in connection with reliability but also measurement error (see 2.11.5).

2.11.4 Sensitivity to change or responsiveness

The extent to which the method of measurement can detect change is described as sensitivity to change or responsiveness (De Morton et al 2010). It is usually considered in relation to change over time or the measure of a clinically important change over time. It is important that any method of measurement demonstrates enough sensitivity to be able to detect changes appropriately with the aim to exclude any changes which occur due to natural variability. In this way, the measurements will then provide important information that will enable the clinician to detect changes after treatment interventions or to track the

progression of the patient's condition. When considering sensitivity to change it is important that it can be presumed there is no error in the standard measurement which the test measurement is being compared against (Karras 1997).

2.11.5 Standard error of measurement

Standard error of measurement (SEM) indicates the amount of spread in the measurement error for a test. It therefore indicates the difference between the testers obtained measurement and the theoretical true measurement (Harvill 2005). As no measurement method is likely to supply exactly the same measurement each time it is tested, it is important to establish whether the error produced is acceptable (Bannigan and Watson 2009). Standard error of measurement is calculated by the following formula

$$SEM = St.Dev \times \sqrt{(1-R)}$$

(R=reliability)

Much of the literature around standard error of measure is concerned with monitoring changes in quality of life measurements particularly in mental health and quality of life (Eisen et al 2007, Den Oudsten et al 2012), however Eisen et al (2007) stated that standard error of measurement corresponded to clinically important change and could therefore be used to measure clinically meaningful change (Eisen et al 2007).

In order to establish the minimal detectable difference or the amount of change which needs to be achieved to reflect a true difference, the standard error of measurement can be used (Portney and Watkins 2009). This measurement allows the clinician to consider whether there has been an actual improvement in the hand size of the patient or whether any change is due to measurement error. Therefore, in order to be sure that a clinically significant change has occurred over time, the change measured would need to be greater than that attributed to measurement error (Ferreira and Herbert 2008).

2.12 Literature review on limb volume measurement in oedematous limbs

A review of the general literature covering measurement in lymphoedema will be presented prior to the review of the literature covering specifically the figure of eight tape measurement method (see section2.12.2).

2.12.1 Review of the literature on measuring limb swelling

Many of the studies that have been carried out to investigate the reliability and validity of the different techniques applied in limb volume measurements in patients with breast cancer related lymphoedema do not include hand measurements. Often the measurements start from the wrist and include the remainder of the arm but not the hand. Mayrovitz et al (2006) suggests this omission of the hand volume from assessment, is due to the lack of a method which can accurately measure the hand size which is easily available and clinically appropriate.

Foroughi et al (2011) investigated the reliability of non-health care professionals measuring arm circumferential measurements to investigate whether this technique could be used for patients to monitor their own limb. These results were compared to measurements taken by a trained assessor and also to perometry. The study showed a moderate to high concordance between the assessor and the perometer and between the circumferential measurements taken by the assessor and those taken by the patient. It was therefore felt that this circumferential measurement method could be used reliably by patients to monitor for any development of lymphoedema. However, this study did not include hand measurements or participants with lymphoedema. Taylor et al (2006) also produced results from a study assessing the reliability and validity of arm volume measurements for patients with BCRL comparing circumferential measurements with volumetry. As hand volume cannot be calculated by using circumference and the mathematical equation to derive the volume of a cone, the hand measurements were omitted from the study. The researchers measured the amount of water displaced by measuring the hand, finishing at the wrist, in the volumeter but this was not included as part of the results and was used simply to subtract the volume displaced by the hand from the total water

displaced by the full limb. It was not stated whether any of the participants had hand oedema. The study did however find high reliability between the volumes obtained via water displacement and circumferential measurements.

Chen et al (2008) carried out a study to investigate the reliability of the methods commonly used for measuring lymphoedema in breast cancer patients. The methods included in the study were water displacement, circumferential measurement and tissue tonometry. The aim of the study was also to consider the limitations of these methods in accurately identifying clinical change in relation to clinical improvement. The study was on a small sample with only 14 patients included when considering water displacement and circumferential measurement and 17 for tissue tonometry. All the patients had previously been treated for breast cancer and had since developed lymphoedema. There were two physiotherapists undertaking measurements which allowed the study to consider both intra and inter-tester reliability. The measurements were all taken by both physiotherapists. The measurements were repeated by the therapists after 10 minutes to provide two sets of each measurement. The physiotherapists were blinded to each other's measurements but not to their own. All of the methods showed fair to excellent reliability with water displacement and circumferential measurement having an intraclass correlation coefficient (ICC) of greater than 0.99. Tissue tonometry was demonstrated to have the weakest reliability as the ICC was 0.66. The authors also considered the standard error of measurement (SEM) and smallest real difference (SRD) which again was greatest for tissue tonometry. However, in this study the hand was not included in any of the circumferential measurements although the dorsum of the hand was included as one of the measurement sites for tissue tonometry and was also included in the water displacement method along with the rest of the upper limb. Also the testers were not blind to their own measurements which would affect the intra-rater reliability and may have introduced bias to the study results.

Inter-tester reliability of water displacement method has been established for the measurement of hand volume. However, in the 2010 cross sectional study carried out by Ribeiro et al, only patients without changes in their upper extremities were included. This allowed the researchers to establish a normative index for hand size in a normal population but did not look at the inter tester

reliability for patients presenting with hand oedema. 100 participants were recruited which allowed measurement of 200 upper limbs. However the study only used subjects between the ages of 21 and 50 which is also not necessarily representative of the age range for BCRL. It is not specified whether the time to ensure the water displacement was completed by allowing more than 5 seconds between drips but it stated that the limb was kept in position in the tank for as long as possible. There were two examiners who both measured each participant's hand once so that each subject had two sets of measurements taken on each hand. In this study even with a young subject group and participants with no upper extremity pathology, the participants found it difficult to keep the hand motionless in the tank. The results demonstrated that the right hand was likely to have a larger volume on average than the left for both males and females, although this group also had subjects who were predominantly right handed (92% of the sample). This would perhaps be important to consider when comparing the different hand volumes in a patient to aim to establish if lymphoedema was present.

There is variation within the literature and clinically regarding the technique of circumferential measurement to monitor limb size. Studies have included different methods of measurement for example, 4cm intervals from the metacarpal phalangeal joints to the axilla (Mayrovitz et al 2007) or 10cm intervals from the wrist (Foroughi et al 2011) or 6-9cm intervals (Sander et al 2002).

Whether the use of these circumferential measurements to establish the limb volume should be used to calculate the volume of a cylinder or a frustum is also not established. Sander et al (2002) examined different mathematical formulas to establish limb volumes. They proposed that as previous studies had been carried out on patients without oedema, this could explain why there was agreement with using the formula for a cylinder. However, they found that using the formula for a frustum resulted in the closest agreement to water displacement values.

Sander et al (2002) attempted to use a geometric volume specifically to measure hand volume and examined the use of the geometric formulas for a cylinder, a frustum, a rectangle and a trapezoidal. The aim of the study was to assess the

intra and inter-rater reliability and validity of these volume measurements from water displacement and geometric measurements, identify if there was relationship between the measurements and to assess whether the methods were interchangeable. The subjects were 50 women who had a diagnosis of lymphoedema and had observable oedema although it was not specified how many of these subjects had hand oedema. There was one physical therapist and three physical therapy students involved in the data collection which may allow the results to be applicable to generalist or non lymphoedema specialist health care professionals. The evaluators performed two sets of measurements and in order to establish intra-rater reliability were blinded to the first set of results. However, the second evaluator was not blinded to the first evaluator's measurements which could affect results by introducing bias. The hand was marked at 3 cm intervals. Callipers were used to take depth and width measurements with the hand positioned on the ulnar border. This enabled these measurements to then be used in the mathematical formula which requires the width and height or depth of the object rather than a circumferential measurement. Water displacement was carried out by a standardised method which included standardised positioning and water temperature. All of the methods used for measuring hand size correlated highly with inter-rater ICC of 0.91-0.98 and intra-rater ICC of 0.92-0.99. The method of using the geometric shape of the frustum had very high ICCs (0.99 for intra-rater and 0.98 for inter-rater) as well as having the smallest standard error of measurement (SEM =16mm), although the cylindrical volumes also had a small SEM (17mm) and similar ICC results. It was acknowledged within the discussion that the lack of blinding for the second evaluator may have lead to the high reliability ratings. It was found that the measurement methods are not interchangeable as the values for each method were different throughout.

Mayrovitz et al (2006) sought to investigate a method to monitor hand oedema which could be used in a clinically setting. Their study involved 33 subjects without hand oedema. Measurements of the hand were made by marking the hand at 3cm intervals and then documenting the depth and width/circumference at each point using digital callipers and a constant tension tape measure respectively. Volumeter measurements were also carried out. The cross sectional area of each hand section was then calculated from the metric measurements by

using the formula for an elliptical area and then the volumes of each segment were calculated by an elliptical frustum model. The segmental volumes were calculated using a trapezoidal method and also by the circular frustum method. The total volumes for each method were calculated using the sum of all the segmental volumes. In order to test the ability of the depth and width measurement technique to measure altered hand sizes, a model of a hand was cast and then clay was added to this to simulate oedema. The results from this study showed all 3 methods were significantly correlated with the water displacement volumes but that the elliptical model correlated most highly (r=0.986) with the water displacement volumes and so it was suggested that the elliptical model was the most valid. It is noted that the study was carried out on normal hands although the volumes with the clay model appeared to also indicate a parallel to the water displacement measurements. However, this still requires a set of callipers as well as a tape measure to carry out and it is not clear whether there was any assessment of inter or intra therapist reliability with this technique. The callipers were also adjusted so that they compensated for the depth of the surface which the subjects hand was resting on – this would have implications for using this method in different settings.

A study by Lee et al (2011) recognised the difficulties which face clinicians in finding an accurate method of hand volume measurement for patients with lymphoedema. They proposed the use of perometry to measure hand size in this patient group. The perometry measurements were compared with water displacement as this has been established as having high reliability, accuracy and responsiveness. Twenty women with lymphoedema and twenty without were recruited to the study. It was not clear how many of these twenty women with lymphoedema also presented with hand oedema. In this study there was strong concordance between the measurement taken by perometry and those by water displacement (Rc = 0.88). The perometer was also shown to have high intra-rater (ICC 3.1 = 0.989) and inter-rater reliability (ICC 2.1 = 0.993). The absolute values from the perometer were relatively high due to it not recognising the interdigital spaces and calculating this with the limb volume, so the recommendations are that positioning would need to be carefully standardised to reduce the measurement bias.

Bulley et al (2013b) investigated standardising the protocol for using a perometer to measure limb volume in both upper and lower limbs. The participants (n=30) within the study did not have oedema and were excluded from the study if they had had any injury in the previous 6 months. Several pilot studies were undertaken to assist in establishing a protocol. It was assessed if any diurinal variation took place or whether differing periods of elevation affected the limb volumes, the optimal position of the limb in the perometer for measurement and also whether a standardised portion of the limb could be measured to allow comparison between different individual's limbs. The optimal position for measurement was investigated and also whether speed of movement of the perometer affected the measurement taken. It was found that there was very little alteration in limb volume so it would therefore be acceptable to perform the measurements at approximately the same time of day. The effect of different positions of rest or elevation on limb volumes was investigated and it was established that the most consistent percentage change occurred in the upper limb following 2.5 minutes of rest and in the lower limbs following 10 minutes of rest. This was then the recommended time allowed as a rest period prior to measurements being taken by the perometer method. There was less variation in the measurements if bony landmarks were used for positioning the perometer and the neutral position for both upper limb and lower limb provided the smallest variation. It was noted, however, that further testing of the protocols were required. This study did not include the measurement of the hand volume as it was not included in the perometry measurement.

A study by Brodovicz et al (2008), which was designed to compare different methods of measuring peripheral oedema in the ankles or lower legs included water displacement, ankle circumference and figure of eight method. The measurements were taken by three testers and the tape method measurements were carried out twice. In this study, circumferential measurement and water displacement had excellent reliability (ICC over 0.9) and figure of eight was more inconsistent (ICC 0.53- 0.66). A tension controlled tape is described as being used for the tape method measurements but it is not clear how this was achieved in the figure of eight method which involved wrapping the tape around the ankle and foot following various anatomical land marks to achieve the figure of eight. All of the 20 subjects included in the study had circumferential

measurements carried out but the figure of eight method was included in a set of two different measurements methods and the subjects were randomised between these two sets. The circumferential measurements were measured and the area marked with semi permeable pen. This mark was made by the first tester and remained visible for subsequent testers which may have assisted with the consistency and the high inter-tester agreement. It was reported that the intra-tester reliability for both the tape measure methods was good. The circumferential method demonstrated ICCs of above 0.98 but the ICCs were not calculated individually for figure of eight method as there were small numbers for this technique. The figure of eight method was reported as difficult to carry out. It was discussed that the volumeter method, although high reliable may be challenging to carry out in a clinical setting.

2.12.2 Figure of Eight Method of Measurement of Hand Size

In order to investigate an alternative method of measuring hand size Pellecchia (2003) examined the figure of eight tape method of measuring hand size. The study was based on the figure of eight method which had been used to measure ankle size and for which the reliability and validity had been established. The study was carried out in two phases. For the first phase which examined reliability, 60 subjects who had had no previous injury to their hand were recruited to the study and two testers were used as well as a third person who recorded the data. Three consecutive measurements were taken by each tester. The ICCs for both inter-tester and intra-tester showed very good reliability (ICC = 0.97 and 0.99 respectively) and both had small standard error of measurements (SEM) especially within each testers results. A second study was undertaken to assess validity, this time recruiting 25 subjects, with no history of hand injuries, and comparing the figure of eight method with volumetry. Two testers were used but one carried out the repeated figure of eight measurements and the other the repeated volumeter measurements with both techniques being standardised. Both testers were blinded to their results. The intra-tester ICCs were again very strong at 0.99 for each tester and method. A Pearson product moment correlation was used to examine validity between the two methods and this was also very strong at 0.94. It was concluded from this study that the figure of eight was a reliable and valid method of hand measurement.

Maihafer et al (2003) proposed that the figure of eight method would be more able to measure hand volume than a single-joint circumferential measurement method as the figure of eight method crossed the dorsum of the hand where swelling commonly occurs. Maihafer et al (2003) discussed that this would improve the purposefulness of the measurement as, due to the looser bound tissues on the dorsum of the hand, the fluid is more likely to accumulate in the dorsum rather than the palmar surface where the skin is attached more firmly to the palmar aponeurosis. As most of the anatomical landmarks required for the method of applying the figure of eight measurement are primarily on the palmar surface of the hand, they are be relatively easy to find and assist in consistency when measuring. For their study, 50 subjects with no hand pathology were recruited. Two student physical therapists were used to carry out the measurements and a third tester recorded the measurements. As both hands were used the sample was 100 hands. Each tester took two sets of measurements for each hand for the figure of eight measurements but one set for the volumeter measurements. The mean of the figure of eight measurements were used for calculating the ICCs. For both testers the intra-tester and inter-tester reliability was determined by ICCs of 0.99. The Pearson product moment correlation, to examine validity between the figure of eight method and water displacement, ranged between 0.94 and 0.95, again indicating high validity. The study also recorded the time taken to perform the figure of eight method as approximately one minute and furthermore that only basic anatomical knowledge was required. The time taken to set up and perform the volumeter test was approximately six minutes which included assuming that constant water temperature was maintained. This would also have an implication for clinical practice in that the speed of the figure of eight measurement method and ease of carrying out would be beneficial in a busy clinical setting. It was concluded that the figure of eight method of measurement was a reliable and valid clinical tool although it was recognised that the measurements had been carried out on healthy subjects.

The reliability and validity of the figure of eight method of measuring hand size was also investigated by Leard et al (2004). As the previous studies in this area had been carried out on subjects with no hand pathology, Leard et al's study (2004) chose to investigate a subject group who had conditions affecting their

hands. 24 subjects were recruited - nine of these subjects had bilateral involvement and so 33 sets of data were obtained. The subjects had a variety of orthopaedic conditions and, except three, were post surgery. Testers were final year physical therapy students and two testers carried out the figure of eight measurements which were repeated three times consecutively and a third tester carried out the volumeter measurements, repeating this twice. Two additional testers acted as data recorders. Practice sessions were completed prior to the measurements being carried out on subjects and the methods were standardised. ICCs were calculated to investigate inter and intra-tester reliability for the figure of eight method. The intra-tester reliability was strong; 0.99 (SEM= 0.28cm) for tester 1 and 0.98 (SEM = 0.4cm) for tester 2. The inter-tester reliability for the figure of eight method was also strong (ICC = 0.99 SEM = 0.28cm). As expected based on previous studies, the intra-tester reliability was also strong for the volumeter measurements (ICC = 0.99 and SEM = 8.6mls).Validity, which was investigated using a Pearson product moment correlation coefficient, was high being 0.92 for both testers with a p value of <0.1. This study calculated the Pearson product moment correlation coefficient on both the first figure of eight measurement compared with the first volumeter measurement but also on the means of the three figure of eight measurements compared to the means of the two volumetric measurements. The results of the second calculation still arrived at a Pearson product moment correlation coefficient of 0.93. The conclusion was therefore, that it may be possible for only one set of measurements to be taken. This is of great value clinically where repeated measurements are time consuming. The study was able to conclude that, despite the testers having minimal clinical experience, they were able to use the figure of eight method with good intra and inter-tester reliability, suggesting that this technique may be developed without extensive training or experience making it useful for generalised clinical practice.

In 2007, Dewey et al used a similar study methodology to assess the reliability and concurrent validity of the figure of eight method in measuring hand oedema in patients with previous burns. Twenty subjects were recruited with 13 having bilateral burns and so both hands were measured which resulted in 33 sets of data. Two testers carried out the blinded figure of eight measurements and a third tester carried out the volumeter measurements. A fourth investigator acted

as the data recorder. Practice sessions for each method of measurement were carried out on the non affected hands and the methods standardised. Three consecutive measurements were taken for the figure of eight method by each therapist. The tester carrying out the volumeter measurements took two measurements. Seven of the patients included in the study were intubated or sedated or unable to stand and for these patients the position of the limb within the volumeter was maintained by the staff members. The ICC results for the figure of eight method were 0.94 for inter-tester reliability and 0.96 for intra-tester for tester 1 and 0.97 for tester 2. The comparison of the results between the figure of eight method and volumeter for both testers showed strong validity with tester 1 being 0.83 and tester 2 0.89 (p value <.01). This study concluded that the figure of eight method was a reliable and valid tool which could be used as an alternative to volumetry, in burns patients.

Each of these studies established that the figure of eight tape measurement method of measuring hand size was valid and reliable. It also required less equipment, time and expense, was simple to use and could also be carried out on patients who have contraindications to the water displacement method. However, it is important to establish that it is reliable and valid with patients who have hand oedema secondary to BCRL as it has not been tested on this subject group. The technique needs to be practical to use in a variety of clinical settings and to be able to be taught to clinicians who are not specialists as it is often generalist practitioners who are monitoring patients with lymphoedema.

2.13 Aims of the study

The aim of the first study (phase 1) was to examine the intra and inter- rater reliability of using the figure-of-eight method of measuring hand size in those with BCRL and to examine the concurrent validity of the figure-of-eight method of measuring hand size in those with BCRL by comparing it to the ‘gold standard’ approach of water displacement

The aim of the second study (phase 2) was to determine if the figure of eight tape measurement method of measuring hand oedema was as sensitive to change as the “gold standard” method of water displacement with a volumeter or the commonly used clinical method of circumferential measurement. In

addition the circumferential method of measurement was not included in phase 1 so the reliability, validity and sensitivity to change of the circumferential method of measuring hand volume in BCRL was investigated in this study (phase 2). This study also re –examined the reliability and validity of both the figure of eight method and volumeter method of measuring hand size when used by an experienced lymphoedema practitioner and confirmed the reliability and validity results of the phase one study. It also considered the natural variability of the size of the unaffected hand.

Chapter 3

3.1 Methodology Phase 1

3.1.1. Aims

The purpose of the study was to determine the reliability and validity of the figure of eight tape measurement method of measuring BCRL hand oedema in order that this simple clinical measure could subsequently be used in assessment and monitoring progress of hand oedema in BCRL. This study was funded by the Physiotherapy Research Foundation through the Chartered Society of Physiotherapy (see section 3.1.7).

The aims of the study were

1. to examine the intra and inter-rater reliability of the figure-of-eight method of measuring hand size in those with BCRL

2. to examine the concurrent validity of the figure-of-eight method of measuring hand size in those with BCRL by comparing it to the 'gold standard' approach of water displacement

3.1.2 Study Design

This study was based on similar published studies by Pellecchia (2003), Maihafer et al (2003), Leard et al (2004) and Dewey et al (2007) (see section 2.12.2).

The sample was a convenience sample of women with hand lymphoedema secondary to treatment for breast cancer who attended, or who were still under management of, the Beatson West of Scotland Cancer Centre, Glasgow UK.

Potential participants who fitted the inclusion criteria (see section 3.1.3.) were identified by the lymphoedema keyworker at the Beatson West of Scotland Cancer Centre and then contacted by the lymphoedema keyworker by telephone or at their clinic appointment and informed about the study. If they were interested in participating they were provided with a patient information leaflet (see appendix A). They were asked if, after reading the information leaflet, they

were happy to participate in the study they would contact the clinician to arrange an appointment for measurements to be taken. The measurement sessions took place in the therapy area at the Beatson West of Scotland Cancer Centre and travel expenses were offered to all participants. All participants in the study gave informed written consent (see appendix B).

3.1.3. Inclusion/exclusion criteria

To be included in the study, participants had to be adult females presenting with lymphoedema affecting their hand following treatment for breast cancer.

Testing with the volumeter involved positioning the arm in a specified manner in the water tank, therefore, enough dexterity and range of movement to allow this to be undertaken with no discomfort was required so participants were excluded if they had co-morbidities affecting their upper limb. Participants were also excluded if they were deemed to be at the end of life stage. The definition for end of life was taken as those whose death was imminent in the next few weeks as it was not appropriate to invite them into this study. Patients who have lymphoedema affecting their hand at this stage in their cancer journey would no longer be measured for limb size as aims of treatment would be to ensure comfort, maintain quality of life as far as possible and to try to ensure the oedema did not prevent achievement of goals the patient had set. Therefore, limb volumes and monitoring of limb size would no longer be considered a priority and would not normally be taken in the clinical setting. This, therefore, made it appropriate to exclude this sample group as they would not be representative of the group of patients on which the measurement method would be used. Also, the researchers were aware that they may not be well enough to stand for long enough to complete the volumeter protocol.

There are no contra-indications for the figure of eight method of measurement but as this was being compared against the volumeter, any contraindications to using the volumeter had to be considered. Therefore, patients with open wounds, abrasions or other skin conditions were also excluded from the study, as the risk of wound infection renders these contraindications for using the volumeter for measurement (Sorenson 1989).

3.1.4. Testers and Recorder

This study required two testers and one recorder.

One of the outcomes from this study was to investigate if the figure of eight tape measurement was a technique which could be used by any health care professional rather than just by trained lymphoedema practitioners. Therefore, in keeping with Pellecchia (2003), Maihafer et al (2003) and Leard et al (2004), novice practitioners, in this case final year health care professionals were recruited as testers.

This process was undertaken by contacting staff on the undergraduate courses for nursing at the University of Glasgow and physiotherapy at Glasgow Caledonian University to ask permission to approach the students and to seek advice on the best way to inform students about the opportunity to participate in the study. Flyers were printed advertising the research project and asking any interested students to email the researcher for more information. There was some difficulty in recruiting testers, as some groups of final year students were on clinical placement when the study was scheduled to take place. Those on placement were unable to commit to the sessions required. An information meeting was held asking all interested students to attend. There was a good attendance at this, with 13 students attending, and generally all of these students were interested in the study. The only restrictions to choice of tester were due to either placement or travelling considerations. After the meeting, two novice practitioners were selected; a newly qualified physiotherapy student and a final year nursing student who was not due on clinical placement until after the period of the data collection. This final decision was made on the availability of these testers to attend the clinical sessions during the scheduled time for the study.

The testers received payment for the sessions that they undertook to cover expenses.

The testers were required to carry out both figure of eight measurements and volumeter measurements on both hands of each of the participants. The order in which they carried out the testing was alternated to minimise any bias. Both

testers had a one hour training session with the researcher (YB), who is also a qualified lymphoedema specialist, on the technique for the figure of eight measurement and in the use of the volumeter.

The recorder was a qualified physiotherapist who was also a qualified lymphoedema specialist and the researcher on the study (YB). A standard form was used to record the data (see appendix C) The recorder measured the length of the cut tape (see section 3.1.5.1.) which had been used for the figure of eight measurement against a meter rule and recorded this in mms. The same recorder also measured the amount of water displaced from the volumeter tank in the calibrated cylinder and used the same form to record this value to the nearest millilitre.

The same two testers and recorder where used for each participant.

3.1.5 Prodecure

Before testing, baseline data was collected from each subject including date of birth, surgical history, the presence of unilateral or bilateral oedema and duration of the presence of oedema.

3.1.5.1. Figure of eight measurement method

The main aim of the study was to investigate the reliability and validity of the figure of eight measurement method. Figure of eight tape measurements were carried out using the technique described in Dewey (2007). The subject's arm was supported on a table with the forearm in pronation, the wrist in neutral and the fingers rested in adduction. The figure of eight measurements were taken by passing a blank 5mm tape around the hand. In order to ensure that the method was valid and reliable, it was important to avoid any potential bias and therefore to guarantee that the testers were blind to the values measured. In order to achieve this, a blank tape was used to ensure the testers were blind to the results. To achieve a blank tape various methods were tried including blacking out the values on a tape measure and also using rope which was marked and cut. However, both these methods had difficulties. It was possible still to see the numerical values on the tape through the blackout paint and also it was difficult to clean between patients without some of the paint being removed.

The rope was expensive and had different mechanical properties to the tape measures used in clinical practice. It was decided that gift ribbon would be suitable as no values were shown but it was also the same width as many tape measures used in clinical practice. In addition, as it was inexpensive, it could be disposed of after each measurement ensuring there were no issues of cross infection between patients. It was also comfortable on the patient's hands.

The tape was placed on the distal aspect of the head of the ulnar on the dorsal surface; it was then placed across the anterior surface of the wrist just distal to the radial styloid. The tape was then passed diagonally across the dorsum of the hand with the distal end of the tape aligned over the fifth metacarpal phalangeal (MCP) joint line. The tape was then taken across the palmar surface of the hand with the distal end of the tape resting along the MCP joint line crease. The tape continued around the second metacarpal head and was placed diagonally across the dorsum of the hand back to the start point. (Figure 5A and Figure 5B). The tape was then marked and cut just beyond the mark. To ensure blinding of the testers and to avoid bias, the marked tape was then passed to the recorder who measured the tape against a wooden rule and recorded the measurement to the nearest millimetre. A new blank piece of tape was used for each measurement.

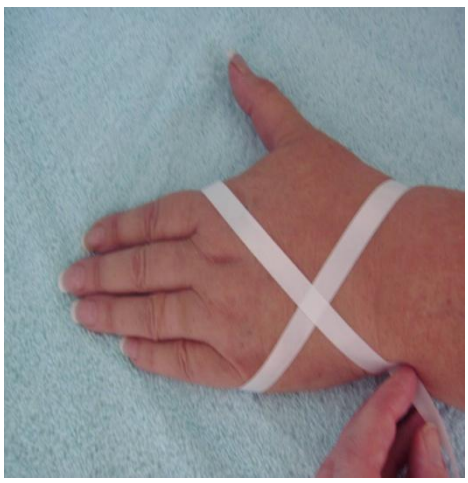

Figure 5A – figure of eight tape measurement method - dorsal view

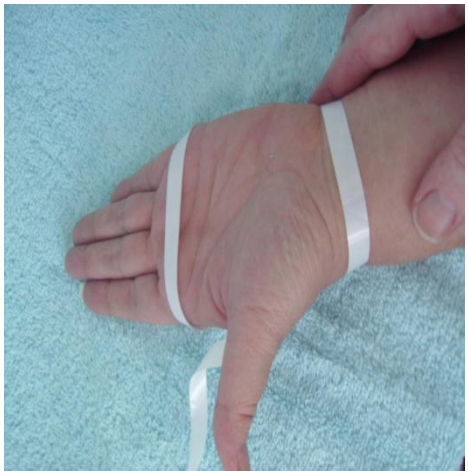

Figure 5B – figure of eight tape measurement method – palmar view

This was repeated three times (three trials) by each tester for each affected hand.

This allowed the intra-tester reliability to be examined. It was important from a clinical perspective to establish that the measurement technique was repeatable. Repeating the measurements three times, was in keeping with the protocols used in the previous studies (Maihafer et al 2003 and Leard et al 2004) and thus allowed a comparison of results.

3.1.5.2. Volumeter/water displacement

The reliability and validity of the water displacement method using a volumeter have been established (see section 2.10.4) and it is generally accepted that this method is the "gold" standard for measuring hand volume (Lymphoedema Framework 2006).

For the volumeter measurements, a hand volumeter was purchased for the study. The volumeter was filled with water and allowed to settle at room temperature. A thermometer was used to ensure the water was always between 20 and 32 degrees centigrade (Pellecchia 2003, Boland and Adams 1996, King 1993). The subject's hand was submerged in the volumeter with the forearm pronated, the fingers resting in adduction and the thumb facing the spout. The subject was asked to lower their hand slowly into the volumeter until the web of the middle finger and ring finger rested on the stop dowel (Dewey et al 2007) (Figure 6). The displaced water was collected in an unmarked beaker (to ensure blinding of testers) and the subject was asked to remain still until there was more than five seconds between each drip at the overflow. After this the subject was asked to remove their hand from the volumeter and to dry it on a towel.

The beaker of dispersed water was then passed to the recorder who transferred the water to a graduated cylinder and recorded the amount of water displaced in millilitres. This process was repeated three times (three trials) by each tester for each hand.

Figure 6 - volumeter

For each tester the order of the tests, figure of eight or volumeter, was alternated.

3.1.6 Advisory Group

In keeping with the Department of Health's (DoH 2005) recommendations, an advisory group was established. This included the researcher, two of the academic co- applicants and three service users, who were all patients of the lymphoedema service at the centre where the research study took place. The service users were recruited by the lymphoedema keyworker within the Beatson West of Scotland Cancer Centre. All three of the ladies, who were keen to be included in the advisory group, had lymphoedema following treatment for breast cancer. The guidelines from the Patient Information Advisory Group (2006) recommends that patients from the target population should be actively involved in the design and the aims of any study, rather than the service users being used for consultation only (INVOLVE 2012, INVOLVE 2009, DoH 2005, Rhodes et al 2001). Although the bid for the research funding had been submitted, the group was able to help to shape the application to ethics and also to raise

recommendations for the future direction of any research subsequent to this project.

The advisory group met at various points throughout the study with three meetings held. Prior to ethical approval being obtained the advisory group were asked to comment on the suitability of the study and service users were asked whether they felt other patients would be happy to be involved in this study. They were all in agreement that this would be the case but they also raised other issues e.g. whether this method of measurement would help to identify change in hand size. This issue was addressed in the second phase of the study (see chapter 4). It was also felt by all three service users that patients would be happy to consent to the study as they would feel they were helping others even if it would not directly benefit individuals taking part. This is in agreement with literature surrounding patient involvement in research projects with patients being keen to be able to give something back to the services which had helped them (INVOLVE 2012, Minogue et al 2005). All the patient information for the study was given to the patients on the advisory group to read and the opportunity for any comments or feedback given to ensure that the information provided was understandable and suitable. The advisory group met again after ethical approval was received and to inform them about the process being undertaken to enlist two novice practitioners. The final meeting was during the course of collecting the data to update the group on how this phase was progressing. It was agreed that the advisory group members would also be invited to the feedback session for all the participants in the study after the results of the study had been finalised to ensure they were informed of the outcome of the project.

3.1.7. Permissions and Approvals

A successful application was made to the Physiotherapy Research Foundation (part of the Chartered Society of Physiotherapists) for funding to support the research project (see appendix D).

An application was made to the West of Scotland Research Ethics Committee and approval for the study was given (see appendix E). There were no significant

changes to the application other than the recommendation that there was no need to inform the patient's GP of their participation in the study. It was felt by the committee that, as there was only one session involved for the patient, no change to treatment and also no intervention involved it was unnecessary paperwork for the GP to receive a letter.

The study was also approved by the two in house committees at the Beatson West of Scotland Cancer Centre – the In House Trials Advisory Board (IHTAB) and the Clinical Trials Executive Committee (CTEC) (see appendix F).

In addition, Research and Development approval was obtained through NHS Greater Glasgow and Clyde (see appendix F). Access letters for the three members of the research team who were not employees of this trust were also given by NHS Greater Glasgow and Clyde Research and Development (see appendix G).

3.1.8. Data Analysis

As no pilot study had been carried out to provide data previous published literature was used to guide the sample size. The mean difference of 0.53cm which was similar to that of Leard et al (2004) was used as the effect size, along with a standard deviation taken from this study of 0.3cm to calculate a sample size with a power of 80%. It was estimated from this that seven subjects would be required to yield a statistically significant result. However, it was anticipated that due to the subjects in this study having hand oedema secondary to BCRL, there might be greater differences in hand size detected. Therefore, the sample size was based on the samples used in previous published literature from studies examining this measurement method with similar methodology (Pellecchia (2003) n= 25, Leard et al (2004) n=24 and Dewey et al (2007) n=20). The figure of 25 participants was chosen to reflect the samples used in the published studies which used the technique on those with hand pathology; Leard et al (2004) carried out his study using 25 participants with nonspecific hand pathology and Dewey et al's (2007) study was on 20 patients following burns. Therefore, the aim was to recruit twenty five participants with hand oedema secondary to breast cancer related lymphoedema to the study.

Descriptive statistics were calculated for both measurements and across both testers. Data were analysed using Statistical Package for the Social Sciences (SPSS 18) and Minitab Statistical Software v15. These were calculated for both figure-of-eight and volumetric measurements. Standard error of measurement (SEM) was also used as a measure of intra-tester and inter-tester reliability as well as giving an indication of the appropriateness of the method for use in clinical settings (Eliasziw et al 1994, Bruton et al 2000).

ICC (3.1) was used for calculating intra-tester reliability. The three measurements taken by each tester for both methods of measurement were used to calculate separate ICCs for each tester for each method (Dewey et al 2007).

For inter-tester reliability ICC (2.1) was used. The mean of each of the three measurements was used to calculate the inter-tester ICC.

SEM was calculated as SEM = SD x $\sqrt{}$ (1- R) were SD is the standard deviation of the measurements and R is the intraclass correlation coefficient for that measurement.

A Pearson moment correlation coefficient was undertaken to examine the concurrent validity between the two methods of measurement. This commonly used statistical criterion and associated statistical test is carried out to examine the relationship between an instrument and an external criterion, in this case the figure of eight tape method and the volumeter (Morgan et al 2005 p196). Portney and Watkins (2009 pge525) have expressed that a correlation of above 0.75 demonstrates a good to excellent relationship, 0.50-0.75 moderate to good, 0.25-0.5 a fair relationship and below 0.25 little or no relationship.

These are standard statistical terms used to examine reliability and validity and have been used in the previous five papers in this field (Farrell et al (2003), Maihafer et al (2003), Pellecchia (2003), Leard et al (2004), Dewey et al (2007)). Calculating the correlation between the two methods allowed not only association of the two measuring methods to be examined but also the strength

of this association (Scott and Mazhindu 2005, Guyatt et al 1995). The strength of this correlation is more important in demonstrating the relationship between the two measures than whether the relation has statistical significance (Guyatt et al 1995).

3.2 Results Phase 1

Twenty five participants were recruited to the study. However one subject was unable to complete the protocol due to fatigue, and thus results are given for 24 subjects (Table 2).

3.2.1 Demographics

The average age of subjects was 51.5 years (range 38-68 years) and subjects presented with hand oedema for a mean of 17.4 months (range 1 to 50). Twenty three subjects had surgery for breast cancer and were tested on average 27.8 months after surgery (range 5 – 84 months) (Table 2). One subject's breast cancer was treated conservatively. Twenty one participants had unilateral and three participants had bilateral hand oedema. For the patients with bilateral oedema, the hand reported by the patient to be most oedematous was taken as the affected hand.

	Mean	Range
Age (years)	51.5	38 - 68
Time since surgery (months) (n=23)	27.8	5 - 84
Duration with hand oedema (months)	17.4	1 - 50

Table 2: Demographic information of sample (n=24)

3.2.2 Descriptive statistics

Descriptive statistics for each of the measurements for the oedematous hand are shown in Table 3.

	Figure of eight mms (n=24)			Volumeter mls(n=24)		
Tester 1	Mean	Range	St. Dev	Mean	Range	St Dev
1st measurement	440.83	400-488	24.09	558.7	410-727	87.1
2nd measurement	438.00	407-482	20.09	556.0	417-737	86.4
3rd measurement	463.79	407-479	21.41	555.8	415-732	84.9
Tester 2						
1st measurement	443.75	405-503	24.32	558.0	415-713	84.2
2nd measurement	444.21	409-508	23.80	553.4	410-720	86.6
3rd measurement	445.00	413-501	22.70	556.3	415-730	87.2

Table 3: Descriptive statistics (means, range and standard deviations (St Dev)) for the figure of eight and volumeter measures for both testers and for each measurement for the affected hand only.

This table shows the mean measurement, range of measurements and standard deviation across each set of measurements for the 24 participants for each tester and for both the figure of eight method and volumeter. The standard deviation for each tester in the figure of eight measurement is under 25mm with tester 2 being more consistent in the figure of eight measurement. The volumeter standard deviation was approximately 87mls maximum for both testers and showed less of a variation between the different measurements.

The difference between the affected and the unaffected hands was calculated to give an indication of the amount of oedema present in the subject group (Table 4). As three patients had bilateral oedema their measurements were not included. There largest difference between the unaffected and affected hands detected by the figure of eight method was 63mm but the mean difference was 23.6mm. For volumeter the range of difference between the affected and unaffected was wide (6.8mls to 336.5mls) and the mean difference was 83mls. The mean of the six measurements taken between the two testers was calculated for each measurement method.

Difference between affected and unaffected hands (n=21)		
	RANGE	MEAN
Figure of eight method	23mm-63mm	23.6mm
Volumeter	6.8mls – 336.5mls	83mls

Table 4. Difference in measurements between affected and unaffected hands. Subjects who reported bilateral oedema were excluded (n=21). Measurements were calculated as the mean of the 6 measurements taken.

3.2.3 Intra-tester and inter-tester reliability

The summary of the ICCs carried out for each method and each tester both for the inter-tester and intra-tester reliability including the standard error of measurement are included in Table 5. The ICCs (3.1) for intra-tester reliability using the figure of eight method were high at 0.89 for tester 1 (Standard Error of Measurement (SEM) = 7mm) and 0.92 for tester 2 (SEM= 6mm). For the volumetric measurement the ICCs (3.1) were 0.99 (SEM = 8.4mls) for both testers.

	Inter-tester reliability ICC (2.1)	Intra-tester reliability ICC (3.1)	
		Tester 1	Tester 2
Figure of eight method	0.89 (SEM=6mm)	0.89 (SEM = 7mm)	0.92 (SEM = 6mm)
Volumeter	0.99 (SEM = 8.4mls)	0.99 (SEM=8.4mls)	0.99 (SEM = 8.4mls)

Table 5. Summary of inter-tester and intra-tester reliability for each tester and each measurement method including SEM (standard error of measurement).

In terms of the inter-tester reliability, using the mean across the three measurements for each patient and then comparing the two testers, the ICC (2.1) for the figure of eight measures for the total group was 0.89 (SEM = 6mm) demonstrating high inter-tester reliability. Similarly inter-tester reliability was high for the volumeter measure with ICC of 0.99 (SEM = 8.4mls).

	ICC (2.1) repeated measurements Figure of eight method	ICC (2.1) repeated measurements Volumeter
Trial 1	0.85	0.99
Trial 2	0.82	0.99
Trial 3	0.85	0.99

Table 6: Summary of inter-tester intraclass correlation coefficients (2.1) for the repeated measurements across each trial for each method of measurements.

Table 6 demonstrates the ICC (2.1) for the repeated measurements across the trials. The figure of eight method demonstrated a strong correlation with all the ICC (2.1) above 0.82 for each trial. This would again indicate that the method had little variability across the trials. The volumeter showed even more consistency with the ICCs being 0.99 for each trial.

3.2.4 Validity

Pearson moment correlation coefficient was undertaken to establish the validity of the figure of eight method. There was a strong and statistically significant correlation between the two methods of measurement for tester 1 ($r=0.700$; $p<0.001$) and for tester 2 ($r=0.752$; $p<0.001$). The scatterplot shown in Fig 7 gives an indication of the relationship between the two measurement techniques showing a positive correlation.

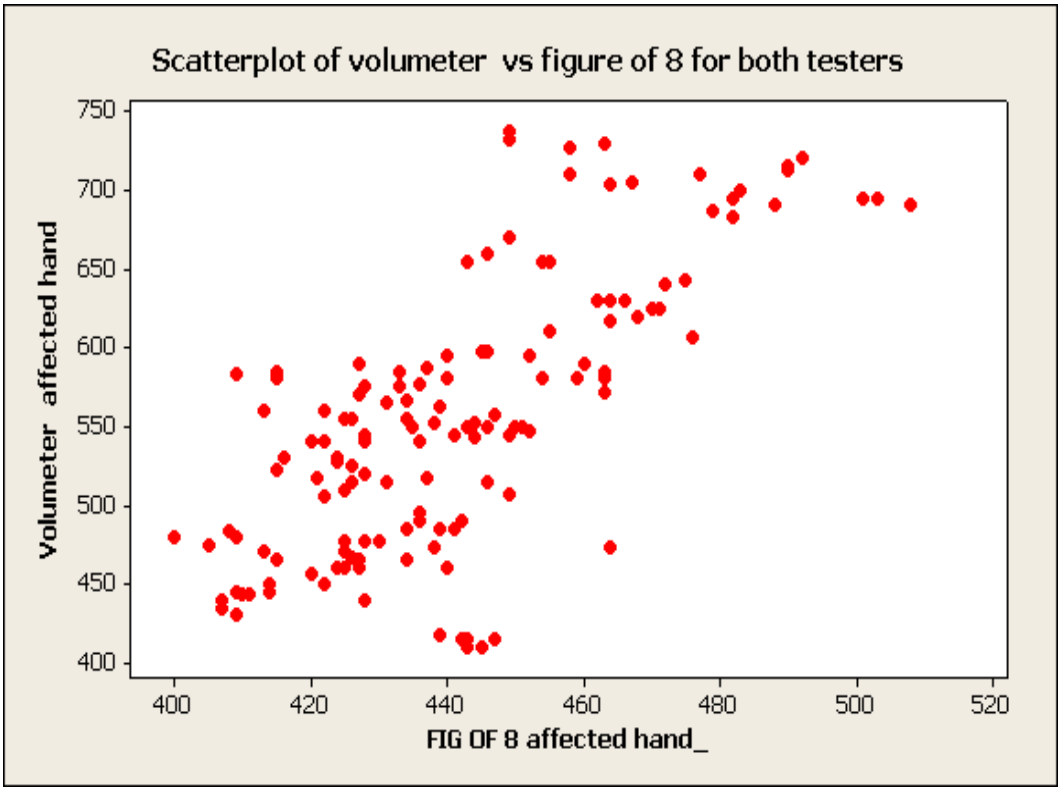

Figure 7. Scatterplot with the figure of eight measurements of the affected hand plotted against the volumeter measurements of the affected hand (n=72)

3.3 Discussion

The results from this study demonstrate good inter-tester reliability for the figure of eight method of measuring hand volume in people with BCRL as shown by an ICC (2.1) of 0.84. There was a high intra-tester reliability using ICC (3.1) for the figure of eight measurement (0.889 for tester 1 and 0.919 for tester 2). Portney and Watkins (2009 pge82) have expressed that the reliability correlation must exceed 0.90 to ensure there is valid clinical measurements but also that any correlation value exceeding 0.75 indicates that there is good correlation. Previous studies using the figure of eight method of measurement have also reported high levels of inter and intra-tester reliability. Maihafer et al (2003) and Pellecchia (2003) tested patients with no hand pathology and reported an intra-tester reliability of 0.99. Leard et al (2004) and Dewey et al (2007) carried out their studies with participants who had hand pathology. The participants in Leard et al (2004)'s study were described as either post surgical intervention or with carpal tunnel syndrome and the participants in Dewey et al (2007)'s study were patients with hand oedema following burns. Both reported high intra-tester reliability for the figure of eight tape method measurement with a range between 0.96 - 0.98 over the two studies. The lower reliability in the present

study may have been due to the fact that the testers were novice practitioners who had only received one hour of training and had no prior clinical experience of patients with lymphoedema. This was similar to Leard et al (2004) who also used final year students but they had more training with a practice time of two hours and measurements on seven individuals with no history of hand pathology and seven people with previous hand injury. They then discussed their results with each other and a senior investigator. However, unlike the current study, the testers were not blinded to their results which could have introduced bias. In Dewey et al (2007) the testers were trained occupational or physical therapists. However the results show that the figure of eight method is a reliable method of measuring BCRL even in novice practitioners.

Similarly, like the present study, the studies by Dewey et al (2007) and Leard et al (2004) focused on subjects with hand pathology. The presence of hand oedema may affect the tension on the tape measure due to the swelling in the subcutaneous tissue. This may lead to difficulty in keeping the tape at a consistent tension which may have resulted in a variation of tape tension being used by these novice practitioners. By using novice practitioners the results from this study are more applicable to clinical practice as often it is generalist (non – specialist) health care practitioners carrying out the measurements to monitor or identify the BCRL.

The standard error of measurement for inter-tester reliability in the Dewey et al (2007) study was very similar to the current study at 5.8mm compared to 6mm respectively. In Leard et al (2004) the inter-tester SEM was only 2.8mm but this may have been small as the subject group being measured did not have oedema.

There was a high correlation coefficient of at least 0.82 and ranging to 0.85 for each of the trials in the present study indicating that even one measurement using the figure of eight method would be reliable rather than having to carry out repeated measurements at each clinical visit. The inter-tester correlation coefficients were higher for the volumeter trials ranging from 0.99 to 0.996 which again emphasises the reliability of this method.

The results of the figure of eight method compared to the volumeter method also correlated strongly (Pearson moment correlation coefficient was 0.70 for tester 1 and 0.75 for tester 2 with both values statistically significant at 5%) suggesting that the figure of eight method is a valid method of measuring hand volume in people with BCRL. This correlation value, however, was less than in previous studies. The Pearson moment correlation coefficients in the previous studies were 0.94 (no p value provided) (Pellecchia 2003), 0.94 for tester 1 and 0.95 for tester 2 (no p value provided) (Maihafer et al 2003), 0.94 for tester 1 and 0.92 for tester 2 ($p<0.01$)(Leard et al 2004) and 0.83 for tester 1 and 0.89 for tester 2 ($p<0.01$) (Dewey et al 2007). The result of the present study may again be a reflection of that fact that the measurements in the present study were taken by novice practitioners who were not accustomed to measuring hand oedema. There was also difficulty in standardising the position of the hand in the volumeter due to the amount of oedema in the hand or lower arm of some patients. In addition, there were a number of patients whose oedema extended into the lower arm. This volume would have been included in the water displacement but not included in the figure of eight measurement and this may have affected the validity measurements. In comparison the previous studies had used patient groups with localized hand pathology and hand oedema only (Leard et al 2004, Dewey et al 2007) or no hand pathology (Maihafer et al 2003, Pellecchia 2003). Although no p values were provided for the Maihafer et al (2003)and Pellecchia (2003) results, the Pearson moment correlation coefficient was slight higher in these studies than in the Dewey et al (2007) paper which used patients with hand pathology.

The figure of eight method of hand measurement, requiring only a measuring tape, is easier to use in the clinical setting compared to the volumeter, especially in community and domiciliary settings. The volumeter method is more time consuming, more costly and the equipment considerably less portable. The figure of eight method is also applicable in some situations where the volumeter is not e.g. where patients have skin conditions or open wounds, which is particularly important for this patient group who have an increased risk of cellulitis (Lymphoedema Framework 2006).

3.3.1 Limitations

A limitation of the study was that there was no details of the type of surgery undergone by each subject who participated in the study other than it is was part of the treatment for breast cancer.

The sample size for this study may also have been a limitation as it was estimated from a combination of data from a previous study and published literature on different populations from the one that this sample was drawn. The mean difference between the testers in this study was 0.9cms which is larger than the mean difference used in the power calculation (0.53cms) (see 3.1.8) as was anticipated with this sample group. The SEM was also higher than 0.3cm which was used in the calculation as the inter tester reliability showed a SEM of 0.58cms. However, the original calculation had only required seven subjects to be included to reach statistical significance and the study was carried out on 24 subjects. There was also an acceptable level of significance reached with all the validity statistics (see 3.2.4) ensuring that the data analysis carried out appears to have been on an appropriate sample size and the findings can be taken to be accurate.

One of the errors associated with the figure of eight method is ensuring a consistency in the tension in the tape especially over the oedematous area (Gjorup et al 2010). However, even allowing for this the intra- tester and inter-tester reliability was found to be strong. It should be noted however, that there were only two testers in the study so the inter-tester data was a comparison between these two testers only. To establish further the inter-tester reliability the study would need to be repeated with more testers.

The volumeter measurements require the patient to keep the limb still once submerged (Gjorup et al 2010). This was difficult to ensure as even conversation or the patient laughing caused a change in the amount of water displaced. However the results for this method of measurement were very high in keeping with it being the “gold standard” for measuring hand oedema.

3.4 Summary

The figure of eight method was found to be a valid and reliable method of measuring hand swelling related to BCRL. The findings of this study would thus support the use of this simple clinical measurement for determining the extent of hand swelling in women with BCRL. However this study did not investigate whether this method of measurement was sensitive enough to detect change in hand size. As measurements of the hand are used as a method of monitoring the change in swelling or the progression of lymphoedema, outcomes of treatment or management, as well as for early detection of oedema, it is important that any measurement method is able to detect small changes. It is also current clinical practice to use circumferential measurement for measuring hand size and so any change of practice should be based on evidence that the new method is more reliable and proven to be valid. Further research to establish if the figure of eight method of measuring hand size in people with BCRL is sensitive enough to detect change in oedema over time as compared to the volumeter or circumferential measurement should be undertaken to provide an evidence base to assist in guiding clinical practice and therefore this was one of the main aims of phase 2.

Chapter 4

4.1 Methodology Phase 2

As detailed in chapter 3, the reliability and validity of the figure of eight tape measurement method of measuring hand size in patients with BCRL was established but in order for this technique to be useful in the clinical setting it was important to also establish whether it was sensitive enough to detect any changes in hand size.

4.1.1. Aims

The purpose of the study was to determine if the figure of eight tape measurement method of measuring hand oedema was as sensitive as the "gold standard" method of water displacement with a volumeter or the commonly used clinical method of circumferential measurement. It was necessary to investigate whether this was the case in order that this simple clinical measure could subsequently be used in assessment and monitoring progress of hand oedema in BCRL.

In addition the circumferential method of measurement was not included in phase 1 so the reliability, validity and sensitivity to change were investigated in this study (phase 2).

The aims of the study were:

1. to examine the sensitivity to change of the figure of eight, circumferential and volumeter methods of measuring hand size

2. to assess the intra-tester reliability and validity of the circumferential measurement of measuring hand size by comparing it with the "gold standard" approach of water displacement

3. to re –examine the reliability and validity of both the figure of eight method and volumeter method of measuring hand size when used by an experienced lymphoedema practitioner and to confirm the results of reliability and validity of the phase one study

4. to consider the natural variability of the unaffected hand size

4.1.2 Study Design

This study was based on a similar published study by Leard et al (2008).

The sample was a convenience sample of women with hand lymphoedema secondary to treatment for breast cancer who attended the NHS Forth Valley specialist outpatient lymphoedema clinic, based at Strathcarron Hospice, for management of their lymphoedema. This sample differed from those in study 1 (see section 3.1.2.) as they were all receiving active treatment to reduce their lymphoedema (see section 2.7.1).

Potential participants who fitted the inclusion criteria (see section 4.1.3.) were identified by the lymphoedema specialists at the NHS Forth Valley specialist outpatient clinic based at Strathcarron Hospice. Appropriate patients attending for the management of their lymphoedema were informed about the study. If they were interested in participating they were provided with a patient information leaflet (see appendix H). They were asked if, after reading the information leaflet, they were happy to participate in the study. The measurement sessions took place at the clinic and were incorporated into routine appointments rather than the patients attend for any extra appointments.

All participants in the study gave informed written consent (see appendix I).

4.1.3 Inclusion/exclusion criteria

The inclusion and exclusion criteria for study two was very similar to that of study one (see section 3.1.3.).

To be included in the study, participants had to be adult females of any age presenting with lymphoedema affecting their hand following treatment for breast cancer at any stage of treatment (exception below). Participants did not necessarily have to be recruited at their first appointment but they had to be at the start of a new episode of treatment. As the aim of the study was to measure

sensitivity to change, the actual treatment programme for each participant was not important to the study.

Those excluded from the study were patients entering the end of life stage i.e. with a few weeks to live as it was not felt it would be appropriate to include them in the study and it may have been difficult for them to stand for the required time to undertake the volumeter measurements (see 3.1.3). Also excluded were patients with co morbidities affecting their upper limb which would affect their ability to carry out the volumeter measurements as they would be unable to achieve the specific position required to standardise these measurements.

Any adults who were unable to give informed consent were excluded.

Due to contraindications of using the volumetric system of measurement, patients with open wounds, abrasions or other skin conditions were excluded from the study (Sorenson 1989) although this would not have excluded them from the other two measurement methods.

4.1.4 Testers and Recorder

The tester for this study was the researcher (YB) who carried out all of the measurements. This meant that the measurements were taken by an experienced trained lymphoedema specialist for this phase of the study rather than novice practitioners as in phase 1.

In order to blind the tester from the results, the figure of eight measurements and the circumferential measurements were taken with a blank tape, as in phase 1 (see section 3.1.5.1.), which was then passed to a recorder, who was the other lymphoedema specialist at the clinic, to measure against a meter stick and record to the nearest millimetre. A standard form was used to record the data (see appendix J).The same recorder also measured the amount of water displaced from the volumeter tank in the calibrated cylinder and used the same form to record this value to the nearest millilitre.

The same tester and recorder were used for each participant.

4.1.5 Procedure

The main aim of the study was to investigate the sensitivity to change of the figure of eight measurement method.

The participants were only required to attend the clinic as part of their normal, agreed management plan. The measurements were taken on two occasions. The initial sets were taken before a new intervention or course of treatment had taken place and then the second set of measurements was taken on review. The measurement sessions added no more than 20 minutes to the patient's normal appointment time. The recorder was blinded to the results from the first set of measurements to the second set as blank forms were used on each occasion so as not to introduce bias.

Before testing, data was collected from each subject including date of birth, surgical history, the presence of unilateral or bilateral oedema and duration of the presence of oedema.

The subjects had measurements taken at the start of the treatment course before any intervention had taken place. Both hands were measured by each method of measurement, figure of eight, circumferential and volumeter, by one tester. These were then recorded. The measurements were repeated three times (three trials) by the tester for each hand by each method of measurement. This allowed the intra-tester reliability to be examined. These measurements were then repeated on the final appointment of the treatment course to provide post intervention measurements.

The study therefore built on the reliability results of the previous study by investigating the reliability of the figure of eight method of measurement when measurements were taken by an experienced lymphoedema specialist rather than novice practitioners. The subject group was also different for this study as the patients who were recruited were all attending for active management of their lymphoedema and had more complex lymphoedema than the subject group in phase one (see section 3.2) Repeating the tests to examine reliability and validity would add to the evidence that this was an appropriate measurement method for use within this population. Repeating the measurements three times,

was in keeping with the protocols used in the previous studies (Maihafer et al 2003, Leard et al 2004) and thus allowed a comparison of results.

4.1.5.1. Figure of eight measurement method

Figure of eight tape measurements were carried out using the technique described in Dewey et al (2007) and for phase 1 of this study. The subject's arm was supported on a table with the forearm in pronation, the wrist in neutral and the fingers rested in adduction. The figure of eight measurements were taken by passing a blank 5mm tape around the hand. In order to avoid any potential bias and to therefore guarantee that the tester was blind to the values measured, a blank tape was used. As in the previous study, this was achieved by using gift ribbon which allowed no values to be shown, was also the same width as many tape measures used in clinical practice, was inexpensive and it could be disposed of after each measurement ensuring there were no issues of cross infection between patients (see section 3.1.5.1).

The same technique for measurement was used as in phase one (see section 3.1.5.1). A new blank piece of tape was used for each measurement.

4.1.5.2. Volumeter/water displacement

The technique described in section 3.1.5.2 was used for the water displacement method of measurement. The beaker of dispersed water was passed to the recorder who transferred the water to a graduated cylinder and recorded the amount of water displaced in millilitres. This process was repeated three times (three trials) by the tester for each hand.

4.1.5.3 Circumferential measurement

The circumferential measurements were taken using the same blank gift tape as described for the figure of eight method to ensure the tester was "blind" to the results. As there is no standard method described for this measurement (see section 2.10.2), it was taken in the method which is generally used clinically which involves a simple circumferential measure around the base of the fingers at the metacarpal phalangeal joint line (see figure 8). The tape was then marked and cut distally to the mark. This piece of cut tape was then passed to the

recorder who measured the tape against the wooden measurement rod and recorded the measurement to the nearest 1mm.

This was repeated three times (three trials) by the tester for each hand.

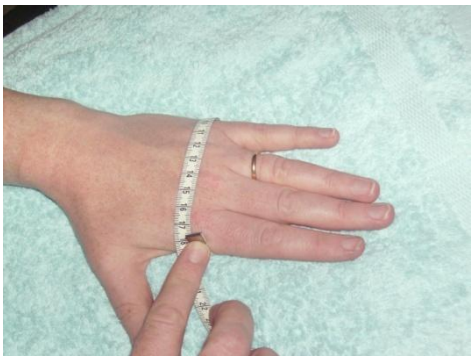

Figure 8: circumferential measurement

4.1.6 Advisory Group

As this was an unfunded study to assess the sensitivity of the measurement technique service users/carers were not specifically involved in its design. This second phase of the study was discussed with the advisory group from the first phase and received their support. The study was discussed with students attending the University of Glasgow Graduate Diploma in Lymphoedema programme and the response to the study was overwhelmingly positive.

4.1.7. Permissions and Approvals

An application was made to the Tayside Committee on Medical Research Ethics B and approval for the study was given (see appendix K). There were no significant changes to the application other than some standard wording to be inserted into the patient documentation. Also, the committee felt there was no need to inform the patient's GP of their participation in the study. It was felt by the committee that, as there was no change to treatment or management, it was unnecessary for the GP to receive a letter.

Research and Development approval was also obtained through NHS Forth Valley and support and indemnity for the study was provided by Strathcarron Hospice.

4.1.8. Data Analysis

To establish an appropriate sample size no formal power calculation was undertaken but data from previous work on the sensitivity of the figure of eight method of measuring hand size was used to provide the sample size required for the present study (Leard et al 2008). The figure of twenty five participants therefore was chosen as this was similar to the published paper which used the technique to investigate responsiveness of detecting hand size changes in patients with hand pathology (Leard et al 2008).

Descriptive statistics were calculated for each of the measurements and for the pre and post intervention data. Data was analysed using Statistical Package for the Social Sciences 19 (SPSS 19) and Minitab (v16). The intra-tester reliability was examined using intra-class correlation coefficients, ICC (3.1). These were calculated for all three measurement methods, circumferential measurement, figure of eight and volumetric measurements to assess the reliability of the tester.

In order to investigate if there was a change in the hand size of the participants paired t-tests were used to compare the pre and post intervention measurements for each method separately. The original proposal was that, provided there was evidence of a statistically significant difference in hand size, Cohen's effect size would be calculated to determine the responsiveness to change for each method. However, as there was difficulty in recruiting the full sample (see section 4.2), it was advised that the Wilcoxon signed rank test was more appropriate to the sample size.

This amount of change in size was then compared between the different measurement methods as an indication as to whether or not the different methods were similarly responsive.

The unit value of each measurement was different (volumeter is measured in mls, whereas the circumferential and figure of eight methods were measured in

mms), therefore, in order to assess whether the measurement methods were similar in detecting a change in hand size, the change between the before and after intervention measurements was considered as a percentage.

The natural variability in change in size of the unaffected hand was also considered by looking at the amount of change as a percentage which occurred over the period of treatment and whether this was measured consistently by the three measurements methods. This also allowed a comparison between the affected and non affected limbs.

4.2 Results Phase 2

Over the period of recruitment, eleven potential subjects fulfilled the inclusion criteria and were invited to participate. All 11 subjects agreed and were recruited for phase 2. One of these participants required further investigations regarding the status of her breast cancer during the time she was attending for treatment and so the second set of measurements were not taken. As this participant did not complete the study her data was removed. Therefore the data reported was for the 10 subjects who completed the study with pre and post treatment measurements.

4.2.1 Demographics

The average age of subjects was 65 years (range 49-86 years) and subjects had hand oedema for a mean of 46.2 months (range 16-117 months). All of the 10 subjects who participated had previous surgery for breast cancer and were, on average, 76.9 months after surgery (range 22-143 months) (Table 7).

	Mean	Range
Age (years)	65	49 -86
Time since surgery (months)	76.9	22-143
Duration with hand oedema (months)	46.2	16-117

Table 7: Demographic information of sample (n=10)

4.2.2 Descriptive statistics

4.2.2.1 Descriptive statistics for the affected hand

Descriptive statistics for each of the measurement methods for the oedematous hand are shown in Table 8. This data was calculated from the mean of the three trials carried out by each method of measurement before and after intervention. The time difference between the measurements taken before and after intervention had a range of five to eleven days with a mean of 9.2 days.

Before treatment the mean measurement of the affected hand for the 10 subjects was 205mms (range 180-240mms) by the circumferential measurement and post intervention it was 206mms (178 – 229mms). The standard deviation for these two sets of measurements was 17mm prior to intervention and 16mms after intervention. There was little difference, therefore, between the pre and post intervention measurements.

For the figure of eight measurement method, the mean measurement was 445mms (range 395-517mms) prior to intervention and 431mms (range 398 – 494mms) post intervention. The standard deviation was 37mm for the measurement prior to treatment and 29mm post treatment. So there was an overall decrease in hand size over time.

The volumeter measurements had a mean of 613.8mls (range 440-820mls) prior to intervention and 599.3mls (range 453.3-773.3mls) post intervention. The standard deviation for this method of measurement was 129.6mls and 110.9mls respectively. This again showed a decrease in hand size over time.

Affected Hand									
	Circumferential (mms)			Figure of eight (mms)			Volumeter (mls)		
	Mean	Range	St.Dev	Mean	Range	St. Dev	Mean	Range	St. Dev
Pre - intervention	205	180-240	17	445	395-517	37	613	440-820	129.6
Post intervention	206	178-229	16	431	398-494	29	599	453.3-773.3	110.9

Table 8: Descriptive statistics (means, range and standard deviations (St Dev)) for the circumferential, figure of eight and volumeter measures for both sets of measurements for the affected hand only, using the mean of the three trials for each method of measurement for pre and post intervention measurements (n=10)

Affected Hand									
	Circumferential (mms)			Figure of eight (mms)			Volumeter (mls)		
Pre intervention	Mean	Range	St.Dev	Mean	Range	St. Dev	Mean	Range	St. Dev
1st measurement	205	180-239	17	445	396-517	36	606.6	435-795	119.6
2nd measurement	205	178-237	17	444	394-514	37	622.2	440-840	146.8
3rd measurement	207	183-243	17	446	395-519	37	612.5	445-845	133.3
Post intervention	Mean	Range	St.Dev	Mean	Range	St.Dev	Mean	Range	St.Dev
1st measurement	206	177-229	18	434	400-490	30	596	450-775	113.2
2nd measurement	206	179-230	15	434	398-492	30	601.5	455-775	110.8
3rd measurement	207	179-230	18	435	395-500	33	600.5	455-770	110.9

Table 9: Descriptive data for each trial for the affected hand pre and post intervention including mean, range and standard deviation (n=10).

Table 9 displays the descriptive data for each trial for the affected hand.

These descriptive statistics showed that for the circumferential and figure of eight methods there was consistency shown across each trial. The mean measurement for each trial, the range and also the standard deviation for each trial are consistent across the three trials (Table 9). This was less so with the volumeter method.

There was also a decrease in hand size detected between the pre and post intervention measurements by the figure of eight and the volumeter methods of measurement but not by the circumferential measurement.

4.2.2.2 Descriptive statistics for unaffected hand

Table 10 shows the descriptive data for each trial for the unaffected hand. All three methods of measurement showed little variation throughout the trials in the mean value, the range and the standard deviation.

As would be expected there was little variation in the measurements for the unaffected hand over the time period of the pre and post intervention on the affected hand. All three measurement methods were also shown to be consistent across the three trials for both sets of measurements.

Unaffected hand									
	Circumferential(mms)			Figure of eight (mms)			Volumeter (mls)		
Pre intervention	Mean	Range	St.Dev	Mean	Range	St.Dev	Mean	Range	St. Dev
1st measurement	199	185-213	11	415	399-446	16	501	405-625	70.6
2nd measurement	195	180-212	11	413	394-444	17	505	410-685	82.2
3rd measurement	197	180-211	9	414	393-445	18	507	410-690	84.5
Post intervention	Mean	Range	St.Dev	Mean	Range	St.Dev	Mean	Range	St.Dev
1st measurement	197	181-220	12	413	390-449	18	511	405-670	81.3
2nd measurement	201	183-240	17	414	395-447	16	513.5	415-665	80.5
3rd measurement	199	182-230	15	414	396-452	17	515.2	410-675	83.4

Table 10: Descriptive data for each trial for the unaffected hand pre and post intervention including mean, range and standard deviation (n=10)

4.2.3 Pre intervention base line difference between the affected and unaffected hand

The difference between the affected and the unaffected hands at the pre intervention measurement session was calculated to give an indication of the amount of oedema present in the subject group (table 11). The mean of the three measurements taken was calculated for each measurement method.

Difference between affected and unaffected hands		
	Range	Mean
Circumferential method	-5mm to 28mm	9mm
Figure of eight method	-7mm to 72mm	31mm
Volumeter	21.7 to 316.7mls	108.4mls

Table 11. Difference in measurements between affected and unaffected hand (n=10). Measurements were calculated as the mean of the 3 pre intervention measurements taken by each method.

The difference between the unaffected hand and the affected hand was calculated by the following method:

Difference = affected hand size – unaffected hand size

Overall the affected hand was larger than the unaffected hand. When using the circumferential method of measurement there were four patients whose unaffected hand measured larger than their affected hand. This gives the negative measurement in the table shown above. There was only one patient whose unaffected hand also measured larger than the affected hand with the figure of eight method of measurement which gives the value of -7mm in the range. None of the patients' unaffected hands measured larger than the affected hands by volumeter.

4.2.4 Difference in measurement pre and post intervention

The change in measurements between the pre treatment measurement and the post treatment measurements were also calculated for each patient and summarised in table 12 to show the range of difference in these measurements

for each method of measurement and also the mean difference. When there was a decrease in the measurements after intervention this was shown as a negative number and when the measurement increased this was recorded as a positive number.

Change in measurements post intervention		
	Range	Mean
Circumferential method	-11mm - +9mm	0.8mm
Figure of eight method	-27mm - +3mm	-10.7mm
Volumeter	-96.7mls - +40mls	-14.4mls

Table 12: Summary of difference between pre and post intervention measurements for the affected hand by each measurement method (n=10) using the mean of each set of 3 measurements taken. A negative number representing a reduction in hand size and a positive number representing a measured increase.

By using the circumferential measurement method there was a range over time of a loss of 11mm through to an increase of 9mm for the affected hand. The mean measurement of this range was an increase of 0.8mms which is so small a value it would indicate no change. For the figure of eight method of measurement and the volumeter method there was a reduction in size for the affected hand post treatment of 10.7mm and 14.4mls respectively. However, the range of measurements by the figure of eight method showed a reduction of up to 27mms but an increase for one patient of 3mms and the volumeter measurement had a range from a loss of 96.7mls to an increase of 40mls.

Table 13 summarises the subjects whose hands measured an increase in size after intervention. This is shown for each measurement method as this was not consistent across the different measurement methods.

Subject 8 measured an increase in hand size by all three methods of measurement and, so despite intervention, it has to be presumed that this subject's hand size had increased over the period of time. This was the only subject whose hand size increased after intervention when using the figure of eight method.

For the circumferential method, there were six subjects whose hand size increased after treatment. Six subjects hand size also increased from pre to post intervention measurements by the volumeter method. There was agreement in this between the circumferential method and volumeter on five of these subjects, one being subject 8 as discussed. However, for three other of these patients (subjects 3, 6, 11) it was recorded that they could not achieve the standardised position in the volumeter for their pre intervention measurements, discussed below. After intervention these subjects all achieved the standardised position in the volumeter, so this may have caused a false increase in their measurements.

It was documented on the subjects data form by the tester if the subject had not been able to achieve the standardised position in the volumeter. In order for patients to ensure that the web space of their third and fourth finger was at the dowel in the volumeter, a portion of their forearm above the wrist was submerged and was also included in the water displacement. Table 13 shows which patients had difficulty achieving the standardised position for using the volumeter prior to treatment. All the patients in this study not only had hand oedema, but also arm oedema. This meant for six of the patients (subjects 3,4,6,7,10,11) the size of their distal arm was too large to comfortably achieve the standardised position in the volumeter and so they immersed their hand to as near the dowel as they were able to manage. This may have caused an underestimation of the volume as less of the arm may have been submerged.

Measurement method	Number of patients with an increase in measurement	Subject number
Circumferential	6	3,6,8,9,10,11
Figure of 8	1	8
Volumeter	6	3,6,7,8,9,11
Patients with difficulty submerging hand to standardised position in volumeter	6	3,4,6,7,10,11

Table 13: Summary of the patient numbers with an increase in measurement after intervention for each measurement method, the subject numbers with this increase and patients with difficulty in achieving the standardised position in the volumeter.

The following figures demonstrate the relationship between the pre and post intervention measurements for each measurement method (Figures 9-11). In each instance the mean for each three trials of measurement have been plotted using the pre intervention measurements and post intervention measurements for each patient (a). A second figure (b) showing all the pre and post intervention measurements for each method has also been included.

Figure 9a shows mean values for each patient for the three trials pre and post intervention using the circumferential method plotted with a line of equality included. It shows an increase in hand size for the majority of the measurements post treatment. In Figure 9b all the measurements (n=30) for this method are plotted and this figure shows that for eleven measurements there was an increase between pre and post intervention measurements but for eleven measurements there was a decrease and for eight measurements there was no change detected.

Figure 10a shows the mean values for each patient for the three trials pre and post intervention using the figure of eight method plotted with a line of equality also included. It shows that the majority of the measurements reduced post treatment. In figure 10b all the measurements for this method are plotted and this shows again that the majority of the measurements decreased post

intervention other than four which increased slightly and one which remained unchanged.

Figure 11a shows the mean measurements from the three trials using the volumeter method for each patient. It shows that six values increased after intervention. Figure 11b, displays all the values for the volumeter method, there were twelve measurements which reduced, fourteen which increased and four were unchanged.

It can be seen that by the figure of eight method most of the hand measurements showed a decrease in size after intervention which was in keeping with clinical findings.

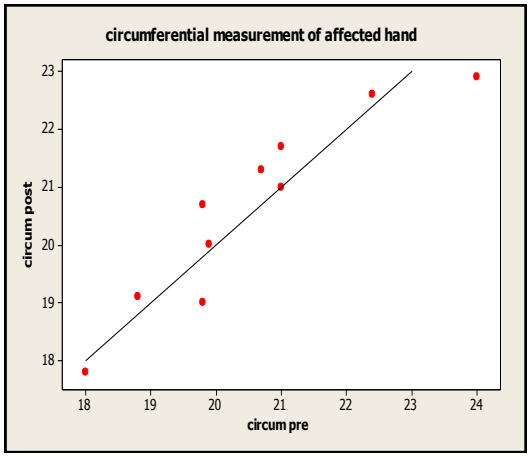

Fig 9a: The mean of the three trials by circumferential method of measurement pre intervention (circum pre) v post intervention (circum post) (n=10). A line of equality has been plotted.

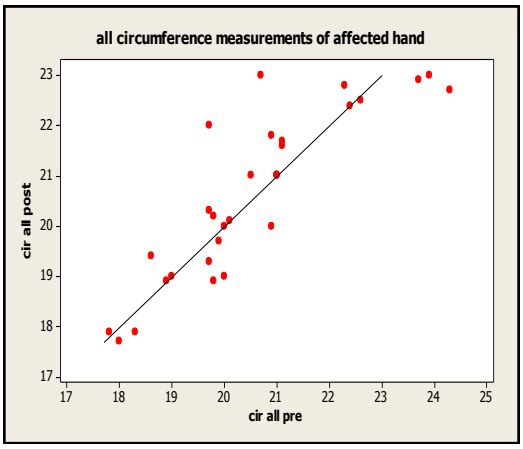

Fig 9b: All circumferential measurements pre intervention (circum pre) v post intervention (circum post) (n=30). A line of equality has been plotted.

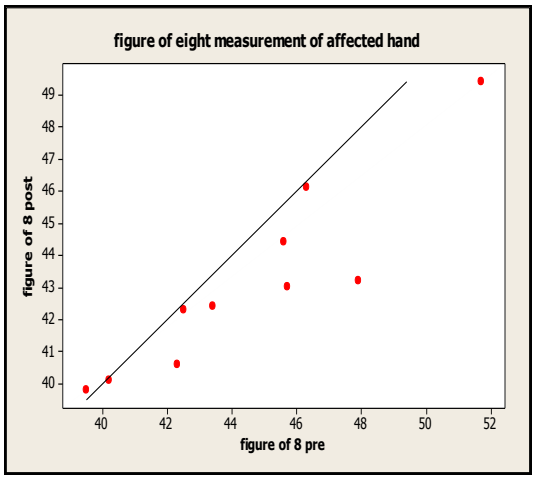

Fig 10a: Mean of the three trials by figure of eight method of measurement pre intervention (figure of 8 pre) v post intervention (figure of 8 post) (n=10). A line of equality has been plotted.

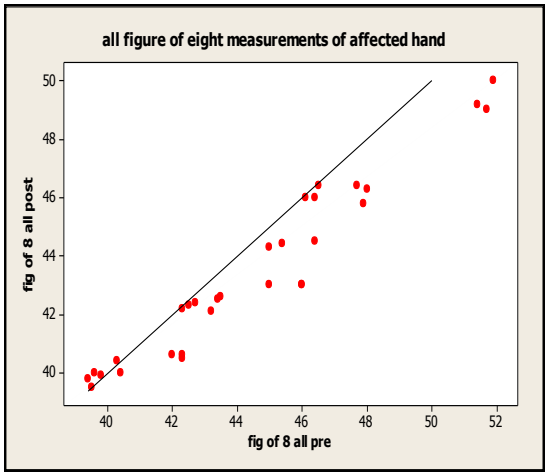

Fig 10b: All figure of eight measurements pre intervention (circum pre) v post intervention (circum post) (n=30). A line of equality has been plotted.

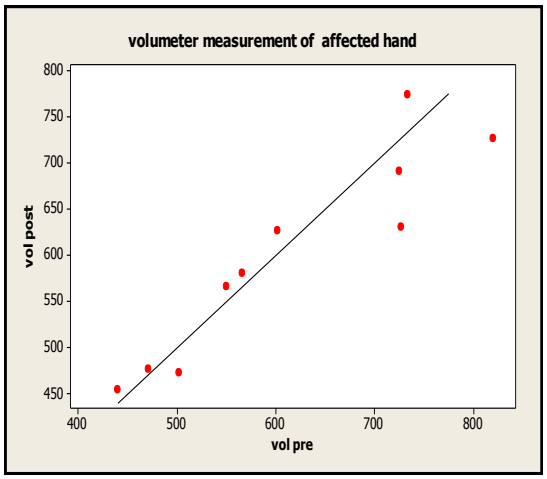

Fig 11a: Mean of the three trials by volumeter measurement pre intervention (vol pre) v post intervention (vol post) (n=10). A line of equality has been plotted.

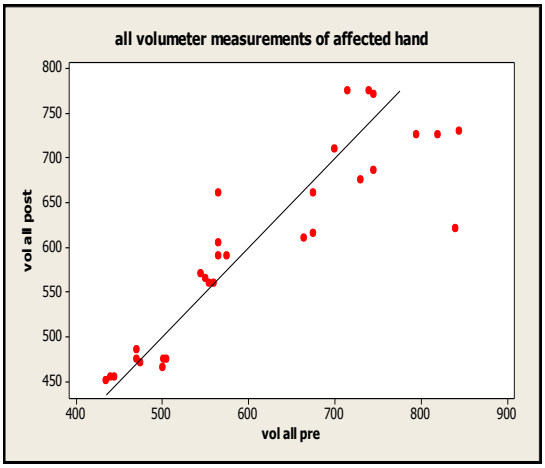

Fig 11b: All volumeter measurements pre intervention (circum pre) v post intervention (circum post) (n=30). A line of equality has been plotted

4.2.4.1 Percentage change in measurement pre and post intervention

The difference in the affected hand before and after intervention was calculated for each method. As the unit value of each measurement was different (volumeter is measured in mls, whereas the circumferential and figure of eight methods were measured in mms) in order to assess whether the measurement methods were similar in detecting the change in hand size, the change between the before and after intervention measurements was expressed as a percentage (Table 14).

Percentage change between pre and post intervention measurements for the affected hand						
	Circumference (mms)		Figure of 8 (mms)		Volumeter (mls)	
Pt. No	Diff	%	Diff	%	Diff	%
1	0	0	-27	-5.9	-96.7	-13.3
3	2	0.9	-17	-3.5	25	4.1
4	-11	-4.6	-23	-4.4	-35	-4.8
5	-7	-3.5	-16	-3.8	-31	-6.2
6	1	0.5	-12	-2.6	40	5.4
7	-2	-1.1	-1	-0.2	13.3	3
8	3	1.6	3	0.8	5	1.1
9	9	4.5	-2	-0.5	15	2.7
10	-7	-3.3	-2	-0.4	-93.3	-11.4
11	6	2.9	-10	-2.3	13.3	2.3
Mean change	0.8	0.32	-14	-3.15	-14.4	-2.2
St. dev	6.4	3	15	3.5	48.3	7.35
Range %	-4.6 – 4.5		-5.9 – 0.8		-13.3 – 5.4	

Table 14: The change in affected hand size for the two sets of measurements, pre and post intervention, for each measurement method and the percentage difference this represents (n=10)

Diff=difference in pre and post intervention measurements, % is percentage change

St.Dev = standard deviation

There does not seem to be any consistency between the measurements when percentage change is examined. The trends in the data were the same as shown previously but by examining the percentage change it was possible to look at the extent of the differences by each measurement method.

There was a maximum loss recorded by the circumferential method of 4.6% in hand size but also a maximum increase of 4.5 %.

The figure of 8 measurement method measured an increase of less than 1% for the patients whose hand size was shown to have increased post intervention. The maximum percentage loss detected by this method of measurement was 5.9%.

For the volumeter method, the maximum loss calculated was 13.3% with the maximum increase being 5.4%.

In summary, only the figure of eight method showed a decrease in hand size for the majority of the patients and the volumeter method showed the most variation in the measurements.

In order to consider the natural variability over the period of time that the measurements were taken, the difference and percentage change were also calculated for the unaffected hand (Table 15).

Percentage change between pre and post intervention measurements for the unaffected hand						
	Circumference (mms)		Figure of 8 (mms)		Volumeter (mls)	
Pt.No	Diff	%	Diff	%	Diff	%
1	18	7.7	27	6.7	-1.7	-0.33
2	-2	-1	-9	-2.1	-44.3	-8.2
3	-1	-0.5	4	0.9	-3.3	-0.5
4	3	1.5	2	0.7	15	3.7
5	-2	-0.1	-11	-2.5	13.3	2.4
6	-3	-1.6	-5	-1.2	6.7	1.6
7	1	0.5	-2	-0.5	-1.7	-0.04
8	-5	-2.5	-6	-1.4	6.7	1.3
9	-2	-1.1	0	0	85	16.9
10	18	8.5	-7	-1.6	67	1.2
Mean Change	2.5	1.14	-0.7	-0.1	14.27	1.8
St.Dev.	8.45	3.83	10.85	2.64	36.7	6.2
RANGE	-2.5 – 8.5%		-2.1 – 6.7%		-8.2 – 16.9%	

Table 15: The change in unaffected hand size for the two sets of measurements, pre and post intervention, for each measurement method and the percentage difference this represents (n=10)

Diff=difference in pre and post intervention measurements, %=percentage change

St.Dev = standard deviation

The unaffected hand also appeared to have some variability over time but less than the affected hand. The means show a very small change of less than 2% by any of the methods. However the figure of eight method was the only one of the measurement methods to record a very small decrease in measurements with a mean reduction in size of 0.1%. The ranges of these measurements show a large amount of individual variability. The percentage change for circumferential measurements ranges from a decrease in size of 2.5% to an increase of 8.5% (equivalent to a reduction of 5mm to an increase of 18mm). The figure of eight method ranged from a decrease of 2.1% to an increase of 6.7% (equivalent to a decrease of 9mm to an increase of 27mm) and the volumeter ranged from a

decrease of 8.2% in volume to an increase of 16.9% (a loss of 44.3mls to an increase of 85mls).

4.2.5 Intra-tester reliability

The phase one study established strong intra-tester reliability for both the figure of eight and the volumeter methods of measurement (see 3.2). This phase one study was carried out with novice practitioners as testers. The circumferential method was not included in the phase one study

The summary of the ICC (3.1) carried out for each method to examine intra-tester reliability including the standard error of measurement (SEM) are shown in table 16 and table 17. Table 16 includes the ICC (3.1) results from the phase 1 study for each of the two testers.

	Intra-tester reliability ICC (3.1)		
	Phase 2	Phase 1	
		Tester 1	Tester 2
Circumference	0.97 SEM=2.6mm		
Figure of eight method	0.99 SEM=3.6mm	0.89 SEM = 7mm	0.92 SEM= 6mm
Volumeter	0.99 SEM=11.1mls	0.99 SEM=8.4mls	0.99 SEM=8.4mls

Table 16: Intraclass correlation coefficients (ICC3. 1) and SEM (St.Dev x √1-R (R=reliability)) for all measurements taken by each method for both the affected and non affected hand for phase 2 compared with the ICC (3.1) reported in phase one.

As these results are assessing the reliability of the tester it was possible to include all the measurements of both the affected and unaffected hand. The ICCs (3.1) for intra-tester reliability were shown to be high using each method with a correlation coefficient of above 0.97 for each. The standard error of measurement was also small for each measurement method. These are comparable with the results from phase one although the correlation is slightly stronger for the figure of eight method in the second phase perhaps as it was an

experienced practitioner acting as the tester. There was a slightly higher SEM for the volumeter method in phase 2 which may relate to the problems with positioning for this subject group (see 4.3.4).

	Intra-tester reliability ICC (3.1)			
	Affected hand		Unaffected hand	
	before	after	before	after
Circumference	0.99 (SEM=1.6)	0.95 (SEM=3.6)	0.95 (SEM=2.2)	0.98 (SEM=2)
Figure of eight method	0.99 (SEM=3.6)	0.96 (SEM=6)	0.98 (SEM=2.3)	0.99 (SEM=1.7)
Volumeter	0.97 (SEM=22.4)	0.99 (SEM=10.8)	0.99 (SEM=7.66)	0.98 (SEM=10.1)

Table 17: Interclass correlation coefficient (3.1) for each method of measurement for both pre and post intervention measurements and for the affected (n=30) and unaffected hands (n=30). SEM is also calculated by formula SEM=St.Dev x √1-R (R=reliability)

Table17 displays the ICC (3.1) of the measurements for each hand, pre and post intervention. Although the ICC (3.1) again indicated a very high level of reliability, the standard error of measurement in the volumeter in the pre intervention measurement of the affected hand was much higher compared to the other measurements. This is perhaps due to the inconsistency of positioning due to the oedema present in the lower arm as previously mentioned.

4.2.6 Validity of the measurement methods

To consider the validity of the different measurements Pearson moment correlation coefficients were calculated. This calculation was carried out using all the measurements for each trial (see table 18). Although the validity of the figure of eight and volumeter had been established using this method in phase one of the study (see 3.2), the validity of the circumferential method was not included in phase 1. In addition it was of interest to re- examine the validity of

the figure of eight method with an experienced lymphoedema practitioner as the tester.

	Circumference before	Figure of eight before
Volumeter before	0.59 (p=0.057)	0.74 (p<0.0001)
	Circumference after	Figure of eight after
Volumeter after	0.64 (p<0.0001)	0.79 (p<0.0001)

Table 18: Pearson moment correlations and p value for affected hand for before and after intervention measurements using all the measurements from the three trials (n=30)

When the data were compared for all trials (30 measurements for each hand) the p value indicated a statistical significance except with the pre intervention circumference and volumeter methods. There was only a weak correlation between the volumeter method and circumferential whereas the correlation between volumeter and figure of eight remains strong (Portney and Watkins 2009).

In phase one (see section 3.2), Pearson moment correlation for the volumeter method and the figure of eight method was similar to the results for phase two (tester one= 0.7, tester two = 0.75) and these results were also statistically significant.

As there had been problems with standardising the position for the volumeter for patients in this second study, and because circumferential measurements are used clinically, the comparability between the figure of eight and the circumferential method was also examined (see table 19). There was a strong correlation between the figure of eight measurements and circumferential measurements indicated by the correlation coefficient of higher than 0.7 in all instances (Portney and Watkins 2009). There was a stronger correlation demonstrated in the measurements taken prior to intervention than post intervention, indicating that there was less strength in the relationship between these two measurement methods after intervention.

	Circumference before
Figure of eight before	0.94 (p<0.0001)
	Circumference after
Figure of eight after	0.83 (p<0.0001)

Table 19: Pearson moment correlations and p value for affected hand for before and after intervention measurements using all the measurements from the three trials (n=30)

4.2.7 Measurement of sensitivity to change

The Wilcoxon ranked signed confidence interval was calculated as a method of investigating sensitivity to change in measurements between the two episodes of data collection. Table 20 summarises the results of these tests.

Wilcoxon Signed Rank CI				
Method	Estimated Median	Achieved Confidence	Confidence Interval	
			Lower	Upper
Difference Circumference	-0.1	94.7	-0.5	0.4
Difference Figure of 8	1.2	94.7	0.2	2.45
Difference Volumeter	8.8	94.7	-19.1	44.1

Table 20: Wilcoxon signed rank confidence interval calculated using the mean from each set of measurements (n=10) CI = confidence interval

The only method of measurement which detected a change in hand size, by this calculation, was the figure of eight method as 0 was not included in the confidence intervals. This indicated that the pre intervention measurements were larger than the post intervention measurements. For the other two methods, there was not enough evidence to suggest a difference between pre and post treatment measurements as the confidence interval included 0 in each case. However, this may be due to the small sample size used.

These results would suggest that the figure of eight method was sensitive enough to detect change in hand size whereas the circumferential and volumeter methods did not have this sensitivity. However, whether the change in volumeter readings was truly reflective of the change in hand size has already been discussed (see section 4.2.4).

4.3 Discussion

It was intended to recruit 25 patients to this second phase of the study but only 11 patients met the recruitment criteria in the timescale available to carry out the data collection. From these 11 patients, only 10 patients were able to complete the full data collection. This smaller sample may have impacted on the findings and so caution needs to be taken when interpreting the data.

4.3.1. Sensitivity to change

One of the aims of the study was to examine the sensitivity to change of the three methods of measuring hand size in patient with BCRL – figure of eight, circumferential and volumeter. The results from the study suggest that the figure of eight method was sensitive enough to detect change in hand size whereas the circumferential and volumeter methods did not have this sensitivity.

A similar study to examine the sensitivity to change of the figure of eight method of measurement was carried out by Leard et al (2008). Leard et al (2008) designed their study to examine whether there was a relative responsiveness between volumeter and the figure of eight tape measurement method in detecting changes in hand size. This study recruited 25 patients who were under treatment at a specialist hand centre. All of the subjects had experienced hand surgery or hand or wrist injuries. The testers were not blinded to their results in the 2008 study as a previous study had been undertaken and established the reliability and validity of the figure of eight tape method (Leard et al 2004). Prior to the study commencing training sessions were carried out and intra-tester reliability was evaluated. The testers for both this phase two study and the Leard et al (2008) study were experienced in their field as a lymphoedema specialist and as certified hand specialists respectively.

Follow up hand measurements for both figure of eight method and volumeter were taken a minimum of two weeks after the original method. Leard et al's study (2008) differed in that there were five testers who all assessed a different number of patients but all the subjects were only assessed by one tester. The method of measurement for both the volumeter and the figure of eight method were standardised in the same way for both the 2008 study and the present study.

Cohen's effect size and also standardized response mean (SRM) were used as responsiveness indexes in the Leard et al (2008) study and the results also demonstrated that both the figure of eight method and volumeter had similar responsiveness to change in hand size.

Leard et al (2008) did not include circumferential measurements in their study.

In the present study neither circumferential nor volumeter measurement detected change in measurement between the pre and post intervention measurements. There is no published evidence to establish if circumferential measurement is a sensitive tool for hand measurement but it is accepted as current clinical practice as a method of monitoring hand size in this patient group.

Volumeter measurement is accepted as the "gold standard" method of measuring hand volume in lymphoedema. However, in this study it did not demonstrate sensitivity to change. This may be due to the difficulty in standardising position in the pre intervention measurement due to the study subjects having arm oedema as well as hand oedema as has been previously discussed (see section 4.2.4). This is a common clinical presentation in patients with BCRL. This study is the first to highlight this measurement problem and suggests that if the volumeter is being used to measure patients with hand oedema which also extends into their upper limb a commercial hand volumeter would not be satisfactory. A volumeter which measured full upper limb volume may be more appropriate for this patient group although that would not provide a separate hand volume to enable changes in the lymphoedema specifically affecting the hand.

4.3.2. Reliability

All three of the measurement methods investigated in the phase two study were shown to be reliable with the ICC (3.1), which demonstrates intra-tester reliability, all above 0.9 (Portney and Watkins 2009). There was also only a small standard error of measurement (SEM) with each measurement method which would be clinically acceptable.

No literature was found to support the reliability of the circumferential measurement method even though it used widely clinically. In this study, the circumferential measurement method showed strong intra-tester reliability in both pre and post intervention measurements when measuring both the affected and unaffected hand. This would indicate that this method is therefore reliable as a clinical tool.

The importance of using limb volume measurement to provide an outcome measure in lymphoedema management has been recognised and this can be achieved in a simple way, by using the circumferential measurements of the limb and then using this in the mathematical formula for calculating the volume of cylinder. It has been recognised, however, that because the hand is not cylindrical, this calculation is not accurate for the hand (Gerber 1998, Mayrovitz et al 2006). Although there have been studies which have compared the measurement of limb volume using circumferential measurement and the water displacement method, these have all been concerned with the arm size (Karges et al 2003, Taylor et al 2006) rather than any studies which have looked specifically at measuring hand size. There was one study, carried out by Foroughi et al (2011), to assess the inter-rater reliability of arm circumference measurement but again this did not include the hand.

Sander et al (2002) compared various geometric measurements of the hand with volumeter and had high ICCs for four methods of calculating the volume of the hand (range of 0.81-0.91). The four methods used in the study were the mathematical formulae for calculating the volume of a cylinder, a frustum, a rectangle and a trapezoid. The hand was measured at 3 cm intervals using a spring loaded tape. The measurements of the hand were taken with the elbow bent at 90 degrees and the hand held in the air. It is difficult to ascertain from

the description of the measurement of the hand what the start point for the first section was but the measurements finished at the marking for the wrist. Sander et al (2002) reported that calculating the volume from these circumferences by using the formula for a rectangle or a trapezoid had the best correlation to the water displacement method. However, the frustum method had the smallest SEM (16mls) and the study recommended that this should be the preferred method of calculation. Using sequential circumferential measurements to calculate the volume of the hand is not common clinically. In the study by Sander et al (2002), the second tester was not blinded to the first tester's measurements which may have increased the reliability measures.

However, the indication that the circumferential method of measurement is reliable as a measurement method may negate the need for complicated mathematical calculations. The standard measurement site used in this study, i.e. across the metacarpal phalangeal (MCP) joint line, has demonstrated good reliability and therefore could be adopted as a clinical standard for this measurement. It is recognised however that the circumferential method may not measure the area where the oedema is most likely to form. As discussed previously (see section 2.12.2.) the anatomical structure of the hand allows the oedema to collect in the subcutaneous tissues on the dorsum of the hand. This area is more proximal than the metacarpal MCP joint line which was used as a standardised measurement point for the study. This area however is included in the figure of eight method of measurement.

Several studies have been carried out to examine the use of the figure of eight method compared to water displacement or circumferential measurement in measuring ankle oedema.

Petersen et al (1999) carried out a study on subjects with visible ankle oedema secondary to a variety of causes (n=29) and a study by Mawdsley et al (2000) used a small sample of subjects with ankle oedema secondary to either chronic or acute ankle sprains (n=15). In both these studies, figure of eight tape method measurement and water displacement were compared.

Peterson et al (1999) had two testers who performed each set of measurements three times on each subject. The inter-rater and intra-rater reliability for both

methods was high (ICC 0.98 for figure of eight and 0.99 for volumeter for both tests). Petersen et al (1999) recommended that the figure of eight method should be implemented for any localised swelling around the subtalar and talar joints due to it being cost effective, time efficient and easy to use but that the volumeter method may be more useful for diffuse swelling. Mawdsley et al (2000) had only one tester for each measurement method. The figure of eight method was repeated three times with the tester blinded to the results, whereas the volumeter measure was repeated twice. Again ICCs of above 0.9 were calculated. These studies both concluded that the figure of eight method was reliable in measuring ankle oedema. The study by Brodovicz et al (2008)(see 2.12.1) also investigated the use of the figure of eight method in measuring ankle oedema but it found this method to be less consistent than the circumferential or water displacement methods. However, as previously discussed there may have been bias introduced with the circumferential measurements as the tape position was marked between measurements.

Although the volumeter method was shown to be reliable in phase two of the present study, there was a larger SEM than the figure of eight or circumferential measurement methods. This was possibly related to the patients' difficulty in positioning their hand in the standardised method in the volumeter when the distal portion of their arm was oedematous prior to treatment (see section 4.3.4.1).

The reliability of the figure of eight method and volumeter in phase two was high which reinforces the findings from phase one (see section 3.2). Taken together, the phase one and phase two studies also demonstrated that the reliability was high with these methods whether the measurements were carried out by a novice practitioner or an experienced lymphoedema practitioner which is important for clinical practice.

4.3.3 Validity

The figure of eight and the volumeter method were shown to be valid in phase two which confirmed the findings from the phase one study (see section 3.3).

In the current phase two study, there was a weaker correlation between the circumferential measurement method and the volumeter, with the Pearson moment correlation coefficient ranging from 0.59 to 0.67 and was only statistically significant in the post intervention measurements. This moderate strength of correlation would bring into question the validity of this measurement method when comparing it to the "gold standard" method of water displacement.

Although it was not included in the aims of the study, it was of interest to compare the figure of eight method with the circumferential method. There was a strong correlation between the figure of eight method and the circumferential method with correlation coefficient of over 0.83 ($p<0.0001$) for all the tests except the comparison between the measurements after intervention when it was 0.78 ($p=0.007$). This would indicate that the two tape measure methods are comparable.

These results indicate that the figure of eight method of measurement correlates strongly with the water displacement method and reinforces the validity as a measurement of hand size in this patient group.

4.3.4 Natural variability

The amount of volume change in the unaffected hand over the time between the two measurement periods was between a loss of 0.1% and an increase of 1.8% depending on the method of measurement used (see section 4.2.4.1). This shows an almost negligible change. Although the mean amount of change was quite small over the three measurement methods, the ranges indicate for some patients there was a large change detected. The volumeter measurements indicted the largest variation with one patient having a change of 16.9% in their unaffected hand. There was, however, no consistent pattern of change between the different measurement methods for increase or decrease in size or the percentage changed in the unaffected hand. The natural variation requires to be further investigated with a larger sample to help identify the trend of the measurements and to help identify the cause of these variations.

Waylatt – Rendall and Seibly (1991) carried out a study to confirm the reliability of a commercially available volumeter in testing hand volume in a clinical setting. The study included normal unaffected hands and oedematous hands. It was found that there was less deviation measured in millilitres in the normal hands compared to the oedematous ones. However, when this was expressed as a percentage, it was still accurate to within 1% as long as the examiner was the same. The study also suggested that there was a variation of approximately 5mls if the subject altered the pressure on the dowel between the fingers (see section 3.1.5.2) or made small changes in their hand position. This study suggested that for a significant change to have been deemed to occur the volume would need to change by 10mls for a normal hand and 12mls for an oedematous hand. In phase two (see tables 12 and 13); there was a change of at least 10mls in the unaffected hand in five patients and a change of at least 12mls in the affected hand of nine patients.

This may have clinical implications if the volumeter was to be used routinely and also for using it as a research tool for patients with BCRL hand oedema.

A study to assess the natural variability of hand volume over time both with healthy adults and adults with lymphoedema would clarify the expected changes within this subject group.

4.3.5. Measurement error and clinical change after treatment

This study has highlighted that further research is required to identify what is a significant change after treatment when managing BCRL hand oedema. When the standard error of measurement for each method is compared with the difference in hand size post intervention, it is interesting to note that the figure of eight method and the volumeter showed a change in value greater than the error of measurement whereas the circumferential method did not.

When examining the circumferential method there was a mean increase of 0.8mm although this ranged from a loss of 11mm to an increase of 9mm (see table 14). The standard error of measurement for this method was 3.6mm when considering the intra-tester reliability (see table 17). This would suggest that,

due to the relatively high error involved, this method of measurement may not be sensitive enough to detect 'real' changes which have occurred.

The results of the water displacement method showed a mean loss of 14.4mls with a range of a loss of 96.7mls to an increase of 40mls (see table 14). The standard error of measurement for this method was 10.8mls post intervention (see table 17). This is slightly smaller than the overall mean change in measurement and may therefore indicate that it would be able to detect clinical changes.

The results of the figure of eight method showed a mean loss of 14mms; ranging between a loss of 27mms to 1mm (see table 14). The standard error of measurement was 3.6mm (see table 17). When this is considered against the mean difference this again indicates that it is perhaps sensitive enough to detect change.

If the standard error of measurement for a measurement method is larger than the expected clinical change in hand size after a course of treatment, it is unlikely that such a measurement method would be appropriate to use clinically as these changes could not be reliably identified. This has implications for monitoring patients' progress as well as assessing the outcomes of treatment. Although hand size measurement is only one of the methods of assessing progress of lymphoedema, the other methods such as palpation, visual appearance and patient self report are subjective. Clinically the aim would be to have an objective measurement which is valid, reliable and sensitive to change, to record alongside these subjective observations.

4.3.6 Limitations

Limitations of the study were firstly the small sample size. Thus data analysis was limited as was the ability to generalise the findings to a population of patients presenting with breast cancer related lymphoedema.

4.3.6.1 Volumeter

The size of the tank of the hand volumeter was not large enough accommodate the volume of the patient's lower arm. This made achieving the standardised

position unattainable for some patients and this may have influenced the accuracy of the measurements taken.

All the subjects recruited for this study had arm oedema as well as hand oedema. Depending on the length of a patient's hand, when placing the hand in the volumeter to the depth of the dowel being at the third and fourth finger web, a certain amount of the distal segment of the forearm was also submerged in the water. As these patients had oedema in this section of their arm, some of them could not fit their wrist and lower forearm into the volumeter due to the size of their arm. This meant that post treatment when their arm size had decreased, they were then able to achieve the correct position in the volumeter and potentially their hand was further into the water, allowing more water to be displaced. This could account for the increase in some of the volumeter measurements following treatment compared to a reduction when using the figure of eight or circumferential measurements.

A commercial hand volumeter was not available in a larger size. It would have been possible to have an upper limb tank in the size which would accommodate the lower section of the limb but this would mean that the water displaced would include limb volume. However, as this population also had arm oedema, which would not necessarily remain stable following treatment or time, calculating the volume of the hand alone using this method would have remained inaccurate.

Stern (1991) carried out a study comparing the test – retest reliability of volumeter measurements between seated and standing measurements. The study reported that although both positions had good clinical reliability, there was less variation when the patient remained seated. This was theorised to being because there would be less pressure placed on the dowel and also less movement during the test as the patient was more stable. This was not used during either phase one or phase two in this study, where subjects were standing, as the aim was to keep the methodology as close to the Leard et al (2008) study as possible but the position chosen may have had some impact on the variation on the volumeter measurements.

However, the small sample size in this study, as well as the difficulties encountered with standardising the method of the positioning within the volumeter which may have affected the accuracy the results.

4.3.6.2 Circumferential measurement

It was difficult to standardise the hand position during the circumferential technique. Because the tape was passed in a circular way around the joints, if the positioning of the fingers altered between measurements, for example the amount of abduction, this may have altered the results of the measurement taken. This could have been standardised for the study by putting the finger together to ensure the fingers were held in a reproducible position. However, this may alter as any swelling in the fingers changes.

The circumferential measurement may also have been taken at a point on the hand which was distal to the oedema on the dorsum of the hand, where swelling often occurs. This is due to the anatomical structure of the hand which results in the skin on the dorsum of the hand being looser (Maihafer et al 2003). In routine clinical practice the circumferential measurement is taken at the base of the MCPs which does not include the looser skin on the dorsum of the hand. Further study is required to ascertain whether changing the position of the circumferential measurement would ensure the method was valid and reliable. This new tape position could then be recommended for clinical practice.

4.3.6.3 Tape measurement

Bear-Lehman and Abreu (1989) carried out a literature review to consider the reliability and validity of the commonly used assessment tools in the assessment of the hand including measuring oedema. The methods discussed in relation to oedema measurement were circumferential measurement and also water displacement. It reported that the measurements using a tape are affected by both the placement and the tension of the tape. Caution was also advised when comparing the affected and unaffected hand size to establish the amount of oedema present as it is recognised there may be other factors affecting hand size rather than oedema such as normal asymmetry or atrophy.

Tape tension error in both of the tape measurement methods was also a potential error as discussed previously (see section 3.3). This may be compounded in the figure of eight method as the tape crosses the potentially oedematous dorsum of the hand. If the subcutaneous tissues change and soften with treatment (International Lymphoedema Framework 2012), it may be easier to pull the tape tighter across these tissues compared to when the tissues are firmer before treatment which may lead to an “artificial” reduction in volume.

4.4 Summary

The figure of eight tape measurement method demonstrated sensitivity to change in hand size over time. It has been proven to be reliable and valid when compared to volumeter which is the accepted “gold standard” method of measuring hand size. This has been shown whether the measurements are carried out by an experienced or novice practitioner.

However, these results were not conclusive, due in particular to the small sample size and the difficulties with standardising the measurement position with the volumeter which may have led to inaccuracies.

Chapter 5

These are the first studies to investigate the use of the figure of eight tape method of measuring hand size in patients with hand oedema associated with BCRL. The studies have shown the figure of eight method to be a valid and reliable tool for this patient group. This has been demonstrated whether it is performed by novice practitioners or an experience lymphoedema therapist.

Results from the phase 2 study also suggest that the figure of eight method may be sensitive to change but other larger scale studies are required to confirm these findings.

The circumferential method of measurement, which is often used in clinical practice, also appears to be valid and reliable in the small sample group which participated in the study. Further studies on a larger sample are required to investigate the reliability, validity and sensitivity to change in hand size for this method.

Phase 2 also demonstrated that measuring hand oedema in a commercial hand volumeter for this patient group is challenging. A larger volumeter would be needed to allow accurate assessment of BCRL and for the volumeter to be considered as the gold standard.

5.1 Clinical implications

The figure of eight method was shown to be reliable, valid and responsive to change compared to the water displacement method, which is recognised as the “gold standard” method for measuring hand oedema, with the methodology based on previous studies to allow a comparison of results (Maihafer et al 2003, Pellecchia 2003, Leard et al 2004, Dewey et al 2007, Leard et al 2008).

The volumeter has been shown to have issues as a measurement tool for this patient group and therefore questions about its definition as “gold” standard for measuring hand size for this group need to be reconsidered.

The circumferential method, which is currently used as a clinical measurement, was also compared with both the figure of eight method and the water displacement method in the second study. It was found to be reliable and valid with the standardised technique used in the study, although it was recognised that this was a small sample study. However, sensitivity to change was not identified with this method. The fact that this technique does not measure across the dorsum of the hand where oedema is normally observed clinically may have an impact on the sensitivity to change when this method is used clinically.

The figure of eight method required no equipment other than a standard tape measure was quick to perform and was shown to be reliable and valid when used by novice practitioners as well as experienced practitioners. The positioning of the tape allows the commonly oedematous area for most patients to be included in the measurement (Maihafer et al 2003) and so gives a more accurate clinical measurement than the circumferential measurement which may not include the oedematous area.

The figure of eight method can therefore be recommended for measuring BCRL affecting the hand. This method of measurement is now taught as a measurement tool on the Graduate Diploma in Specialist Lymphoedema Management programme at the University of Glasgow and used is being used locally in clinical practice.

5.2 Future research

5.2.1 Volumeter

The studies have also highlighted the difficulties in using a commercial hand volumeter with this patient group. Although this is recognised as the “gold standard” method of measuring hand oedema, the added complication of arm oedema in this patient group made it difficult to achieve the standardised position for measurement in people with arm oedema. The phase 2 study involved a second test measurement and, in some cases, as the subject’s arm oedema reduced over time with treatment, at the second measurement more of the limb was submerged and so resulted in a false increase in limb volume being recorded. As the limb volume of the arm, as well as the size of the hand, is

variable for this patient group, in order to establish a measurement of the hand the measurement method needs to only measure the hand and not the lower arm or above the wrist. Future research may require a custom built volumeter or the manufacturers to produce a larger sized hand volumeter which either allowed for the increased volume of the arm of patients involved. Alternatively a different protocol could be used which marked the depth the hand was lowered into the larger tank and which was repeated at the retest measurement (Boland and Adams 1996). This would, however, involve measuring and recording the length of the hand from the finger tip to wrist and then a method evolved to ensure that this was the depth submerged. This requires to be investigated to ensure that it was practical clinically and to ensure that with hand oedema, it was possible to have limited error in measuring the length of the hand even as this oedema changed.

5.2.2 Natural variability and clinical importance

The two studies have highlighted the need to establish the natural variability in hand size. In study 2, results demonstrated considerable change in the size of the unaffected hand over time. It is know that there may be a difference in the size of the dominant hand compared to the non dominant hand and therefore accurate measurements which are sensitive to change in hand size are required to be able to monitor the progression of lymphoedema. The natural variability of the hand could also have an impact on what amount of change in hand size can be recorded as a positive clinical change (Ribeiro et al 2010). However, limb volumes or measurements are only part of an assessment and evaluation of the tissues and function are also very valuable in setting clinical outcomes. To be able to identify the natural variability in hand size over a period of time would help to establish an acceptable minimal clinically important difference.

5.2.3 Measurement of oedema affecting the dorsum of the foot

Lymphoedema from other causes other than breast cancer may develop in the lower limb and can affect the dorsum of the foot. At present circumferential measurement is the standard method for measuring the size of the foot and monitoring for any changes in size. As with the hand, the volumeter is recognised as the “gold standard” method of measurement for foot size. However, this is

not used clinically due to the same difficulties with this method as with the hand. The figure of eight tape measurement method may be preferable to the circumferential method as the tape would again cross the area most commonly oedematous. The studies which have been carried out to assess the reliability and validity of this method in the foot have all examined its use for ankle measurement (Tatro – Adams et al 1995, Petersen et al 1999, Mawdsley et al 2000) and have not examined subjects with foot oedema. The figure of eight method may be a useful clinical tool to assist in monitoring foot oedema however that requires further study.

Conclusion

This is the first study to consider the reliability and validity of a tape measurement method of measuring hand size in patients with breast cancer related lymphoedema The figure of eight method of measuring hand size was found to be a reliable and valid measurement tool for measuring hand oedema in patients presenting with breast cancer related lymphoedema. The results also indicate that the figure of eight method may be sensitive to change over time. However, this requires further study with a larger sample, as the present study was small and the results inconclusive, prior to being able to definitely recommend this measurement technique for use in clinical practice.

The figure of eight tape measurement method is suitable for all patients, is inexpensive, quick and does not require specialist training. The circumferential measurement method was also shown to be valid and reliable in the small sample study although the standardised method used does not cover the area on the hand where the oedema is most commonly situated and so further research into this method is necessary to establish whether it is sensitive to change in hand size. The study also highlighted the difficulties with volumeter, the “gold standard” method of measuring hand size, in a patient group with hand oedema and lower arm oedema which is often the presentation of this patient group.

Appendices

Appendix A – Phase 1 study - Patient information sheet

Appendix B – Phase 1 study – Consent form

Appendix C – Phase 1 study – Data collection form

Appendix D – Phase 1 study – Physiotherapy Research Fund application

Appendix E – Phase 1 study – Communication from ethics

Appendix F – Phase 1 study - IHTAB and Research and Development approval

Appendix G – Phase 1 study - Access letters

Appendix H – Phase 2 study – Patient information sheet

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Appendix K – Phase 2 study – Communication from ethics

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Appendix A Phase 1 study - Patient information sheet

University of Glasgow

NHS Greater Glasgow and Clyde

SUBJECT INFORMATION SHEET (Full Version)

To test a method of hand measurement for patients with breast cancer related lymphoedema (BCRL)

(Reliability and validity of the figure-of-eight method of measuring hand size in patients with breast cancer related lymphoedema (BCRL))

You are invited to take part in a research study that is being funded by the Physiotherapy Research Foundation (part of the Chartered Society of Physiotherapy Charitable Trust). Before you agree to participate it is important that you read the following leaflet carefully and understand what is required. Please feel free to contact me if anything is unclear or if you would like more information. My details are provided at the end of this leaflet.

Please take time to consider whether or not you are interested in becoming involved in this research and remember you are not under any pressure to participate.

Thank you for taking the time to read this leaflet.

Purpose of the study:

Breast-cancer-related-lymphoedema (BCRL) can result in a swelling of the hand and/or arm that often occurs following treatment for breast cancer. The swelling can make it difficult to use the arm and can be unsightly.

Physiotherapists aim to reduce the lymphoedema (swelling) however good measurement techniques are required to determine if treatment(s) have been effective or not. The best way to measure the swelling is to submerge the hand/arm into water and measure the amount of water displaced. This method is not always possible in the clinical setting so this study will investigate an alternative method that involves wrapping a simple measuring tape around the hand in a specific figure-of-eight style. In this study 25 people with BCRL will have their hand measured by both the water displacement method and the tape measure method and by two different therapists. The results of the two measures and between the two therapists will be compared. If the tape measure is as accurate as the submersion measure then we can recommend this simple clinical measure for routine use in clinical practice and in future research studies. The objectives of the study are to assess if the tape measure method is as good as the water immersion method in measuring hand swelling and to see if different

people taking the measurements come up with the similar results (i.e. are the methods reliable).

Am I a suitable participant?

You will be most welcome to participate if you have had breast cancer and have developed swelling in your hand.

However you **will not be suitable** to participate in this research if any of the following apply to you: -

- If you are not able to attend the therapy area at the Beatson West of Scotland Cancer Centre
- If you have any open wounds
- You have severe limitations in using your arm such that you wouldn't be able to lift it to place it in the water measurement system

The study will require 25 patients to have their hand measurements taken.

What will happen to me if I take part?

Your Breast Cancer Nurse or Physiotherapist has identified that you may be suitable to participate in this research. If you received this information then you may be experiencing swelling in your arm or hand.

After reading this leaflet and having any questions answered, if you are happy to participate please complete the consent form, which the Physiotherapist will provide. Signing the consent form will give the researchers permission to include you in the study.

After you have consented, you will be contacted with an appointment to attend the therapy centre at the Beatson West of Scotland Cancer Centre.
If you are happy to continue a copy of your consent form will be given to you and a copy kept by the researchers.

What will the measurements involve?

A Figure-of-eight measurement around your hand will be taken using a standard tape measure with the numbers blackened out to ensure that the testers can't see the results. When the measurement is taken the tape is passed to another person known as the recorder who will place the tape against a standard measuring tape and record the measurement to the nearest 1mm.
You will also be asked to allow water displacement measurements to be taken. For this you will be asked to stand, if possible, and place you hand in to a tank of water with the fingers stretched out. You will be asked to keep your hand in this

tank for 45 seconds and then to remove it slowly. As you put your hand into the tank water will be displaced and this will be collected and measured.

Two different practitioners (nurses or physiotherapists in their final year of training) who have received training in the measurement techniques, will take the measurements and they will take each measurement 3 times. So you will have you hand/arm measured 12 times in total.

How long will the measurement session take?

The session should take no longer than 45 minutes and only 1 session will be required.

Where will the session take place?

The measurement session will take place in the physiotherapy department in the therapy area at the Beatson West of Scotland Cancer Centre.

Travel Expenses
All participants will be reimbursed travel expenses for attending the measurement session at the Beatson West of Scotland Cancer Centre.

Do I have to take part?
The decision to take part is up to you. If you decide to take part you will be given this information sheet to keep, have any questions answered and be asked to sign a consent form. You are free to withdraw from the study at any time and without giving any reason. There will be no consequences that affect you in any way and there will be no impact on your future treatment if you decided not to take part.

What are the possible disadvantages and risks for taking part?

There are no disadvantages or risks associated with participation in this study.

What are the possible side effects of taking part in this study?
There are no side effects associated with participation in this study.

What are the possible benefits of taking part?

You will be contributing towards research that may or may not help to establish a more effective method of measuring and monitoring hand oedema in patients who develop lymphoedema related to breast cancer.

What if something goes wrong?

If you are harmed taking part in this research there are no compensation arrangements. If you wish to complain or have concerns about any aspect of the way you have been approached or treated during the course of this study then contact **Dr Anna O'Neill, Deputy Head of Nursing and Health Care at the University of Glasgow, 59 Oakfield Ave. Telephone – 0141 330 4278**

Will my taking part in this study be kept confidential?
Your identity will be kept anonymous, you will be numbered for identification and your information will be treated with the strictest of confidence. All research information will be stored securely at the University of Glasgow. On completion of the study it is anticipated that the findings will be published but individuals will not be identified within the publication. A full report of the results will be provided to all patients who participated in the study.

Who is organising and funding the research?
The lead researcher for this study is Yolande Borthwick. Co-researchers are Margaret Sneddon, Lesley McAlpine and Dr Lorna Paul. Funding is provided by the Physiotherapy Research foundation (part of the Chartered Society of Physiotherapy Charitable Trust)

Who has reviewed the study?
This study has been approved by West of Scotland (1) Research Ethics Committee. This study also received approval from the In House Advisory Aboard of the Beatson West of Scotland Cancer Centre and the Clinical Trials Executive Committee of the Beatson West of Scotland Cancer Centre.

How can I get further information?

If you require further information relating to this research, please do not hesitate to contact me, **YOLANDE BORTHWICK** on the following:

Email: yolande.borthwick@clinmed.gla.ac.uk

Or
LESLEY McALPINE Tel: 0141 –301 - 7003

Or
Dr LORNA PAUL Tel: 0141- 330- 6876

THANK YOU VERY MUCH FOR YOUR TIME

Appendix B Phase 1 study – Consent form

University of Glasgow

NHS Greater Glasgow and Clyde

Patient Identification Number: _____

CONSENT FORM

Title of Project:

To test a method of hand measurement for patients with breast cancer related lymphoedema (BCRL)

Reliability and validity of the figure-of-eight method of measuring hand size in patients with breast cancer related lymphoedema (BCRL)

Project Researcher: Yolande Borthwick
Dr Lorna Paul
Lesley McAlpine
Margaret Sneddon

Please initial box

1. I confirm that I have read and understood the Subject Information Sheet, dated 1.09.2009 V2, for the above study. I have had the opportunity to consider the information, ask questions and have my questions answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my present or future medical care being affected. ☐

3. I agree to my GP being informed of my participation in this study. ☐

4. I understand that the results of this study will be published ☐

5. I understand that data generated from this study will be stored securely in the University of Glasgow and will be destroyed after 5 years. ☐

Name of patient	Date	Signature of participant
Name of Researcher	Date	Signature of participant

Appendix C Phase 1 study – Data collection form

DATE:

Patient Number:

AGE:

YEAR OF DIAGNOSIS/ TREATMENT: SURGERY : YES ☐ NO ☐

LENGTH OF TIME WITH HAND OEDEMA:

HAND MEASUREMENT

RIGHT		LEFT	

BILATERAL OEDEMA: YES ☐ NO ☐

FIGURE OF 8 HAND MEASUREMENTS

AFFECTED HAND	1	2	3
TESTER 1			
TESTER 2			
UNAFFECTED HAND	1	2	3
TESTER 1			
TESTER 2			

VOLUMETER

AFFECTED HAND	1	2	3
TESTER 1			
TESTER 2			
UNAFFECTED HAND	1	2	3
TESTER 1			
TESTER 2			

Appendix D Phase 1 study – Physiotherapy Research Fund application

Physiotherapy Research Foundation
DIRECT LINE: 020 7306 6617
DIRECT FAX: 020 7314 7855
E-MAIL: attewm@csp.org.uk

Yolande Borthwick
Nursing and Health Care
University of Glasgow
59 Oakfield Avenue
Glasgow
G12 8LW

26 March 2009

Dear Yolande

Grant holder(s): **BORTHWICK, SNEDDON & McALPINE**

Project title: **The reliability and validity of the figure-of-eight method of measuring hand-size in patients with Breast Cancer Related Lymphoedema (BCRL)**

Project Ref. No: **PRF/08/2**

I am pleased to confirm that your response to the conditional offer of funding from the Physiotherapy Research Foundation has been approved and you have been awarded **£9,909**. Please note that this figure includes £176 for the Controlled Trials Limited registration fee and an allocation of £600 for presentation at a future CSP Congress (as set out in our letter of 11 December 2008).

Enclosed are two copies of the PRF research project Deed. Please read through the Deed carefully and if you wish to enter the agreement you, your employer and your finance officer should sign the last page of Schedule 2. Please return one copy to me, the other should be retained by yourself.

In all correspondence relating to the project, including invoices submitted in respect of the grant award, please quote the project reference number: **PRF/08/2**

The grant is administered by payment quarterly in arrears, from the commencement of the project, on production of an invoice which **must be substantiated by copies of proof of expenditure**. In accordance with the Deed, all invoices must also be itemised to correspond with the financial schedule and an 'Accounts Sheet' is therefore enclosed for this purpose which details the financial support requested. Please ensure that your Finance Dept completes this sheet and returns it with every invoice

submitted for payment. Failure to do so could result in either the invoice not being paid or payment being delayed.

As previously advised, evidence of Ethics and Research Governance approval is a condition of PRF funding, as is registration with Controlled Trials Limited.

Do not hesitate to contact me if you have any queries.

Yours sincerely

Marion Attew
Research and Development Officer
R&D Unit

Encs.

Appendix E Phase 1 study – Communication from ethics

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde
West of Scotland REC 1
Western Infirmary
Dumbarton Road
Glasgow
G11 6NT

Telephone: 0141 211 6238
Facsimile: 0141 211 1847

07 July 2009

Mrs Yolande G Borthwick
Teaching Assistant
University of Glasgow
59 Oakfield Avenue,
Glasgow G12 8LW

Dear Mrs Borthwick

Study Title:	**Reliability and validity of the figure-of-eight method of measuring hand size in patients with breast cancer related lymphoedema (BCRL)**
REC reference number:	**09/S0703/81**
Protocol number:	**1 30.03**

The Research Ethics Committee reviewed the above application at the meeting held on 07 July 2009. Thank you for attending to discuss the study.

Ethical opinion

The committee had several questions for the investigator which were answered to their satisfaction. The committee did however require the undernoted minor amendments to the Study Design and Information Sheet:

Study Design:

a) The committee feel that in this instance there is no need to inform the GP.
b) Question A35 - 2nd box should have been ticked.
c) Question A64-1 - Lead Sponsor's name should be added.

Information Sheet:

a) A further sentence should be added in respect of their being no impact on future treatment if you decide not to take part.
b) Add a sentence indicating how many participants are being recruited.
c) Typographical errors should be amended where appropriate i.e. "Immersion" instead of "Emersion" etc
d) Purpose of the Study - Ist para - last sentence should read "The swelling can make it difficult to use the arm".
e) Page 2 - Ist bullet point should read "If you are not able to attend the therapy at the Beatson etc".
f) Page 3 - 2nd para - should read "The session should take no longer etc"

g) Page 3 - bottom - contact details should be added for Anna O'Neill.
h) Page 4 - "Who has reviewed this study" should read - This study has been approved by West of Scotland (1) Research Ethics Committee".

The above amendments should come back to the secretary for checking and filing.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Letter from Statistician		14 May 2009
letter from Head of Trial Co-ordination		29 May 2009
Participant Consent Form	1 30 03	
Participant Information Sheet	1 30 03	
Letter from Sponsor		
Covering Letter		
Protocol	1 30 03	
Investigator CV		04 June 2009
Application	2.0	02 June 2009

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/S0703/81	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Andrea M Torrie

Dr John Hunter
Chair

Email: andrea.torrie@ggc.scot.nhs.uk

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*
"After ethical review – guidance for researchers" SL-AR2
Site approval form (SF1)

Copy to: *Dr Julie Lang R & D WIG*

Appendix F Phase 1 study - IHTAB and Research and Development approval

Our Ref: F:/Andrea/IHTAB/170409_lp_letter
Direct Line: ++44 (0)141 301 7186
Direct Fax: ++44 (0)141 301 7187

28th May 2009

Dr Lorna Paul
Reader in Nursing and Health Care
Faculty of Medicine, University of Glasgow
Glasgow G12 8LL

Dear Lorna

Re: **Reliability and validity of the figure-of-eight method of measuring hand size in patients with breast cancer related lymphoedema (BCRL)**

I can confirm that the above proposal was reviewed and approved by the In House Trials Advisory Board (IHTAB) on 17th April 2009. The main comments noted at the meeting are detailed below for your information:

- Funding already secured - 10K over 9 months;
- Validity and reliability study. 25 patients;
- Patients gets measured 3 times for each test by both testers (12 measurements in total);
- Very well designed, particularly in the way have arranged for measuring method to be blinded. JP had one issue with sample size calculation. JP gave a paper to help advise on sample size calculation;
- Not really got true "gold standard" as it is being done by a novice. Would it not be worthwhile performing "gold standard" measurement by an expert in addition to the blinded measurements? Tests are repeated 3 times to ensure reliability of test. A very similar protocol is being used for post hand surgery so they have followed this. LP taken comments on board either get an expert to do a test or ensure adequate training for novice;

⇒ Approved.

Please do not hesitate to contact me should you require any further information or help.

Yours sincerely

Andrea Harkin
Head of Trial Co-ordination

Research & Development
R&D Management Office
1st Floor, Tennent Institute
Western Infirmary
GLASGOW G11 6NT
Tel: 0141 232 9447

NHS
Greater Glasgow and Clyde

Our Ref EP/LR
Enquiries to Dr Erica Packard
Direct Line 0141 211 8544
e-mail: *Erica.Packard@ggc.scot.nhs.uk*

18th Nov 2009

Mrs Yolande G Borthwick
Teaching Assistant
University of Glasgow
59 Oakfield Ave
Glasgow
G12 8LW

R&D Management Approval

Dear Mrs Borthwick

R&D Reference: GN09ON310
Project Title: Reliability and validity of the figure-of-eight method of measuring hand size in patients with breast cancer related lymphoedema (BCRL)
Protocol no: V1 dated 30.03.09

I am pleased to confirm that Greater Glasgow Health Board is now able to grant **Management Approval** for the above study.

As a condition of this approval the following information is required during the lifespan of the project:

1. SAES/SUSARS – If the study is a **Clinical Trial** as defined by the Medicines for Human Use Clinical Trial Regulations, 2004 (CTIMP only)
2. Recruitment Numbers on a quarterly basis (not required for commercial trials)
3. Any change of Staff working on the project named on the ethics form
4. Change of CI
5. Amendments – Protocol/CRF etc
6. Notification of when the Trial / study has ended
7. Final Report
8. Copies of Publications & Abstracts

Please note: Testers can not start until research access letters have been issued.

Please add this approval to your study file as this letter may be subject to audit and monitoring.

Yours sincerely

EPackard

Dr Erica Packard
Research Coordinator

Appendix G Phase 1 study - Access letters

NHS
Greater Glasgow and Clyde

Research & Development
R&D Management Office
1st Floor, Tennent Institute
Western Infirmary
GLASGOW G11 6NT
Tel: 0141 232 9447

Mrs Yolande Borthwick
Teaching Assistant
University of Glasgow
59 Oakfield Avenue
Glasgow
G12 8LW

15th October 2009

Dear Mrs Borthwick

Letter of access for research

Study Title: Reliability and validity of the figure-of-eight method of measuring hand size in patients with breast cancer related lymphoedema (BCRL)

As an existing NHS employee you do not require an additional honorary research contract with this NHS organisation. We are satisfied that the research activities that you will undertake in this NHS organisation are commensurate with the activities you undertake for your employer. Your employer is responsible for ensuring such checks as are necessary have been carried out. This letter confirms your right of access to conduct research through **NHS Greater Glasgow and Clyde** for the purpose and on the terms and conditions set out below. This right of access commences on October 2009 and ends on May 2010 unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

You are considered to be a legal visitor to **NHS Greater Glasgow and Clyde** premises. You are not entitled to any form of payment or access to other benefits provided by this organisation to employees and this letter does not give rise to any

other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through **NHS Greater Glasgow and Clyde**, you will remain accountable to your employer **NHS Forth Valley** but you are required to follow the reasonable instructions of your nominated manager **Dr David Dunlop** in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with **NHS Greater Glasgow and Clyde** policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with **NHS Greater Glasgow and Clyde** in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on **NHS Greater Glasgow and Clyde** premises. Although you are not a contract holder, you must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of a contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

NHS Greater Glasgow and Clyde will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we

reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

If your circumstances change in relation to your health, criminal record, professional registration or any other aspect that may impact on your suitability to conduct research, or your role in research changes, you must inform the NHS organisation that employs you through its normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely

Dr Melissa McBride
R & D System Manager

Research & Development
R&D Management Office
1st Floor, Tennent Institute
Western Infirmary
G11 6NT
Tel: 0141 232 9447

NHS
Greater Glasgow and Clyde

Our Ref: MMcB/LR

14th Jan 2010

Stephanie Innes
6 Kyles View,
Largs
North Ayrshire
KA30 9ET

Dear Ms Innes

Letter of access for research

This letter confirms your right of access to conduct research through NHS Greater Glasgow & Clyde for the purpose and on the terms and conditions set out below. This right of access commences on **14th Jan 2010** and ends on **14th March 2011** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at NHS Greater Glasgow & Clyde has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to NHS Greater Glasgow & Clyde premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through NHS Greater Glasgow & Clyde, you will remain accountable to your Academic Supervisor.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with NHS Greater Glasgow & Clyde policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with NHS Greater Glasgow & Clyde in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on NHS Greater Glasgow & Clyde premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice(http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

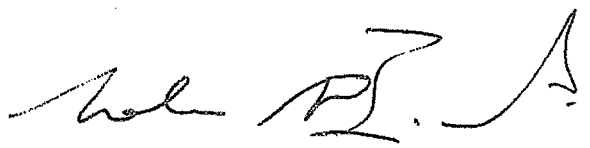
You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

NHS Greater Glasgow & Clyde will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely



Dr Melissa McBride
R&D System Manager

Research & Development
R&D Management Office
1st Floor, Tennent Institute
Western Infirmary
G11 6NT
Tel: 0141 232 9447

NHS
Greater Glasgow and Clyde

Our Ref: MMcB/LR

14th Jan 2010

Megan Reid
80 Barrachnie Road
Garrowhill
Glasgow
G69 6PQ

Dear Ms Reid

Letter of access for research

This letter confirms your right of access to conduct research through NHS Greater Glasgow & Clyde for the purpose and on the terms and conditions set out below. This right of access commences on **14th Jan 2010** and ends on **14th March 2011** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at NHS Greater Glasgow & Clyde has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to NHS Greater Glasgow & Clyde premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through NHS Greater Glasgow & Clyde, you will remain accountable to your Academic Supervisor.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with NHS Greater Glasgow & Clyde policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with NHS Greater Glasgow & Clyde in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on NHS Greater Glasgow & Clyde premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice(http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

NHS Greater Glasgow & Clyde will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely

Dr Melissa McBride
R&D System Manager

Appendix H Phase 2 study – Patient information sheet

PARTICIPANT INFORMATION SHEET (Full Version)

To test the sensitivity of a method of hand measurement for patients with breast cancer related lymphoedema (BCRL)

(To test the sensitivity of the figure-of-eight method of measuring hand size in patients with breast cancer related lymphoedema (BCRL))

My name is Yolande Borthwick and I am required to undertake a project as part of my M.Sc course and invite you to take part in the following study. However, before you decide to do so, I need to be sure that you understand firstly why I am doing it, and secondly what it would involve if you agree. I am therefore providing you with the following information. Please read it carefully and be sure to ask any questions you might have and, if you want, discuss it with others including your friends and family. I will do my best to explain the project to you and provide and further information you may ask now or later.

Please take time to consider whether or not you are interested in becoming involved in this research and remember you are not under any pressure to participate.

Thank you for taking the time to read this leaflet.

Purpose of the study:

Breast-cancer-related-lymphoedema (BCRL) can result in a swelling of the hand and/or arm that often occurs following treatment for breast cancer. The swelling can make it difficult to use the arm and can be unsightly.

Therapists aim to reduce the lymphoedema (swelling). However, good measurement techniques are required to determine if treatment(s) have been effective or not. The best way to measure the swelling is to submerge the hand/arm into water and measure the amount of water displaced. This method is not always possible in the clinical setting so an alternative method that involves wrapping a simple measuring tape around the hand in a specific figure-of-eight

style is being investigated. Although this has been shown to be reliable and valid, it is important to ensure that this new method is sensitive enough to detect any changes in hand swelling due to treatment or over time. The objective of the study therefore is to assess if the figure of eight tape measure method is as good as the water immersion method in detecting any changes in hand swelling.
In this study people with BCRL will have their hand measured by the standard circumferential measurement which is currently used in clinics, the water displacement method and the tape measure method. They will then receive the treatment which has been discussed and agreed with their lymphoedema practitioner. At their review appointment or at the end of the intensive treatment session just as measurements would routinely be taken, the measurements will be repeated and recorded. The results of the different measurements will be compared. If the figure of eight tape measure is as accurate as the submersion measure then we can recommend this simple clinical measure for routine use in clinical practice and in future research studies.

Am I a suitable participant?

You will be most welcome to participate if you have had breast cancer and have developed swelling in your hand.

However you will not be suitable to participate in this research if any of the following apply to you: -

- If you are not able to attend the Specialist Lymphoedema Out Patient Clinic at Strathcarron Hospice
- If you have any open wounds
- You have severe limitations in using your arm such that you wouldn't be able to lift it to place it in the water measurement system

The study will require 25 patients to have their hand measurements taken.

What will happen to me if I take part?

Your Lymphoedema Specialist has identified that you may be suitable to participate in this research. If you received this information then you may be experiencing swelling in your arm or hand.

After reading this leaflet and having any questions answered, if you are happy to participate please complete the consent form, which the Lymphoedema Specialist will provide. Signing the consent form will give the researchers permission to include you in the study.

The management of your lymphoedema will be undertaken as planned with your lymphoedema specialist. The only thing which is different is that the three

methods of measurement will be made before and at some point during the course of your treatment.

If you are happy to continue a copy of your consent form will be given to you, a copy kept by the researchers and a copy filed in your medical notes.

What will the measurements involve?

The standard circumferential measurement around the base of your fingers will be taken using a blank tape to ensure that the tester can't see the results. When the measurement is taken the tape is passed to another person known as the recorder who will place the tape against a standard measuring stick and record the measurement to the nearest millimetre.

A figure-of-eight measurement around your hand will be taken using a blank tape to ensure that the tester can't see the results and then again the tape will be passed to the recorder who will place the tape against a standard measuring stick and record the measurement to the nearest millimetre.

Your hand will also be measured using the water displacement method. For this you will be asked to stand, if possible, and place your hand in to a tank of water with the fingers stretched out. You will be asked to keep your hand in this tank until there is more than 5 seconds between each drip from the overflow spout and then to remove it slowly. As you put your hand into the tank water will be displaced and this will be collected and measured.

A lymphoedema specialist will take the measurements and they will take each measurement 3 times. So you will have your hand/arm measured 9 times in total on each occasion. These measurements will be taken when you would normally have your limb measured to monitor your swelling but instead of just the standard circumferential measurement of your hand these additional measurements would be taken too.

How long will the measurement session take?

The session will add approximately 20 minutes to the treatment session and will be included in the sessions which you were to attend the clinic for management of your lymphoedema.

Where will the session take place?

The measurement session will take place in the Specialist Lymphoedema Out Patient Clinic at Strathcarron hospice

Do I have to take part?
The decision to take part is up to you. If you decide to take part you will be given this information sheet to keep, have any questions answered and be asked to sign a consent form. You are free to withdraw from the study at any time and without giving any reason. There will be no consequences that affect you in any way and there will be no impact on your future treatment if you decided not to take part.

What are the possible disadvantages and risks for taking part?

There are no disadvantages or risks associated with participation in this study.

What are the possible side effects of taking part in this study?

There are no side effects associated with participation in this study.

What are the possible benefits of taking part?

You will be contributing towards research that may or may not help to establish a more effective method of measuring and monitoring hand swelling in patients who develop lymphoedema related to breast cancer.

What if something goes wrong?

If you believe that you have been harmed in any way by taking part in this study, you have the right to pursue a complaint and seek any resulting compensation through Strathcarron Hospice who is acting as the research sponsor. Details about this are available from the research team

Will my taking part in this study be kept confidential?

Your identity will be kept anonymous, you will be numbered for identification and your information will be treated with the strictest of confidence. All research information will be stored securely at the University of Glasgow and be retained for 5 years. On completion of the study it is anticipated that the findings will be published but individuals will not be identified within the publication. A full report of the results will be provided to all patients who participated in the study.
If you withdraw from the study at anytime then all identifiable information will be withdrawn from the study, however any data that has been collected which is not identifiable will still be included in the results from the study.

Who is organising and funding the research?

The lead researcher for this study is Yolande Borthwick. Co-researchers are Margaret Sneddon, Margaret Anne Garner and Dr Lorna Paul. There is no direct

funding for the study but the course of study for the M.Sc has had part funding University of Glasgow, Strathcarron Hospice and a grant from Help the Hospice.

Who has reviewed the study?

The management team at Strathcarron Hospice and the Graduate School of the School of Medicine at the University of Glasgow have reviewed the study.

The Tayside Committee on Medical Research Ethics B, which has responsibility for scrutinising all proposals for medical research on humans in Tayside, has examined the proposal and has raised no objections from the point of view of medical ethics. It is a requirement that your records in this research, together with any relevant records, be made available for scrutiny by monitors from the University of Glasgow and NHS Forth Valley, whose role is to check that research is properly conducted and the interests of those taking part are adequately protected

How can I get further information?

If you require further information relating to this research, please do not hesitate to contact me, **YOLANDE BORTHWICK** on the following:

Email: yolande.borthwick@glasgow.ac.uk

Or

Margaret Anne Garner – 01324826222

Or
Dr LORNA PAUL Tel: 0141- 330- 6876

Thank you for taking the time to read this Information Sheet and for considering taking part in this study.

Appendix I Phase 2 study – Consent form

Patient Identification Number: _____

CONSENT FORM

Title of Project:

To test the sensitivity of a method of hand measurement for patients with breast cancer related lymphoedema (BCRL)

To test the sensitivity of the figure-of-eight method of measuring hand size in patients with breast cancer related lymphoedema (BCRL)

Project Researcher: Yolande Borthwick
Dr Lorna Paul
Margaret Anne Garner
Margaret Sneddon
Dr Claire Miller

Please initial box

1. I confirm that I have read and understood the Subject Information Sheet, dated 31.3.11, for the above study. I have had the opportunity to consider the information, ask questions and have my questions answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my present or future medical care being affected. ☐

3. I understand that if I withdraw any **non-identifiable** data collected will be retained and used in the study. ☐

4. I understand that relevant sections of my research notes and data collected during the study may be looked at by individuals from Strathcarron Hospice or from NHS Forth Valley, where it is relevant to my taking part in this research. I give permission for these individuals to have access to these records. ☐

5. I understand that the results of this study will be published ☐

6. I understand that data generated from this study will be stored securely in the University of Glasgow and will be destroyed after 5 years. (All data will be anonymised but the CI (Yolande Borthwick) will have access to the names and addresses of the participants in the study.) ☐

Name of Participant	Date	Signature of Participant

Name of Researcher	Date	Signature of Researcher

Appendix J Phase 2 study – Data collection form

DATE:

Patient Number:

AGE:

YEAR OF DIAGNOSIS/ TREATMENT: SURGERY : YES ☐ NO ☐

LENGTH OF TIME WITH HAND OEDEMA:

BILATERAL OEDEMA: YES ☐ NO ☐

CIRCUMFERENTIAL MEASUREMENTS

AFFECTED HAND	1	2	3
UNAFFECTED HAND	1	2	3

FIGURE OF 8 HAND MEASUREMENTS

AFFECTED HAND	1	2	3
UNAFFECTED HAND	1	2	3

VOLUMETER

AFFECTED HAND	1	2	3
UNAFFECTED HAND	1	2	3

Appendix K Phase 2 study – Communication from ethics

NHS Fife | NHS Forth Valley | NHS Tayside

East of Scotland Research Ethics Service

Tayside Committee on Medical Research Ethics B
Research Ethics Office
Tayside Academic Health Sciences Centre
Ninewells Hospital & Medical School
Residency Block, Level 3
George Pirie Way
Dundee
DD1 9SY

Mrs Yolande G Borthwick
Nursing and Health Care
57 Oakfield Ave
Glasgow
G12 8LL

Date:	26 April 2011
Your Ref:	
Our Ref:	LR/11/AL/0109
Enquiries to:	Mrs Lorraine Reilly
Extension:	Ninewells extension 40099
Direct Line:	01382 740099
Email:	Lorraine.reilly@nhs.net

Dear Mrs Borthwick

Full title of study: **To test the sensitivity of the figure-of-eight method of measuring hand size in patients with breast cancer related lymphoedema (BCRL)**

REC reference number: **11/AL/0109**

Thank you for your letter of 13 April 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered by a sub-committee of the REC at a meeting held on 25 April 2011. A list of the sub-committee members is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Response to Request for Further Information		13 April 2011
GP/Consultant Information Sheets	1	26 January 2011
Investigator CV		20 February 2011
CV - Dr Loma Paul		14 February 2011
Participant Information Sheet	2	31 March 2011
Protocol	1	26 January 2011
Letter from Statistician		14 February 2011
REC application		27 January 2011
Participant Information Sheet	1.1	24 February 2011
Participant Consent Form	2	31 March 2011
Covering Letter		20 February 2011
Letter from Sponsor		18 February 2011
CV - Ms Margaret Sneddon		16 February 2011
CV - Mrs Margaret Garner		17 February 2011
CV - Dr Claire Miller		14 February 2011

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

11/AL/0109	Please quote this number on all correspondence

Yours sincerely

L Kelly

Mrs Sandra Forbes
Chair

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments
"After ethical review – guidance for researchers"

Copy to: Irene McKie, Strathcarron Hospice
NHS Forth Valley R&D Office

NHS
Forth Valley

Date: 6 May 2011
Your Ref:
Our Ref:
Direct Line: 01324 677564
Email: allyson.bailey@nhs.net
R&D ref: FV 575

Mrs Yolande G Borthwick
University of Glasgow
59 Oakfield Ave
Glasgow
G12 8LL

Dear Mrs Borthwick

Study title: To test the sensitivity of the figure-of-eight method of measuring hand size in patients with breast cancer related lymphoedema (BCRL)
NRES number: 11/AL/0109

Following the favourable opinion from the Tayside Committee on Medical Research Ethics B on 25 April 2011, I am pleased to confirm that I formally gave Management Approval to the study above on 6 May 2011.

This approval is granted subject to your compliance with the following:

1. Any amendments to the protocol or research team must have Ethics Committee and R&D approval (as well as approval from any other relevant regulatory organisation) before they can be implemented.

2. You and any local Principal Investigator are responsible for ensuring that all members of the research team have the appropriate experience and training, including GCP training if required.

3. All those involved in the project will be required to work within accepted guidelines of health and safety and data protection principles, any other relevant statutory legislation, the Research Governance Framework for Health and Community Care and IHC-GCP guidelines. A copy of the Framework can be accessed via the Chief Scientist Office website at: http://www.cso.scot.nhs.uk/Publications/ResGov/Framework/RGFEdTwo.pdf
and ICH-GCP guidelines may be found at http://www.ich.org/LOB/media/MEDIA482.pdf

4. As custodian of the information collected during this project you are responsible for ensuring the security of all personal information collected in line with NHS Scotland IT security policies, until the destruction of this data.

5. You or the local Principal Investigator will be required to provide the following reports and information during the course of your study:

- A progress report [**annually**/
- Recruitment numbers on a **monthly** basis (if your study should be added to the NIHR research Portfolio you will receive a separate letter from the R&D Office detailing the steps to be taken)

- Report on SAEs and SUSARs if your study is a Clinical Trial of an Investigational Medicinal Product
- Any information required for the purpose of internal or external audit and monitoring
- Copies of any external monitoring reports
- Notification of the end of recruitment and the end of the study
- A copy of the final report, when available.
- Copies of or full citations for any publications or abstracts

The appropriate forms will be provided to you by the Research and Development office when they are needed. Other information may be required from time to time.

Yours sincerely

pp DR. IAIN WALLACE
Medical Director

CC: Dr Lorna Paul
University of Glasgow
Nursing and Health Care
Faculty of Medicine
59 Oakfield Avenue
Glasgow
G12 8LW