School of Physiotherapy

The development and validation of the Breast Lymphoedema Severity Symptom (BLYSS) questionnaire

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Declaration

To the best of my knowledge and beliefs the information contained in this thesis does not contain material previously published by another person except where acknowledgment to those authors is made.

The material presented in this thesis has not been accepted for any other award of degree or diploma at any other university.

Signature

Christine Smith

Date:

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Abstract

Background and research questions- Breast cancer is the most common cancer not only affecting Australian women, but women world-wide. Breast lymphoedema is a recognised complication of breast cancer treatment. Due to improved diagnosis and treatment, more women are surviving breast cancer. As a consequence, preventing and treating those complications associated with breast cancer, such as breast lymphoedema, are paramount. Yet a lack of standard diagnostic criteria and measuring procedures make identifying the prevalence and incidence of this condition challenging. As a result, initiating and comparing research is difficult and hampers evaluation of the effectiveness of treatment and translation into clinical practice. The objectives of this project were to:

1. identify features of breast lymphoedema considered important in the literature, to clinicians, and to affected patients.
2. incorporate those features, as items into a valid and reliable questionnaire, that would be simple and convenient to administer.
3. develop a definition for breast lymphoedema.

Methods- In the first part of the study a literature search and clinician interviews were conducted to identify a pool of items that may be relevant to include in a health status questionnaire for women with breast lymphoedema. Duplicate items were reduced and remaining items were integrated to form an item elicitation questionnaire. Next, 50 patients with medically diagnosed breast lymphoedema were interviewed to determine how breast lymphoedema affected their lives. The item elicitation questionnaire was used to facilitate these interviews. Items were evaluated against three criteria; severity, frequency and importance. Those items that satisfied the criteria were included in the first draft of the questionnaire. At this stage the questionnaire was formatted and then pilot tested with five clinicians and two groups of nine patients.

Another 30 patients diagnosed with breast lymphoedema were invited to participate in the next part of the study. Reliability was determined using duplicate

administration of the BLYSS questionnaire, with a 24 hour interval. Patients were also timed to determine the approximate length of time to complete the BLYSS questionnaire.

Aspects of validity, including face, content, construct, discriminant and convergent validity were determined by administration of the General Health-12 Questionnaire (GHQ-12) (1) and evaluation of the cosmetic appearance of the breast following breast conservation therapy using the modified Harris scale (2). Harris Scale scoring was performed by two experienced health professionals from the Breast Clinic at Royal Perth Hospital.

During the first part of the study, a group of experts in the area of lymphoedema was formed. The purpose was to develop a consensus definition for breast lymphoedema using methods based on the Delphi technique. This is a type of consensus method using group facilitation with experts in the given field.

Results- Sixty six items were identified from the literature and 31 from the clinician interviews. Nine items were retained after the 50 patient interviews and screening against the pre-determined criteria. Two additional items were identified during analysis of the first 10 interviews. As a result these items were added to the item elicitation questionnaire and satisfied inclusion criteria for questionnaire items. The questionnaire underwent several revisions before undergoing the first round of pilot testing. After two rounds of pilot testing, consensus was generated from all clinicians and patients and no further reviews were undertaken.

Thirty seven articles on the use of the terms breast oedema and/or breast lymphoedema and whether and how this was defined, were identified from the literature. As no existing definition for breast lymphoedema was identified, a consensus group was formed. Seven experts were contacted, and agreed to participate. Three rounds of email correspondence were undertaken and a definition formulated, based on the location, nature, timing and differential diagnosis of breast lymphoedema.

Following this, the reliability and validity of the BLYSS questionnaire were determined. Reliability was established as excellent at 0.948. On average the 30 patients took 2 minutes and 14 seconds (standard deviation of 0.72) to complete the BLYSS questionnaire.

Discrimination, convergence and criterion validity were determined by considering the associations between the BLYSS questionnaire and two other forms of assessment. These were the modified Harris score (2) and the GHQ-12 (1).

There were significant correlations between the BLYSS and GHQ-12 (1) scores (Spearman's rho=0.58; p=0.05 at the first administration, and Spearman's rho=0.50; p=0.05 at the second administration of the BLYSS questionnaire and GHQ-12 (1)). There was a significant association between the two clinicians' modified Harris scores (2) (Kappa coefficient 0.59; percentage agreement 77%). There were poor correlations between the BLYSS questionnaire and both clinicians' modified Harris scores.

Discussion- The development of the BLYSS questionnaire was undertaken to measure health status in women with breast lymphoedema as a result of breast cancer treatment. This project has addressed two issues critical to the forward progression of research concerning breast lymphoedema. In particular, a working definition for breast lymphoedema was constructed using a consensus technique and applied to the validation part of the study. Also a patient self-reported health status questionnaire was developed.

The approach to questionnaire development was designed to not only maximise the chances of developing a useful questionnaire that struck a balance between patients' needs (that it contained items considered important to patients with breast lymphoedema), clinicians' needs (that it would be simple and convenient to administer), and scientific needs (to establish its validity and reliability).

The BLYSS questionnaire will be useful for clinicians treating breast lymphoedema. It will also be useful as a condition specific outcome measure for research projects acquiring evidence for clinical practice. The definition not only can be applied to patients in clinical and research settings, but provides a template for further discussion and works.

Conclusion- To date the BLYSS questionnaire is the only valid and reliable tool available to measure health status in women with breast lymphoedema as a result of breast cancer treatment. The design, development and validation of the BLYSS questionnaire has integrated and encompassed three concepts integral for the development of a health status measure; patient participation, scientific value and clinician acceptability.

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Presentations

2012

Smith C, Briffa K, Bellamy N. The Breast Lymphoedema Severity Symptom (BLYSS) Questionnaire: Development and Validation. Programme handbook and presented at the 9th Australasian Lymphology Association Conference; 2012 May 24-26; Cairns, Australia.

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Smith C, Briffa K, Bellamy N. The development of the Breast Lymphoedema Severity Symptom (BLYSS) Questionnaire. Programme handbook and presentation at the 7th Australasian Lymphology Association Conference; 2008 Mar 27-29; Fremantle, Australia.

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Smith C, Briffa K, Bellamy N. The development of the Breast Lymphoedema Severity Symptom (BLYSS) Questionnaire. Programme handbook and poster presentation at the 7th Australasian Lymphology Association Conference; 2008 Mar 27-29; Fremantle, Australia.

Awards

2011

Awarded the best student prize in the Women's Health stream of the programme at the Australian Physiotherapy Association conference

2010

Awarded the best poster prize at the Australasian Lymphology Association conference

List of abbreviations

ALA	Australasian Lymphology Association
BCT	Breast Conservation Therapy
BLYSS	Breast Lymphoedema Severity Symptom questionnaire
GHQ-12	General Health Questionnaire-12
ICC	Intraclass Correlation Coefficient
ISL	International Society of Lymphology
LENT/SOMA	Late Effects of Normal Tissue/ Subjective, Objective, Management and Analysis
NBOCC	National Breast and Ovarian Cancer Centre
VAS	Visual Analogue Scale
WOMAC	Western Ontario and McMaster osteoarthritis index

Chapter 1.0
Introduction

Breast cancer is the most common cancer affecting Australian and western women. However with increased recognition of breast cancer risk, the advent of mammographic screening programmes, and advances in the treatment of breast cancer, early detection of breast cancer is associated with improved survival prospects. Women may now be offered breast conservation therapy (BCT) which includes neoadjuvant therapies (chemotherapy or hormonal), surgical removal only of the cancerous tissue and immediate surrounding breast tissue, lymph node dissection (sentinel node biopsy with or without axillary clearance) and adjuvant treatments (chemotherapy, radiotherapy, monoclonal antibody therapies and/or hormonal therapies). These treatments enable women to retain the breast without compromising survival prospects. Prior to these advances, mastectomy was the only option.

However, as with any intervention, there are side effects associated with breast cancer treatment. One of these side effects is breast lymphoedema. Breast lymphoedema can not only affect the cosmetic appearance of the treated breast, but can impact on the patient's physical function and quality of life. Some women will opt for a prophylactic mastectomy instead of BCT to avoid the physical, cosmetic and psychological effects of breast lymphoedema. This is not only distressing for the woman, but also those involved in breast cancer treatment, as BCT aims to offer a woman survival likelihood on par with mastectomy whilst salvaging the breast.

Although a recognised complication of BCT compared with arm lymphoedema, there is a scarcity of research on breast lymphoedema. Rates of breast lymphoedema have been reported at 6-80% (3-8), which suggests breast lymphoedema can be a major complication of breast cancer treatment. However a lack of standard measuring procedures, reporting criteria and the lack of a definition for breast lymphoedema make comparing research studies difficult. This is also reflected when evaluating the effectiveness of treatment for breast lymphoedema.

1.1 The aim of the study

The aim of this project was to develop a questionnaire for women with breast lymphoedema (the BLYSS questionnaire). This questionnaire will be useful for any clinician treating breast lymphoedema in addition to providing a condition specific outcome measure for research projects acquiring evidence for clinical practice. The definition will provide a template for further discussion and work.

1.2 The study objectives

The specific objectives of the study were grouped into two parts:

Part A: Consisted of development of a questionnaire to measure health status in women with breast lymphoedema (the BLYSS questionnaire)

Part B: Consisted of establishment of the reliability and validity of the BLYSS questionnaire

Prior to commencement of these studies, ethical approval was sought and granted by the Human Ethics Committee of Curtin University and Royal Perth Hospital Ethics Committee (see Appendices 1 and 2, pages 136 and 137). In addition, ethical approval was sought and granted for Part B of the study from the Sir Charles Gairdner Group Human Resource Ethics Committee (see Appendix 3, page 138).

1.3 Resources

Financial resources were allocated as part of the budget associated with the Masters study. This budget allowed for provision of stationery, purchase of a licence to use the GHQ-12 (1) and travel re-embursement for patients. Interviews were conducted by the principal researcher as part of the clinical load.

Chapter 2.0
Literature review

Breast cancer is not only the most common cancer in women in Australia but also women worldwide (9). As a result of improved detection and treatment of breast cancer, there are higher and longer survival rates and consequently the side effects related to treament are receiving more attention (9). One complication of breast cancer treatment is breast lymphoedema. However a lack of, or inconsistent standard measuring procedures and reporting criteria (4) not only makes comparing research difficult, but also hampers evaluating the effectiveness of treatment for clinical and research purposes. To address this, a questionnaire was developed to measure health status in women with breast lymphoedema. The development of this questionnaire was based on rigorous scientific method to create as comprehensive and robust a questionnaire as possible. In this chapter narrative review of the limited literature related to breast lymphoedema will be provided.

2.1 Breast lymphoedema

2.1.1 Breast cancer-prevalence and survival

For Australian women, breast cancer is the most common to affect both them (10) and also Western women (11). In Australia in 1982 there were 5,289 newly diagnosed women with breast cancer compared with 12,614 women in 2006 (10). This number is expected to be 22% higher by 2015, with approximately 15,409 women likely to be diagnosed with breast cancer (10).

However there has been an increase in relative survival for women after breast cancer diagnosis. The five-year relative survival for Australian women increased from 72.6% between 1982-1987, to 88.3% between 2000-2006 (10). Survival trends show relative survival improved during 1995-2007 for Australian women diagnosed with primary breast cancer and survival was persistently higher in Australia for these women during this period (12).

Increased survival results in more women who have been treated for breast cancer. In 2006 there were an estimated 143,967 women diagnosed with breast cancer in the previous 25 years (10).

2.2 Breast conservation therapy

2.2.1 Treatment

For early breast cancer (breast cancer restricted to the breast with or without ipsilateral lymph node involvement) (13), BCT consisting of breast surgery and adjuvant radiotherapy (with or without hormonal and/or chemotherapy), is a recognised alternative to mastectomy (14) that has survival outcomes equivalent to mastectomy (15-17). The advantage of this treatment option is a better cosmetic outcome with a high degree of local cancer control (18). However, the paradox of achieving successful treatment outcomes is the development of side effects (17,19). Since there are now many long term breast cancer survivors, side effects are of prime importance (20).

2.2.2 Side effects

As patients survive longer there is an increased likelihood for the development of long term radiation sequelae (21-23). Skin complications due to irradiation that occur within 90 days of treatment are considered acute, while those occurring subsequently are considered late (24). Acute side effects of breast irradiation can include fatigue, local inflammation, moist and dry desquamation (25) and oedema (26). Late complications of radiotherapy treatment include fibrosis (19,22,27), vascular damage (telangiectasia), tissue atrophy and skin pigmentation (25,28,29). These reactions can range from undetectable or minimal, to unacceptably severe (30).

The effects of breast surgery may cause secondary problems after radiotherapy (31). Common complications from breast and axillary node surgery include breast oedema, seroma, haematoma, infection or scarring (31). Breast oedema has been characterised as occurring before or during external beam radiotherapy and is related to lymphatic flow disturbances as a result of axillary dissection (3). Although the lymph vessels themselves appear to be radioresistant, radiotherapy affects both the healing process by delaying the growth of lymphatic networks into repairing tissues,

and by hindering the proliferative response of normal lymphatic to inflammatory stimuli (4).

When radiotherapy is given to a damaged breast and a damaged dermal lymphatic network (such as from the complications listed), the potential for partial or whole breast swelling is increased (8,31). Lymph nodes unlike lymph vessels "are radiosensitive to conventional doses of radiotherapy, initially responding with lymphocyte depletion, followed by fatty replacement, then usually by local fibrosis" (4)(p2794).

2.3 The challenge of breast lymphoedema assessment

Arm lymphoedema is more commonly described and reported as a complication of breast cancer treatment than breast lymphoedema (8). When lymphoedema occurs in the upper limb, volume changes can be objectively quantified through bioelectrical impedance spectroscopy (32), water displacement, serial circumferential measurements and optoelectric volumetry (4). However, volumetric measures alone are poor indicators of severity, prognosis and treatment response and do not provide information about other soft tissue changes associated with lymphoedema such as fibrosis (4,33). A limitation of volume circumferential measurements, based on current lymphoedema grading systems, is their inability to be used for non-limb oedema assessment (4,33). There is currently no method of quantifying lymphoedema in the breast (33-35).

In clinical practice, qualitative descriptors and scales such as the Lymphoedema Quality of Life Inventory, the American Physical Therapy Association scale, the Casley-Smith lymphoedema staging scale, the Late Effects of Normal Tissue/ Subjective, Objective, Management and Analysis (LENT/SOMA) measure and the Common Toxicity Criteria version 2 are available lymphoedema ratings (33). However, the American Physical Therapy Association scale grades lymphoedema based on limb circumference discrepancy (33). The Casley-Smith scale consists of three-stage lymphoedema scale based on fibrotic and skin changes, the presence of pitting and the effect of elevation (33). As this scale does not have established validity and reliability (33) for patients with breast lymphoedema, its use is limited.

The LENT/SOMA measure contains objective and analytic components rated on a four-point scale, based on unspecified arm circumferential measurements (33). The American Physical Therapy Association scale, the LENT/SOMA measure and the Common Toxicity Criteria version 2 scales do not have established validity and reliability (33). The Lymphoedema Quality of life Inventory questions the way lymphoedema can affect quality of life and activities of daily living and has established validity and reliability in patients with upper and lower limb lymphoedema (36,37) but validity and reliability has not been established in patients with breast lymphoedema (33). The Common Toxicity Criteria version 2 grades lymphoedema on a four-point scale and although the Common Toxicity Criteria version 2 allows grading in non-limb oedema, validity and reliably has not been assessed (33). Sensitivity and specificity has been established in other lymphoedema questionnaires (38). These authors found that the visibility of swelling (as a method to assess the amount of swelling) was highly reliable and in agreement with ratings from experienced clinicians (38). None of these descriptors and scales have been specifically designed for breast lymphoedema, nor are they widely used in lymphoedema related research (33), probably because not all of these questionnaires have established reliability or validity.

In patients treated with breast conservation, breast lymphoedema is reported to be the more frequently seen complication than arm lymphoedema (4,7,39,40). Lymphoedema of the breast is an often overlooked side effect of breast cancer treatment (5,41), and the resulting problems minimised (42,43). Rates of breast lymphoedema have been reported at 6-80% (3-8). However, the lack of standard measuring procedures and reporting criteria make comparing research reports difficult (7).

2.3.1 Limitations in the literature

As identified, measuring breast lymphoedema remains difficult. In addition to this further limitations exist when comparing the literature on breast lymphoedema.

2.3.1.1 Definition of terms

One barrier to research and reporting of breast lymphoedema is the lack of a clear and widely accepted definition of the condition. Not only is this a barrier for

research, failure to recognise the condition also contributes to the significant effects it has on the physical, emotional and psychological wellbeing of affected women. The creation of a definition for breast lymphoedema is discussed in Chapter Five, Defining Breast Lymphoedema, page 77.

Most authors do not provide a definition of breast oedema or lymphoedema (as shown in Table 5.3, Chapter 5, Defining Breast Lymphoedema, page 86) which makes the articles difficult to compare and to apply in clinical practice. As illustrated in Table 5.3, Chapter 5.0, Defining Breast Lymphoedema, page 86, some authors use both and/or alternate between the terms breast oedema and breast lymphoedema in their texts. This makes it difficult to determine the true nature of the condition being discussed and assessed. Other unclear, undefined terms such as persistent oedema (45) are used in the literature adding further confusion in regards to what is being discussed.

Few articles define the condition but of those authors who do, definitions are subjective in nature (3,5,31) or ambiguous; “such as palpation of a pasty oedema in the affected breast in comparison with the contralateral side” (43)(p646). Other authors try to define the topic clearly, including signs and symptoms as reported in the literature to be associated with breast lymphoedema (57-59). However these are only limited to that article, making it difficult to compare, interpret results and apply to clinical practice. As a consequence of this, the term breast lymphoedema will be used throughout this literature review, except where comment is made on the diversity of terms different authors use.

2.3.1.2 Study design

Although the majority of articles on breast lymphoedema are observational or retrospective in nature (3,8,49), there is at least one published prospective study (60). The best study design is dependent upon the research question. For example, a study identifying risk factors needs to be a prospective cohort in nature, not a randomised control trial, whereas if the effectiveness of an intervention is being questioned, a control group is necessary. Observational studies do not encompass direct intervention by the researcher, and usually involve survey instruments, interviews, or review of medical notes including documentation by the researcher on the natural

course of events, noting who is and who is not exposed, and who does and does not develop the disease (61). These types of studies provide a useful insight into a condition, allow researchers to study the long term effects of variables and sidestep the ethical and practical problems associated with establishing large and cumbersome medical studies (62). This type of study design lacks control over the experiment (in regards to control groups) and independent variable/s and randomisation, potentially creating bias and masking cause and effect relationships (62,63). Alternatively this type of research may suggest correlations where there are none (62,63).

Retrospective research involves examining data that could have been collected previously, often from medical notes or surveys (61). The researcher has no direct control of variables as these events occurred in the past or these are no longer manipulable and the inferences from these studies are weaker than those studies in which the researcher can control variables (61).

Other articles reported in the breast lymphoedema literature are case studies (50,56,64). A case study is an extensive report designed to analyse and understand those factors important to the cause, care and outcome of an individual's health status (61). Case studies are the most practical approach to research due to the direct relevance to patient care and it provides insight into the totality of an individual's experience which maybe missed in a group study (61). However these are also the least rigorous approach because of the lack of control, weak internal validity and limited external validity (61).

Few breast lymphoedema articles are prospective in design (43). Prospective studies, such as that by Degnim et al (60), are more reliable due to the greater control of collection methods, involve examining variables through direct contemporaneous recording (61).

2.3.1.3 Outcome measures

The range and variety of outcome measures used in articles on breast lymphoedema also contribute to the difficulty comparing research, and evaluating the effectiveness of treatment for clinical and research purposes. Some authors use scales defining the appearance of breast lymphoedema as mild, moderate or severe (3,5) and within

these scales provide a description of what each term or oedema encompasses (3,58). Several authors use patient concerns, such as breast swelling, heaviness, redness and/or pain (7,42,43) as outcome measures. However, the origin of these reporting criteria and their association with breast lymphoedema were not identified by these authors (7,42,43). Clinical observation and palpation is commonly used as a way of evaluating an intervention for breast lymphoedema (7,8,42). The limitations of these are the lack of standardised measurement procedures and difficulty of their translation into clinical practice.

2.4 Features of breast lymphoedema

Many features of breast lymphoedema are described in the literature, yet swelling is the most consistently referred to (3-5,7,8,31,41,43,47,50,56,64).

Swelling is described as intermittent, chronic or persistent (45), includes part of or the whole breast (6,31,55), engorgement or enlargement (58). It is unclear whether these terms all refer to swelling or relate to it. This ambiguity makes interpreting articles and applying results difficult.

Some authors report that breast oedema is more likely to occur in large-breasted women (45,58) but only one author clarified what was considered large-breasted (59). Another author reported that the development of breast oedema was not related to breast size (32). Others have stated that swelling can be in part or all of the breast (6,31,55) or that engorgement (55,58) can be with or without pain (58). Pathophysiologically it is plausible that women with larger breasts are at greater risk of breast lymphoedema as during radiotherapy larger breasts receive higher doses of radiation at the extremes of the latitudinal field due to the radiation scatter, causing more damage to lymphatics (31).

2.4.1 Characteristics of breast lymphoedema

A number of characteristics of breast lymphoedema are frequently reported in the literature, as shown in Table 2.1, page 10. Other reported characteristics are that the

Table 2.1 Characteristics of Breast Lymphoedema

Characteristic	Author/s
Pain	Clarke et al 1982 (3), Kirshbaum 2000 (31), Goffman et al 2004 (7), Stevenson et al 2005 (56), Jahr et al 2008 (43), Fu et al 2009a (35) and Lawenda et al 2009 (41)
Nipple pain	Lawenda et al 2009 (41)
Discomfort	Clarke et al 1982 (3), Kirshbaum 2000 (31) and Jahr et al 2008 (43)
Erythema	Stevenson et al 2005 (56), King et al 2001 (64), Loprinzi et al 1996 (47) and Ronka et al 2004 (8)
Heaviness	Clarke et al 1982 (3), Kirshbaum 2000 (31), Goffman et al 2004 (7), Fu et al 2009a (35) and Lawenda et al 2009 (41)
Peau de orange	Clarke et al 1982 (3), Loprinzi et al 1996 (47), Kirshbaum 2000 (31), King et al 2001 (64), Goffman et al 2004 (7), Ronka et al 2004 (8), Stevenson et al 2005 (56) and Lawenda et al 2009 (41)
Fibrosis	Clarke et al 1982 (3), Fu et al 2009a (35) and Lawenda et al 2009 (41)

lymphoedematous breast is tight, tender (31), is larger (8,41), has induration (64), hyperpigmentation (31), skin thickening (8), distortion (42), skin changes (35, 41), and is non-pitting and red (31).

However the literature also describes tightness (35), tenderness on palpation (8), ache (41), redness (7), atrophy/retraction (23), architectural distortion (64), skin colour changes (41), an increase in skin thickening (53), pitting or non-pitting (41) and discolouration (31). It is unclear whether these are separate entities to the previous similarly described characteristics, if these are the same, are these what patients report or whether it has been observed, or both. Although women's perceptions of breast lymphoedema would seem important and relevant, there is little in the literature describing them.

Due to lymph stasis (4,65) and the impaired lymphatic proliferation responses, cellulitis (35) and repeated bouts of cellulitis (4) are common in the breast treated for breast cancer. However an absence of fever (67) and the lack of identifiable pathogens that occur in some patients are inconsistent with infection (36). Moreover, patients can be unresponsive to antibiotic treatment or prophylactic antibiotics fail to prevent attacks of cellulitis or acute inflammatory (55,56,67) episodes, which suggests another cause for the appearance of the breast (49, 66). Some authors have termed this pseudo-cellulitis (6,66) and delayed breast cellulitis (6,8,56) however breast lymphoedema must also be a consideration as the inflammatory changes associated with lymphoedema (erythema and oedema) can be mistaken for infection (55). This has received some but limited recognition by some authors (55,56,).

Patients with breast lymphoedema may experience pins and needles (paraesthesia) (41), hyperaemia (7), burning (35), increased breast size (31), lymphangitis (35), firm and thickened subcutaneous tissues (43), numbness (35) and changes in skin texture and integrity (42). Lopsidedness (31), fullness (41) and uncomfortable (4) are other terms used to described the lymphoedematous breast.

2.4.2 Consequences of breast lymphoedema

The consequences of breast lymphoedema are significant. In regards to appearance, breast lymphoedema is said to detract from the cosmetic outcome (3,4,7). The serious emotional and psychological effects of breast lymphoedema are also addressed in the literature (35,55). Frustration, fear, negative body image, disfigurement, isolation (55), body image problems, depression, fear of recurrence and difficulties of adjustment (31) are all reported consequences associated with breast lymphoedema. Although identified in the literature, these consequences have not been explored by using previously established psychological tools, such as the General Health Questionnaire or the Hospital Anxiety Depression Scale. Both of these tools have established validity and reliability and have been used in other studies of patients with breast cancer (1,68). The use of such tools would have provided more quantitative evidence about the magnitude of impairment caused by breast lymphoedema.

Breast lymphoedema is reported to impair quality of life, impede in the ability to work, affect activities of daily living including performing chores and hobbies, and cause economic burden, delay in resuming previous social activities and sexual difficulties (31,35,43). Breast lymphoedema is also reported to cause difficulties involving clothing and underwear, especially a brassiere which is more likely to cause indents on the breast (42).

The physical consequences of breast lymphoedema are also extensive. It has been reported that breast lymphoedema is associated with fatigue (69), loss of glenohumeral joint range of motion (43), and oedema that feels pasty on palpation (43).

2.5 Diagnostic evaluation of breast lymphoedema

The literature on diagnostic evaluation of lymphoedema usually focuses on upper limb lymphoedema, whilst breast lymphoedema does not receive this attention (43). Being able to accurately measure the breast is important, however problems are associated with measuring the female breast, including positioning of the patient and varying tissue mass and texture (70).

Methods including bioimpedance spectroscopy, cosmetic and functional outcomes including software programmes, grids and scales, water displacement, casting, anatomical measures used to fit brassieres, thermoplastic moulding, the Grossman-Roudner measuring device, photographs, breast magnetic resonance imaging, mammography and ultrasound are all proposed for the breast volume and cosmesis measurement (71).

2.5.1 Bioimpedance spectroscopy and tonometry

Bioimpedance spectroscopy and tonometry are measures that may enable the measurement of changes in the breast however neither has been properly validated, and still need to be established. Moseley and Piller (70) conducted a pilot study of 14 women who had breast conservation surgery for breast cancer more than 12 months previously (70). This time frame permits exclusion of breast oedema due to anticipated causes, such as surgery and radiotherapy. Covariance ranged from 0.20-0.86%, which indicated reliability, and although duplicate measures using the same

tester were performed, the time interval between tests was not specified, nor whether marks were visible from previous electrode and tonometer placement. Another barrier for the use of Bioimpedance spectroscopy maybe the relative cost of the machine and ongoing costs of the electrodes, particularly given the paucity of information in regards to breast lymphoedema.

2.5.2 The Breast Retraction Assessment

The Breast Retraction Assessment, created by Pezner et al (72), is an objective assessment of the amount of cosmetic retraction in patients who have had BCT as part of breast cancer treatment. The Breast Retraction Assessment involves "using a measurement grid determining values by locating the x-and y-co-ordinates for the nipple of each breast and values are then calculated by vector geometry employing the Pythagorean theorem" (72)(p327). These authors reported that in comparison to qualitative forms of cosmetic analysis, the Breast Retraction Assessment is a quantitative objective test that eliminates observer bias, is easily reproducible between observers, and the grid is simple to construct and can be employed at any institution. Although these authors did not discuss breast lymphoedema as a potential component of breast retraction, it was noted that each cosmetic change must be analysed separately for its own set of related factors (73).

2.5.3 Cosmetic and functional scales

Evaluations of the cosmetic and functional outcomes after BCT using a variety of scales have been studied by other authors (2,3,74-79). However the validity and reliability of these scales has not been determined (3,78,79), nor was breast lymphoedema considered as contributing to adverse cosmetic and functional outcomes (74-76). However one author did assess, grade, and acknowledge arm lymphoedema (77).

Although the reproducibility of the subjective methods of cosmesis evaluation of BCT are questioned (even when completed by experts), these are still in use today (80). This is likely due to the utility and practicality of these methods. More objective methods (72,75) are based on breast symmetry evaluation (80). However these methods do not take into account other aspects of the appearance of the breast such scarring, colour or skin texture (80) which may be indicative of breast lymphoedema.

2.5.4 The Breast Symmetry Index and the Breast Cancer Conservative Treatment Cosmetic software

The Breast Symmetry Index with the use of the Breast Analysing Tool software (80,81) and the Breast Cancer Conservative Treatment Cosmetic software (82) evaluate breast cosmesis after breast cancer treatment. Both programmes show good inter-observer agreement (81,82). Despite this, these programmes are not used in routine clinical practice in Australia. It is not clear why this is the case; however lack of awareness of these programmes, cost and access to technologies necessary to use them may be prohibitive factors in both the public and private settings.

2 .5.5 Water displacement, brassieres and the Grossman-Roudner cone

Water displacement based on the Archimedes principle involving the displacement of water within a large calibrated cylinder has been used to assess breast volume (71,83). Limitations to this method are that it is only suitable for breast volumes that are less than 425cc. If breasts are firmer, this method overestimates the volume and patients do not find the method easy to perform (71,83).

Brassieres are a logical assumption as a guide for breast size. Current brassiere sizing has its origins in 1935 and since then this has been based on two measurements; around the ribcage underneath the bust and the fullest part of the bust (84,85). Yet the female breast has a very complex three dimensional geometry (85) that brassiere sizing does not take into account which limits its value as an outcome measure for research.

The Grossman-Roudner breast measuring device is a variable cone device that can be placed over the breast. Breast volume is then read from a scale at the overlap of the cut radius of the cone (71). This is a cost effective and reliable measure however validity is questionable as not the entire breast is contained in the cone (71,83).

2.5.6 Breast magnetic resonance imaging

Breast magnetic resonance imaging is used for the differential diagnosis of breast disease (86-88) and has been shown to be highly specific in the differentiation of fibrosis versus tumour recurrence (88). However there are limitations with the use of this modality as therapies such as surgery and radiotherapy (86,88) can induce

morphological changes and enhancement within the breast, mimicking recurrent disease (87,88). Chemotherapy may also suppress enhancement of breast magnetic resonance imaging and mask residual disease (86). Researchers and clinicians do not advocate the use of routine breast magnetic resonance imaging in the early (12-18 months after the end of radiotherapy) post treatment period, because it is reported that the contrast enhancement linked with inflammatory changes caused by radiotherapy severely impairs interpretation of breast magnetic resonance imaging (88). Other limitations such as the cost, access and the inability to use this utility to measure breast lymphoedema may also be a limitation for use with this condition (83). However some authors have used magnetic resonance imaging when they found it difficult to be certain that breast induration developing many years after radiotherapy was solely explained by fibrosis or by fat necrosis (89). These authors found a close correspondence between breast oedema in magnetic resonance imaging and the severity of induration (89), and suggested that parenchymal oedema might be due to impaired lymphatic drainage (89).

2.5.7 Mammography

Mammography may also have a role in the assessment of breast volume (83) and breast lymphoedema. Although mammography shows good correlation with breast volumes, there is an associated risk with radiation exposure (71). Breast oedema presents as increased density and changes on mammography (46,90). Differential diagnosis needs to be established as increased breast density, skin thickening and architectural distortion may be due to a number of causes (88,89,91). These include post-surgical oedema, radiation induced oedema, lymphatic spread of cancer, congestive heart failure, infection, post surgical retraction, abscess formation, fat necrosis (88,89,91) and breast lymphoedema.

2.5.8 Breast ultrasound

Breast ultrasound has been identified as a useful quantitative measure of cutaneous oedema and cutaneous breast thickness for patients treated for breast cancer (52,59,92). Breast oedema is shown by changes on ultrasound (46) and has been used as an outcome measure in one study of breast lymphoedema (8). This method may be problematic because the diffuse acoustic shadowing caused by scar tissue may also represent recurrence of breast cancer (8).

Despite the overlap between changes as a result of treatment and tumour recurrence, characteristic appearances on breast magnetic resonance imaging, mammography and ultrasound can usually distinguish these two entities (88,91). This is recognised by comparing findings on previous and successive studies (88,91).

2.6 Management of breast lymphoedema

Evaluating the effectiveness of the management of breast lymphoedema can be particularly challenging, as it is hampered by the lack of standardised objective measurement methods (4,35,54). Current treatment for breast lymphoedema includes medical and physical options, but there is little consensus on the best management (34). As stated earlier, antibiotics are often prescribed due to the cellulitic appearance of the breast, suggesting an infective process. Physiotherapeutic intervention includes manual lymphatic drainage, a very gentle massage applying light pressure to the skin or superficial fascia in the direction of the venous and lymphatic drainage of the involved structures (93). It is used to facilitate the lymphatic system to increase lymph transport (5). Manual lymphatic drainage can produce dramatic responses to breast oedema (7,42) and is considered the treatment of choice for the management of breast lymphoedema (5,31). However, there is no high level evidence supporting the effectiveness of manual lymphatic drainage. Central to the limitation of breast lymphoedema research is that there are no outcomes available at present, with known validity and reliability, to objectively assess the efficacy of these interventions.

The paradox of achieving successful treatment outcomes for breast cancer is the development of side effects (17,19). As there are now many long term breast cancer survivors, the side effects are of prime importance (20). Breast lymphoedema can be a complication of BCT. A lack of standard measuring procedures and reporting criteria make comparing research in the area of breast lymphoedema difficult. Moreover, evaluating the effectiveness of treatment for clinical and research purposes is hampered by the lack of standardised measurement methods. To address this we are developing an instrument to measure health status in women with breast lymphoedema.

A questionnaire design was chosen for this project, as breast lymphoedema evaluation is not only about measuring the size and shape of the lymphoedematous breast, but includes other factors about how a woman feels and how this condition affects activities of daily living. Most of the current measures are concerned with the diagnosis of breast lymphoedema, the size of the breast and are limited in terms of reliability and validity. In the next section of this chapter the methods for questionnaire design will be reviewed.

2.7 Questionnaire development

A questionnaire is in essence "a vehicle for human communication, an activity that is both highly complex and prone to failure" (94)(p1264). Designing one is a sophisticated craft (94) and the process of developing a questionnaire is much harder and more time consuming than most people realise (61). Although a questionnaire has the potential to evaluate patient care, patient treament programmes and the effectiveness of these programmes, developing questionnaires can be an expensive, time consuming and an effort driven task (95).

Some authors have delineated methods of questionnaire development into two types. The "Rolls Royce model" (96)(p890), or the sophisticated method is commended to those researchers who have sizeable resources and an interest in questionnaire development (96). Clinical investigators inexperienced in questionnaire development have responded by creating ad hoc measures described accordingly as the pragmatic approach or the "Volkswagon model" (96)(p890). As a result their questionnaire development is constrained by a failure to attend appropriately to what patients consider important, as well as to issues such as clinical credibility, reproducibility, responsiveness and validity (96).

As discussed previously, there is no known valid questionnaire assessing the full spectrum of items associated with breast lymphoedema. Current measures are hampered by a lack of a consensus definition for breast lymphoedema, limited reliability and validity data and an absence of comprehensive assessment of items of health status (97). These considerations are important when developing and selecting an outcome measure (97).

Other important considerations for patient self reported questionnaires are to be comprehensive, psychometrically robust but brief enough to be of practical use in clinical settings (97). These issues are germane to evaluating comparative treatments (97). The value of an accurate health status assessment is that it permits an instantaneous comprehension of an individual patient's present status and to measure change over time (97). Such a tool should be a multidimensional measure of health status, to provide a comprehensive understanding of the impact of (97,98) breast lymphoedema.

In the area of psychology a lot of work has been undertaken on questionnaire development. In order to achieve adequate levels of reliability, validity and responsiveness, the questionnaire needs to be robust, rigorous and complete. In this area of health when the word instrument is used, it implies a structured questionnaire that has been formally tested (99).

2.7.1 Style of questionnaire development

Several concerns must be addressed before health status measures can be used for clinical purposes (99). Initially the design of the questionnaire followed by the evaluation of the method need to be established before the questionnaire can be used in the clinical setting (99). Steps in instrument development and testing are outlined in Table 2.2, page 19 (96,100,101).

Using these methods, investigators have developed questionnaires for application in diverse conditions including asthma (102), breast cancer (103-104), chronic illness (105), chronic obstructive pulmonary disease (106,107), oncology (99,108,109), incontinence (110) and melanoma (111).

2.8 Questionnaire and patient population

The first, and critical step is to exactly define what the questionnaire is designed to measure (100). This initial definition will assist the investigator design appropriate development protocols, and will enable other users of the measure to recognise its applicability to their own patients and studies (100). Leading on from this, the precise clinical diagnosis and patient characteristics should be identified (100). At the time this study was commenced, there was no widely accepted definition of

Table 2.2 Steps in questionnaire development and testing

A. Development 1. Specifying measurement goals and patient population 2. Item generation 3. Item reduction 4. Questionnaire formatting *B. Testing* 5. Pretesting 6. Reliability 7. Validity 8. Responsiveness 9. Interpretability

(96, 100,101)

lymphoedema, either in the literature, or used by clinicians in Western Australia. This was raised as a potential limitation of the study at the 7th ALA Conference, held in Fremantle Western Australia in 2008. In response to this feedback a consensus group was formed to define breast lymphoedema. This is discussed in Chapter 5, Defining Breast Lymphoedema, page 77.

2.9 Item generation

The next task in questionnaire development is the generation of a list of all potentially relevant items (96,100). In a sophisticated questionnaire design model, the most frequently used method of item generation is a review of the disease specific literature, followed by discussion with health care professionals working in the area with this patient group (96,100,112). Items collated from these sources provide the basis for unstructured interviews with patients (96,112,113). During these interviews, the dimensionality or extent of all of the characteristics of the symptomology of items should be explored (96,114).

Probing enables a description of experiences more fully (115) and using an item elicitation questionnaire facilitates this. The presence, frequency and importance of items provides a comprehensive probe to cover all possible areas of dysfunction associated with the disease being studied (96,114). There are various approaches to determining item importance (96). The easiest is to ask patients to rate on a Likert scale (from very important to not important at all) the importance of each item that is

a problem for them (96,116). A Likert scale assesses the degree to which the respondent expresses a particular point of view (61). However the nature of the probes will depend on the amount of detail required by the researcher and which questionnaire design approach is being applied (96).

A random sample of patient participants will imply a sampling of the complete spectrum of disease severity under consideration and inclusion of patients from all subclasses such as age, sex and duration of the disease (96). In a refined approach, detailed semi-structured interviews with 50 to 100 patients should determine all areas of dysfunction (95). For 100 subjects the 95% confidence interval near a proportion of 50% will be from 40% to 60% and with 50 subjects the 95% confidence interval near a proportion of 50% will be approximately 35% to 65% (96,100).

In a pragmatic approach existing questionnaires are reviewed as well as consulting with one or two experts in the field of interest (96). Items are chosen as the researcher thinks is appropriate (96).

2.10 Item reduction

The item selection phase of questionnaire development often generates a large pool of items (96,100). The researcher must reduce this list, retaining those items that will be most suitable for the final questionnaire (100). Two authors have expanded on the relevant issues in regards to item reduction and therefore are cited as the authoritative works (96,100).

If investigators intend to apply the final questionnaire to subgroups within that population (e.g. mild, moderate and severe disease), then it is important to ensure that all of the subgroups are represented during development and validation (100). Essential elements for retaining items include how many patients who identified the items as a problem (item frequency) and the importance associated with each item (96). There are numerous approaches to item reduction.

Rasch analysis is a commonly used statistical method for item reduction and validation of health status tools (117). This item response theory model identifies

those items of redundancy and poor fit, ensures the scatter of items (of less severe and more severe health status) and construct validity (117,118). However, Rasch analysis is not without its controversies including the need for a high degree of software insight, a large number of observations and an infinite data set with unidimensionality (117,118,119). If there are lots of items and refinement of items during Rasch analysis, questionnaires maybe very reliable but they are also much less valid. Moreover, this analysis has strong assumptions not easily matched by the observations (119). For these reasons we elected not to use the Rasch analysis method for item reduction.

One method is to ask patients to name those items they have experienced as a result of their disease (100). For each positively named item, they rate the importance of that item on a Likert scale (100). This scale offers multiple options depending on the context of the scale e.g. strongly agree to strongly disagree or none to extreme (100,112,114). Some authors have defined the frequency not as the quantity of patients experiencing a specific item, but how often that item occurs e.g. none, daily, weekly, fortnightly, monthly or less (114). While mathematically simple, however, combining frequency and importance criteria is conceptually challenging (95). In a sophisticated questionnaire developmental model, factor analysis or principal-component analysis can be used (61,112,114). The disadvantage of using this method is that items that are not strongly correlated with one another are excluded (61,100). These excluded items may be important to patients (100). Some authors believe that the priority should be on the relative importance one puts on the impact of an item and not its relationship with other items (100). Consequently these authors are reluctant to use factor analysis for item reduction (100). Other authors suggest researchers must be cautious how factors are interpreted (61). A simple approach is to multiply the frequency of each item by its mean importance (96,100). This results in having retained those items with the greatest frequency – importance product for the final questionnaire (96).

Aspects such as the purpose of the questionnaire also need to be considered (96,100). If the measure is an evaluative questionnaire (a questionnaire measuring difference within subjects over time)(100,113), there is little point including items that are unlikely to change over time either as a result of an intervention or through the

natural progression of the disease (96,100). Including these items would compromise the questionnaire's responsiveness and increase the time to complete the questionnaire (96,100). Exclusion of items because of apparent unresponsiveness may be unwise particularly if the questionnaire is to be used to assess an intervention, and the item is considered very important by patients (100). Furthermore, with future innovation in treatment, items that currently appear unresponsive may in the future be impacted in a positive way.

In a discriminative questionnaire (a questionnaire measuring differences between subjects at one point in time)(100,113), if virtually all patients experience the item, then it will not be useful to be included (96,100). However, if the final questionnaire will be used to grade the extent to which a problem affects respondents, then items that the entire population find a problem may still prove very useful in discrimination (96). Although some questionnaires may be capable of being evaluative, discriminative or predictive, it is difficult to simultaneously achieve maximum efficiency in all three (96).

A comprehensive set of items will inevitably include some redundancies (100). If two items have a high impact score, one approach to decide whether to include one or both, is to test whether the items are highly correlated, by using the Spearman rank order correlations (100). This strategy is particularly appropriate for a discriminative questionnaire, as highly correlated items will add little to distinguish varying severity of health status from one another (100). This approach is not as suitable for evaluative questionnaires (100). Although items correlate with one another at the item reduction phase, this does not guarantee that they will change in parallel when measured serially (100). A final consideration in item reduction is the way the items will be aggregated (96). Each dimension being measured requires adequate representation for two reasons; a) to decrease the variability in responses found in stable patients and b) to minimise the impact of idiosyncratic responses to individual questions (96).

The item reduction phase results in the researcher having a suitable number of items for the questionnaire (100), sufficient for content validity, yet not excessive resulting in respondent burden or fatigue. These are then grouped into domains.

The easiest method to determine domains is to use common sense, clinical experience and previously described domains in established questionnaires to group items (100). However intuition has its limitations including differing intuitive sense amongst different people, investigator uncertainty to item placement and although people's intuition may agree, they may be wrong (100). Previously described domains are not an option if the questionnaire is a new measure (100).

Factor analysis is the most popular statistical correlation method used to create questionnaire domains (100). The disadvantage of this method is that if the emergent groupings are counterintuitive, how to proceed thereafter is not self evident (100). Factor analysis is not applicable in the pragmatic approach if only one item is generated or if too few subjects are used. Moreover it will not enable the identification of subscales, if this was an intent of this approach. Item reduction is not a consideration with a pragmatic approach to questionnaire development, as during this phase the investigator simply selects the number of items one chooses to use (96).

2.11 Questionnaire formatting

2.11.1 Response options

Response options are the categories or scales available for responding to the questionnaire items (96,100). A closed or forced option is one in which respondents select one or more of the choices (112). These may be of a dichotomous response preference (e.g. yes or no, agree or disagree) or, where the questionnaire is designed to determine the degree of severity, a wide range of options must be available (96,100,112). There are three grading principles when developing response options- exhaustiveness (or inclusiveness), exclusiveness and balancing categories (112). Exhaustiveness or inclusiveness ensures that the response choices provide a sufficient range to cover all respondents (112). Exclusiveness means that for each item, the patient can only pick one answer to the question (112). An evaluative questionnaire must be able to detect changes for each item, albeit small (96,100). To assure this researchers use a Visual Analogue Scale (VAS) or a Likert scale (61,112). A VAS is a line, usually 100mm in length, anchored by extremes of the item being measured, which participants mark indicating their status for that item (96,112).

Likert scales have been discussed previously. Although there is no evidence to support use of one scale over the other, the Likert scale is easier to administer and interpret (100).

There is also no agreement in the literature in regards to the number of response options to use (61,100,112). The main justification for using a larger number of response categories is that fewer categories are insensitive to real differences (112).

The items in the questionnaire need to include time specification (96,100,114). However it is unclear whether the time frame alters data interpretation (114). Some authors give a range of time frames (96,114). Others suggest two weeks on the basis of their intuitive impression that this time frame is near the upper limit of what participants can accurately remember (100). The time frame also needs to consider the likelihood that the participant will have experienced the situations described in the questionnaire.

2.11.2 Access to prior results

Whether participants should be shown their prior scores when repeating self assessment health status remains controversial (114). The traditional approach is not to permit participants to see their responses on previous occasions, so as to avoid bias-a tendency to score the same even if change has occurred (96,100). Some authors (96,100) have found that showing participants their earlier responses improves the validity of the questionnaire, without negatively affecting the responsiveness (96,100). Other authors have noted no difference between blind versus informed administration approaches (114).

2.12 Pilot testing

After a questionnaire has been developed, all aspects of the questionnaire-as whole and individual questions, need to be assessed thoroughly before final administration (112). This is referred to as pilot testing or pretesting (61,96,112). When questionnaires are first administered, there are envitably some problems with participants not correctly understanding items, and problems with the wording or format of the questionnaire (61,100,112).

It is essential to pretest the questionnaire in a small number of participants before embarking on the next stage of validation (61,100). The literature is inconsistent in regards to the size of this number in the literature. Some authors suggest somewhere between 75 and 100 respondents provide a useful pilot test (112), whereas in the sophisticated model of questionnaire development, a random selection of about 20 participants may be considered sufficient (96). Yet other investigators suggest approximately five to 10 participants (61,100), whilst the pragmatic approach may involve only two or three subjects (96).

During pilot testing participants are asked to explain how they understood each item, what the question meant to them, and why they chose a particular response option (61,100). Discrepancies between what was intended and what was understood are noted, as are any questions that made the subject feel uncomfortable or embarrassed (95,99). Consistent problems in wording are also recorded (100). As well as testing individual items, the questionnaire as a whole is assessed (112). The flow of the questionnaire, time to complete, respondent interest and attention should all be carefully checked with participants (112). Any necessary changes are implemented, and the revised version is pilot tested again using the same procedure, until no more changes are required (61,96,100).

With the pragmatic approach the questionnaire is only changed if obvious problems arise (96). In the construction and pilot testing phases, most investigators will choose a strategy that falls somewhere between the sophisticated and pragmatic approach (96,100). The advice to pilot test is probably one of the most ignored suggestions regarding questionnaire design (112). Time constraints, over confidence combined with inexperience, and practical difficulties all too often cause investigators to skip this whole stage (112). Some authors consider this a risk not worth taking (112).

2.13 Different types of questionnaires

Another consideration with questionnaire development is the type of questionnaire being created. There are different major types of questionnaires (120,121) as illustrated in Table 2.3, page 26.

Table 2.3 Different types of questionnaires and examples

- Disease specific: the Asthma Quality of Life Questionnaire, Karnofsky Performance Status Scale
- Site or region specific: the Oxford Hip Score, the Shoulder Disability Questionnaire
- Dimension specific: Beck Depression Inventory, McGill Pain Questionnaire
- Generic: Short Form 36-item questionnaire, Nottingham Health Profile
- Summary items: Question about limiting long standing illness in the General Household Survey
- Individualised: McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR), Schedule for the Evaluation of Individual Quality of Life (SEIQoL)
- Utility: Health Utility Index (HUI)

(123)(p8)

2.13.1 Disease specific questionnaires

Disease specific questionnaires are designed for the diagnostic group, condition or population being investigated (98,120,121). As disease specific questionnaires have been exclusively developed to assess the particular health problem being studied (120-122), they have relevant and high content validity (120). Disease specific questionnaires have greater likelihood to identify important change over time in the disease being studied (120). In addition acceptability to patients and completion rates should be high as the questionnaire has clear relevance to the patient's presenting problem (121). Disease specific measures may be advantageous in regards to ease of administration, cost and simplicity in scoring, making them ideal for use in clinical practice (120).

An obvious disadvantage of these types of questionnaires is that they are not intended for use in the general population (120,121). Moreover, the nature of disease specific questionnaires prevents comparisons of responses between patients with different conditions. (121). Another drawback of disease specific questionnaires is that they may miss health problems not associated or anticipated with that disease,

unlike a measure with a broader range of items (121). This can be minimised dependent upon the approach taken for questionnaire development (96).

2.13.2 Site or region specific questionnaires

Some questionnaires have been created to assess health problems in a specific site or region of the body. The site-specific focus of these questionnaires is both an advantage and a negative feature. An advantage of a site specific questionnaire is that content items should be particularly relevant to patients with a disease in a very specific body region (121). These patients should also be particularly sensitive to changes associated with interventions in that region (121). However, their very specific focus means they are (121) not likely to detect (any) changes in broader health, overall quality of life or unexpected side effects of interventions (121).

2.13.3 Dimension specific questionnaires

Dimension specific questionnaires focus on one particular aspect of health status (124). The key advantage of these types of questionnaires concerns the level of detailed assessment associated with the topic of interest (121). These questionnaires are also clinically sensible and may be more responsive (113).

The potential problem with dimension specific questionnaires is the exclusion or resultant reduction of information on other dimensions, otherwise the size of the questionnaire could burden the patient (121). A cautious approach concerning the significance of the proposed specific dimension is therefore required (121). Other weaknesses are that these types of questionnaires may restrict some cross-condition comparisons and their applications may be limited in terms of populations and interventions (113). Also in order to retain their sensitivity and psychometric properties, these questionnaires are often long (125).

2.13.4 Generic questionnaires

Generic questionnaires are planned to describe a broad range of health states and the consequence of illness, summarising health related quality of life (113,120,121). Health related quality of life is a multidimensional concept that encompasses physical, mental, emotional and social functioning (120).

Generic measures allow for the comparison of different populations and different programmes, an important objective for policy making and decision analysis (98,120). These questionnaires permit comparing benefits of different health interventions and allocating resources (120). Cumulative knowledge ascertained by generic questionnaires establishes the relative burden of different diseases and the relative merit of different interventions (120).

Generic questionnaires may reduce respondent burden, compared with combinations of a number of different questionnaires (98,121). A disadvantage associated with generic measures is a loss of detail (at some level) in regards to significance to any single illness, and consequently the risk of some loss of significance when applied in any specific context (121,122). Of particular importance to clinical trials is that these questionnaires have less pertinent items to the specific disease, and as a result maybe less sensitive to changes that could occur as a result of a condition-specific intervention (121). However a generic questionnaire maybe of some use when no disease specific questionnaire exists in a particular area (121).

2.13.5 Summary items

Summary items are single questionnaire items that request participants to summarise various aspects of their health status by the use of one, or a very small number of questions (113,121). The brevity of summary items is the most apparent advantage in that questionnaires of this type make the least demands on the participant's time (121). Other advantages include evidence of validity and of the predictive value, and the reproducibility of summary item questionnaires (121).

Although the brevity of a summary item questionnaire can be an advantage, it can also be disadvantageous. These types of questionnaires a) cannot show opposing trends in different health dimensions, b) response categories for summary item questionnaires are restricted and c) this type of questionnaire prohibits making more specific conclusions about specific health aspects from these answers (121).

2.13.6 Individualised measures

Individualised measures are questionnaires that allow the respondent to select issues, domains and concerns that are not pre-decided by the researcher's list of

questionnaire items (121,124). This type of questionnaire addresses the respondent's own concerns as opposed to standard questions that could be of less relevance to that individual (121,124). This in turn contributes to supporting the content validity of the questionnaire (121).

The main disadvantage of individualised measures is that they need to be individually managed by experienced personnel to capture the depth of a respondent's concerns (121). Other disadvantages are that individualised measures require greater resources and time commitments for both researchers and respondents and therefore can be less feasible than other questionnaire methods (121). Also as these measures relate to individuals, it may be less possible to draw comparisons between respondents (122).

2.13.7 Utility measures

Utility measures use preference based methods eliciting the personal preferences of individuals regarding health status (113,121,124). Strengths of this type of questionnaire are that a single number represents the net impact on quality and quantity of life, the measure provides the possibility of a cost-utility analysis and incorporates death as part of the questionnaire. However there is difficulty with interpreting utility values as this type of questionnaire does not allow assessment of the impact on different aspects of quality of life (113). Of ethical concern is the poorly understood judgement of quality of life and utility measures (126) and who is in the best position to provide the utility measures (125). A utility measure may lack responsiveness (113), there is disagreement over the methodology associated with a utility measure (126) and the need for skilled interviewer/s (125).

2.14 Criteria for developing a questionnaire

Eight dimensions are discussed when considering developing, examining and using a questionnaire (121). These are appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility (96,98,100). Although discussed in the literature the aspects of appropriateness, precision and interpretability are less likely to appear (121). Despite being clear from the literature how important these dimensions are, there is no standardised method associated with these aspects, further limiting their use. Due to the time limitations associated with

the project, the dimensions of appropriateness, responsiveness and precision were not assessed. Therefore these criteria will not be discussed.

2.14.1 Reliability

Reliability is the degree to which a measure is consistent and free from random error (61,112,127). It is a very important property of any questionnaire because when used as an outcome based measure it is critical to confirm that any changes detected in research or treatment are due to the intervention and not due to problems in the questionnaire (121). An unreliable questionnaire therefore may underestimate the beneficial size obtained from an intervention (121).

Reliability is assessed in regards to two different features: internal consistency and reproducibility (61,121,128). Internal consistency refers to the amount to which items measure the same characteristics (61). However it has been debated that extreme attention to internal reliability can lead to the exclusion of important items, especially those items that reflect the intricacy and variety of the condition (121).

Reproducibility more directly evaluates whether a questionnaire is capable of measuring a variable with consistency (61,121,128). This is assessed by the test-retest method (61,121). The degree of agreement is examined between scores of the same patient on two separate occasions (121,129). The postulation is that there is no change in scores, based on the reflection of no considerable change in health status of the patient (being measured) between tests (129). The time interval between tests needs to be considered carefully (61). There is no exact agreement on a suitable time interval (121). However intervals need to be sufficiently apart to avoid fatigue, learning or memory effects, but close enough to escape authentic changes in the underlying dimension of health (61,121).

A common approach to assessing test re-test reliability is by means of a correlation coefficient (61,121,129). The ICC is a reliability coefficient that is determined by using variance estimates acquired through an analysis of variance (61,130). Consequently it reflects the amount of correspondence and agreement among ratings (61,130). Reliability is conveyed as a number ranging between zero and one (61,129). The larger the reliability coefficient, the more repeatable or reliable is the

test score (129). “A reliability coefficient value of 0.90 and greater is reported to be excellent; a reliability coefficient value of 0.80 to 0.89 is good; a reliability coefficient value of 0.70 to 0.79 is adequate, and a reliability coefficient value below 0.70 may have limited applicability” (129)(p46).

2.14.2 Validity

Validity is another characteristic of a well designed questionnaire (61,112). Validity is an evaluation of the extent to which a questionnaire measures what it claims to measure (61,112,127). Types of validity are shown in Table 2.4, page 32.

2.14.2.1 Face and content validity

Face validity is an opinion of the content of the questionnaire (61,112,121). This is the weakest form of measurement validity (61). Content validity refers to how well the questionnaire comprises or samples the health factors to be measured (61,112,128). Together these aspects of validity focus on whether the items clearly assess the planned subject matter and if the range is sufficiently covered (121). As neither face nor content validity can be readily measured statistically, the questionnaire itself needs to be examined (121). How the questionnaire was developed and the rigor of this process will determine its scientific quality (96,131).

A sophisticated design approach will maximise the chances of constructing a useful questionnaire (96). This format increases confidence in the validity of the index to be considered as the primary measure of outcome in subsequent studies (95). A pragmatically designed questionnaire only considers face validity and disregards reproducibility and responsiveness (96).

The level of patient participation also needs to be considered (121). However knowledgeable about an illness, experts cannot entirely substitute the direct experience that patients provide of health problems (121).

Several studies have shown that there is disparity between patients’, doctors’ and relatives’ ratings of the patients’ quality of life (132). Using measures that are not patient centered may not cover domains important to patients and therefore may not be valid measures (128,132,133). In a teleconference with N. Bellamy, Professor

Table 2.4 Types of Validity

- Face validity**:**
  a judgment of the content of the questionnaire and the weakest form of measurement validity
- Content validity:
  refers to how well the questionnaire comprises or samples the health factors to be measured
- Criterion validity:
  reflects whether a questionnaire is valid insofar as its results are compatible to those of a criterion standard, or another gauge generally accepted as more precise or an established "gold standard"
- Construct validity:
  refers to the ability of a questionnaire to measure an abstract concept
- Convergent validity:
  this is where to measures will correlate highly or yield similar results if the two measures reflect the same underlying phenomenon
- Discriminant validity:
  this is where measures of different traits will have low correlation or will yield different results

(61, 112)

(October 2010) if such measures do not capture the lived experience of the disease, they are unlikely to be responsive to change after treatment (132). This has implications for interpreting the validity of the measure, determining the effectiveness of interventions and consequently the relative quality of service and the allocation of resources (132).

2.14.2.2 Criterion validity

Criterion validity reflects whether a questionnaire is valid insofar as its results are compatible with those of a criterion standard, or another gauge generally accepted as more precise or an established gold standard (61,112,121). Criterion validity is often separated into two parts, concurrent validity and predictive validity (61). In the absence of a gold or criterion standard, researchers have used validation strategies from psychologists who have been labouring with the problem of how to determine whether questionnaires really measure what they are presume to measure (113). These strategies include establishing the content and construct validity of the questionnaire (113).

As there is not a good criterion variable against which to measure the questionnaire, criterion validity will not be explored in this study.

2.14.2.3 Construct validity

Construct validity refers to the ability of a questionnaire to measure an abstract concept (61, 112). It has been described as the most rigorous approach to establishing validity (113).

The internal structure of a questionnaire can be thought of a set of supposed relationships between underlying concepts (121). Inclusion of subscales within a questionnaire implies that the questionnaire measures different underlying concepts by offering alternate subscale scores, rather than all items simply being added to produce one score of one fundamental concept (121).

2.14.2.4 Convergent and discriminant validity

These two types of validity are based on whether the questionnaire measures what it is designed to measure, as well as not measuring what it is not meant to measure (61). Convergent validity is where two measures will correlate highly or yield similar results if they reflect the same underlying phenomenon, whilst discriminant validity is where measures of different traits will have low correlation or will yield different results (61).

2.14.3 Interpretability

Interpretability is interested with how meaningful the scores of a questionnaire are (100,113,121). Researchers have commented on the difficulty faced by clinicians to decipher meaningful interpretation of results of questionnaires, as opposed to other measures e.g. interpreting blood sugar results (113,121). Not being familiar with use could possibly be the cause (100,121) but also because health professionals seldom use health related quality of life measures in clinical practice (100).

Investigators have begun to make efforts to make scores more interpretable (121). One approach has been to express the scores in terms of the statistical distribution of the results of a specific study, the effect size obtained from the degree of change; and the variability in stable subjects (100). The limitation with this approach

however is there is still no indication as to the level of impact on the patient (if any) (100). One method to address this is to ascertain a conceivable range within which a minimal clinically important difference sits (134). This is the minimum level of change of an outcome measure that is thought to be clinically relevant (100,129,134).

A different approach to be considered is to compare scores (dependent on the availability) of representative data from the general population (121). There are other widely used questionnaires such as the Short Form-36, WOMAC osteoarthritis index and the Australian/Canadian hand osteoarthritis index (AUSCAN) functional subscales have normative data to compare results but this approach has limited scope of application for disease specific and condition specific questionnaires (121,135-137).

2.14.4 Acceptability

It is critical that any questionnaire be acceptable to patients. This aspect of outcome measure development has received less investigation than other issues, such as reliability and validity (98,113,121) and consequently there is little agreement as to what represents acceptability (121).

Ideally a measure should minimise distress to patients already living with health problems (121). This is also important in order to obtain high response rates to questionnaires, to make results easy to interpret, more generalisable and less prone to bias from non-response (121).

Failure to complete questionnaires may be due to a variety of reasons including the health status of respondents, taking into account other disabilities, particularly cognitive or visual (121). Difficulty in understanding the questionnaire including the layout, appearance, legibility and use of language unfamiliar to the respondent are all reasons thought to contribute to incomplete or non-completion of questionnaires. The method of questionnaire delivery may also be a factor in incomplete or non-completion of questionnaires (121). Poor or incomplete questionnaire response rates due to formatting and wording can be discovered and remedied during the early pretesting and pilot tests (61,121,138) included in a sophisticated questionnaire design approach.

One potentially ill conceived assumption of the acceptability of a questionnaire is its length and time to complete (121). There are numerous reasons influencing the time taken to complete a questionnaire. Such issues may include the characteristics of respondents and the format of the questionnaire (121). Some patients appreciate the chance to report on their experiences and concerns (98).

In general, acceptability should be addressed at the design stage (113,121,138). This is considered in a sophisticated approach but neglected in a pragmatic approach to questionnaire design and development. However the easiest and most straightforward ways assess acceptability is the length and response rates of questionnaires (98,121).

2.14.5 Feasibility

Not only does patient burden need to be considered but so does staff, researcher and institutional burden in amassing and processing information (98,121). Data from patients is frequently gathered in the context of routine clinical patient care. To collect, administer and collate questionnaires requires additional staff effort and may jeopardise clinical care (121).

However these burdens can be reduced by the content and appearance of questionnaires (121). Data collection procedures should be simplified and adapted to accommodate clinical routine (98). It is essential the questionnaire topic has an emphasis on answering questions relevant to the clinician (98).

The real test of any health status measure is in its routine clinical use (128). An import concept for any researchers is that validation is an incremental process (113). A properly constructed measure establishes its validity with repeated use over time (113,139). The more often a questionnaire is used, and the more varied the situations in which it performs as expected, the greater the confidence in its validity can be (113). Guyatt et al (113) suggest it is better to conclude that strong evidence for validity of a questionnaire has been obtained in a number of different settings and studies than not to "conclude that a questionnaire has "been validated" (113)(p44).

Rates of breast lymphoedema have been reported at 6- 80% (3-8) however a lack of standard measuring procedures and reporting criteria make comparing research difficult. This is also reflected when evaluating the effectiveness of treatment for breast lymphoedema. The development of the BLYSS questionnaire was undertaken in response to the need for a clinically useful instrument aiming to capture all dimensions of breast lymphoedema. The objective was to identify items considered important to affected women and incorporate them into a valid and reliable questionnaire that would be simple and convenient to administer.

Chapter 3.0
Methodology

In the management of breast cancer, BCT can have better cosmetic outcomes than mastectomy without compromising survival outcomes (18). However, in some women BCT can be complicated by breast lymphoedema. Rates of breast lymphoedema have been reported at 6-80% (3-8), however a lack of standard measuring procedures and reporting criteria, make comparing research studies difficult. Moreover, evaluating the effectiveness of treatment for clinical and research purposes is hampered by the lack of standardised measurement methods. To address this, an instrument was developed to measure the health status in women with breast lymphoedema.

3.1 Part A: Instrument development

3.1.1 Ethical considerations

Prior to commencement of the project ethical approval was sought and granted from the Human Research Ethics Committees, Curtin University, Western Australia; Royal Perth Hospital, Western Australia (see Appendices 1 and 2, pages 136 and 137) and Sir Charles Gairdner Hospital, Western Australia (Appendix 3, page 138).

All patients received written and verbal information regarding this study. Written informed consent was obtained before inclusion. There was no obligation for patients to participate in this study. Those patients who chose not to participate, or who withdrew from the study, were assured that this would not affect their on-going or future physiotherapy management.

All interviews were conducted in a private consulting room in the Physiotherapy Department at Wellington Street Campus, Royal Perth Hospital, or in a private consulting room in the Breast Clinic at the Wellington Street Campus, Royal Perth Hospital. Privacy and confidentiality were maintained in accordance with standard clinical practice. All patients were offered travel re-imbursement of $10. No data enabling identification of individual participants was or will be used in publication or

other reports of the results. De-identified data will be stored at Curtin University for five years.

3.1.2 Instrument development strategy

As shown in Figures 3.1 and 3.2 (pages 39 and 40) a stepwise development and validation process was undertaken. The project comprised of two sections:

- Part A: Instrument Development
- Part B: Evaluation of the BLYSS questionnaire

In this part of the study, questionnaire items were generated and reviewed. This process commenced with generating a pool of questions, followed by a process of item reduction to eliminate redundant or duplicate items. The resulting list of items was then formatted into a questionnaire and a method of scoring developed. Part A concluded by pilot testing the questionnaire.

3.1.2.1 Generating a pool of questions

The initial pool of questions was generated from three sources; i) relevant published material, ii) clinicians who treat patients with breast lymphoedema and iii) patients who have previously been treated for medically diagnosed breast lymphoedema at the Physiotherapy Department at Royal Perth Hospital.

3.1.2.2 Literature review

An initial literature search was conducted by entering key words and phrases into the electronic databases MEDLINE and CINAHL from January 1980 to February 2008. However given the paucity of literature identified in these databases, Google Scholar was added to the databases searched. This approach proved more successful. Search terms used are listed in Table 3.1, page 41. Published and unpublished studies were considered, including proceedings from lymphology and lymphoedema conferences. Reference lists of identified articles were also examined to identify relevant literature.

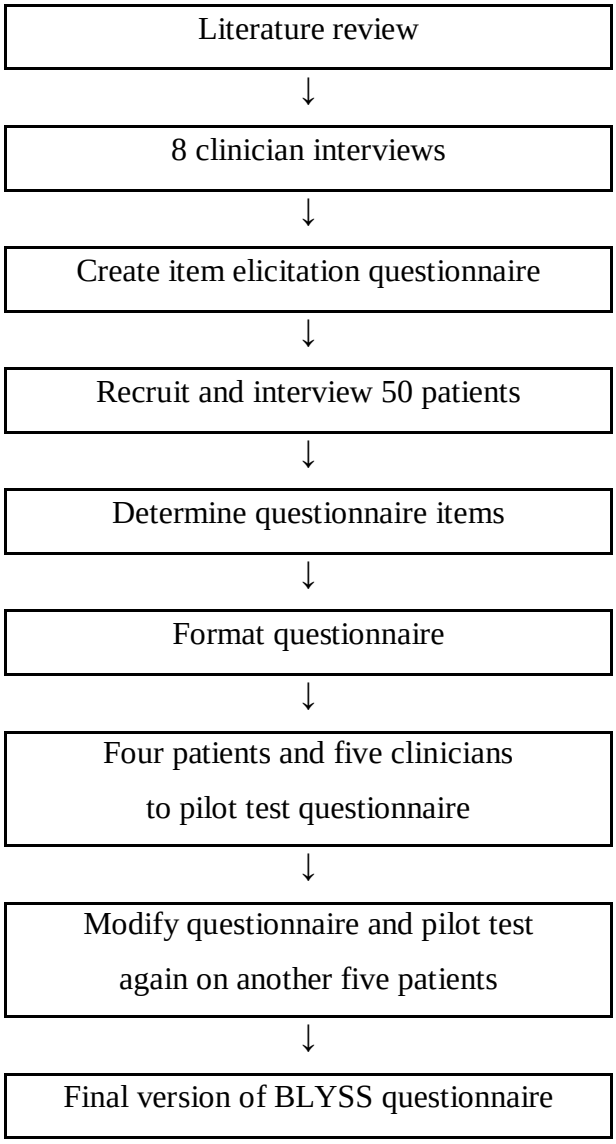


Figure 3.1 Part A- Instrument development

As discussed in the literature review, the literature identifies numerous characteristics and consequences of breast lymphoedema. However the information derived from these needed to be put into the context of the study design (including whether and how breast lymphoedema was defined). Most of the papers identified reported retrospective or observational studies followed by case studies. Although these provide a useful insight into breast lymphoedema, they lack scientific rigor and cannot address questions of treatment effectiveness.

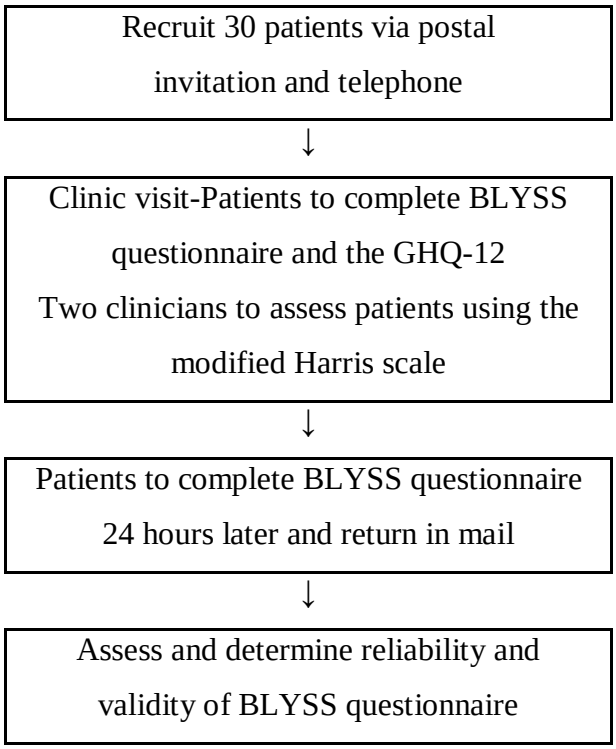


Figure 3.2 Part B- Evaluation of the BLYSS questionnaire

Sixty-six items were identified from the literature to be associated with breast lymphoedema, as shown in Chapter Four, Results, Table 4.1, page 57. These were grouped into five domains: signs; symptoms; physical dysfunction; psychosocial factors; and functionality.

3.1.2.3 Interviews with clinicians treating patients with breast lymphoedema

Ten clinicians who treat patients with breast cancer were interviewed to determine their perceptions of breast lymphoedema. Although no formal sample size calculation was undertaken to arrive at a group of ten clinicians, it is reasonable to extrapolate from previous questionnaire development projects utilising the same design that 10 clinicians from various relevant professions should be more than ample to develop a comprehensive list of items. For example Professor Bellamy (the Associate Supervisor of this project) and Buchanan developed the list of items for the first stage of the WOMAC osteoarthritis index that proceeded down the following steps in this proposal to ultimate validation and is now included in

Table 3.1 Words and key phrases used for the literature search

Breast lymphoedema/lymphoedema
Breast oedema/edema
Breast oedema after treatment for breast cancer
Breast cellulitis following BCT
Mastitis and BCT
Breast oedema and axillary dissection and breast cancer and radiotherapy
Factors influencing the cosmetic outcomes in BCT
Post surgical changes of the breast after breast cancer surgery
Skin and cosmesis and BCT
Radiotherapy and BCT
Acute toxicity in BCT
Fibrosis and radiotherapy for breast cancer

virtually all clinical studies of interventions for osteoarthritis of the hip and/or knee (140) .

3.1.2.3 (i) Recruitment

Clinicians in Perth who treat patients with breast lymphoedema were identified through professional networks and invited to participate in the study. Ten clinicians, two from each of the following professions, were invited to participate: breast clinic staff (medical physicians), breast surgery (consultant medical staff), radiation oncology (consultant medical staff), physiotherapy and occupational therapy. They were mailed a written invitation detailing the research project and their obligations if they agreed to participate (Appendix 4, page 139). A reply paid envelope addressed to the researcher and a consent form (Appendix 5, 141) accepting or declining project involvement was included in the package. Those who consented to participate were contacted to arrange a suitable time for an interview.

3.1.2.3 (ii)Interviews

Demographic information including gender, profession, number of years worked in their profession, the number of patients with breast cancer and the number of patients

with breast lymphoedema treated per year was collected from each clinician (Appendix 6, page 142).

Semi-structured interviews were conducted with the clinicians (Appendix 7, page 143). They were asked, based on their clinical interaction with patients with breast lymphoedema, how much of a problem breast lymphoedema was and if noted this was a problem, why. Clinicians were also asked if they were seeing more, fewer or unchanged numbers of patients presenting with breast lymphoedema. Reasons in regards to these responses were also explored. Clinicians were asked to identify, describe and comment on items they believed would be important to be included in a questionnaire to evaluate the health status of such patients. Initially, to avoid bias and to explore the range and dimensionality of all of what they considered to be related to breast lymphoedema, clinicians were not given any indications or examples of the sorts of items that may be included. They were also asked to indicate which items they considered most important.

For each item a clinician identified to be associated with breast lymphoedema, they were asked if this item varied between patients, how frequently it occurred, how severe it was and how important it was. For all three situations (frequency, severity and importance), they were asked to comment from their perspective as a clinician and also to describe their perception of the patient's perspective. For example, a red lymphoedematous breast may indicate an infection to a clinician, whereas may be considered as unsightly for a patient. Clinicians were provided a scale to rate their responses as shown in Figure 3.3, page 43.

Once responses to the open-ended question were exhausted, any of the 66 items identified from the literature review that had not already been identified by the clinician were raised in turn. They were asked whether each additional item was one item they would associate with breast lymphoedema. If so, the severity, frequency and importance of that item was explored using the same rating scale.

Items from the literature (Table 4.1, page 57) were collated with the 23 additional items identified by clinicians (Table 4.2, page 59), as a preliminary pool of items. This was used to develop an item elicitation questionnaire for the patient interviews.

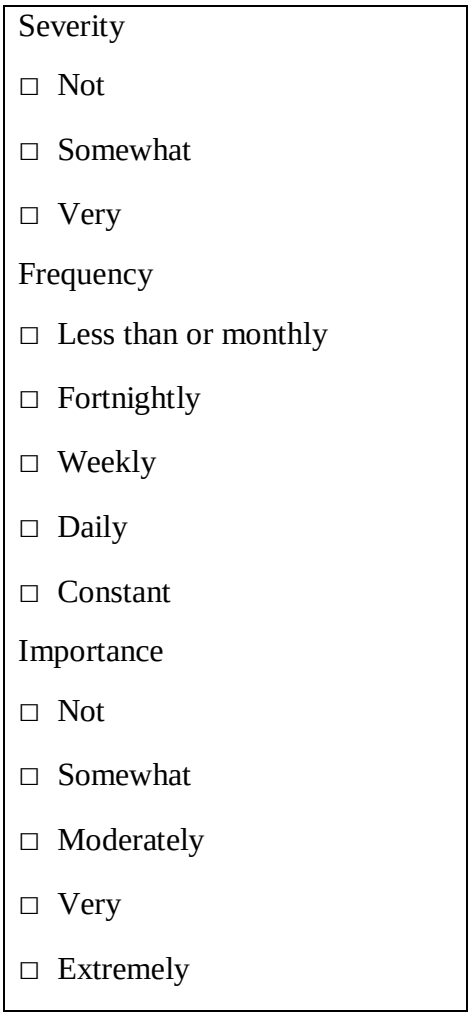


Figure 3.3 Rating scale for clinicians

An item elicitation questionnaire aims to understand the breadth and depth of the item (115) by asking closed ended, then open ended questions probing into all of the characteristics and properties associated with that item. Items identified were screened for duplication and sorted into five domains:

- Symptoms (9 items)
- Signs (7 items)
- Physical limitations (6 items)
- Emotional (14 items)
- Social (7 items)

3.1.2.4 Interviews with patients with breast lymphoedema

This part of the study involved interviewing 50 previously treated patients with breast lymphoedema to determine signs and symptoms of breast lymphoedema. In a sophisticated approach to questionnaire development detailed semi-structured interviews with 50 to 100 patients should be sufficient to determine all areas of dysfunction (96).

3.1.2.4 (i) Recruitment

Patients who had previously been treated for medically diagnosed breast lymphoedema at the Physiotherapy Department at Royal Perth Hospital and in the private sector were invited to participate in the next step of the item generation process. The inclusion criterion for these patients was a medical diagnosis of breast lymphoedema secondary to treatment for breast cancer (ductal and invasive only). Exclusion criteria were current adjuvant chemotherapy or radiotherapy; skin breakdown or open wounds; local, recurrent or metastatic disease; and inability to communicate sufficiently well in English to participate in the interview. Patients taking (adjuvant) hormonal therapy were not excluded. Patients who had previously been treated for breast lymphoedema at the Physiotherapy Department at Royal Perth Hospital were posted information and consent forms (see Appendix 8 and Appendix 9, page 145 and page 147) in regards to the study. Patients recruited by private lymphoedema practioners were informed of the study and, with permission, contact details of interested patients were forwarded to the researcher. Interested patients were telephoned to explain the purpose and procedures of the study, and information and consent forms (see Appendix 8 and Appendix 9, page 145 and page 147) were posted to those who remained interested.

At the time these data were collected there was no widely accepted definition of lymphoedema either in the literature or used by clinicians in Western Australia. This was raised as a potential limitation of the study at the 7th Australasian Lymphology Association (ALA) Conference, held in Fremantle Western Australia in 2008. In response to this feedback a consensus group was formed to define breast lymphoedema. As this was not part of the original project, being able to access a large number participants, less known to the researcher was not feasible. The limitation of this approach does have implications for the generalisability of the

definition adopted. This is discussed in Chapter 5, Defining Breast Lymphoedema, page 77.

All 80 eligible patients were posted an invitation to participate (Appendix 8, page 145) irrespective of whether they lived in the city or a rural area to enhance patient recruitment. It has been documented that many mailed questionnaires do not obtain return rates greater than 50% (95). Also whole population recruitment facilitates sampling of the complete spectrum of disease severity under consideration and inclusion of patients from all subclasses such as age, severity and duration of the disease (96). The invitation outlined the purpose of the study and what women would be asked to do if they volunteered. Included in the mail out was a consent form to complete and return if they were willing to be contacted by telephone for further information (see Appendix 9, page 147). If the form was not returned there was no further contact. Those who returned the form were telephoned to establish eligibility, and ongoing interest, and appointments were made for those who chose to participate.

At the appointment patients received further information concerning the study. In particular the researcher's interest in the area, and the aims and methods of the study were explained in detail. Patients with reservations were reassured that declining to participate, would not have ramifications on provision of future physiotherapy. If the patient agreed to participate, the interview began. Notes were taken during these interviews but no names were recorded. Twenty-nine patients were recruited with the first mail-out. At this stage all non- responders to the initial mail out were recontacted (with ethical approval as an amendment received from Royal Perth Hospital), asking for reconsideration in project participation, including a consent form (Appendix 10 page 148). Another 51 letters were sent and recruitment of 21 patients was achieved, therefore reaching the target of 50 patients for Part A of the study.

3.1.2.4 (ii)Interviews

Interviews commenced with clinical and demographic questions (Appendix 11, page 151). Royal Perth Hospital medical records were accessed to collect clinical information. Where the required information could not be retrieved from the medical

notes, patients were asked about the disease related characteristics of their breast cancer (such as tumour size, tumour grade, histological type and receptor status). Demographic information including age, martial status, handedness, country of birth and occupation were collected.

This progressed to open-ended questions about how breast lymphoedema affected the patient's life. When more detail was required about the identified item, the item elicitation questionnaire (Appendix 12, page 155) provided a resource for the investigator to encourage further responses and discussion by referring to the concepts and items identified from the literature and/or from clinical experience.

Patients were asked whether or not they experienced an item. If a positive response was generated, the dimensionality of the item was explored to identify the extent of all of the characteristics and properties that patient associated with the item. If the patient reported experiencing an item she was asked how often it occurred (frequency), and how important it was to her. Patients were provided the same scale the clinicians had been provided in the earlier part of the study to rate their responses (see Figure 3.3, page 43).

As any unforeseen items identified during the patient interviews could not be added to the questionnaire after completion of the patient interviews, the first 10 interviews were analysed prior to interviews 11 to 50. This enabled any unexpected items identified by patients as associated with breast lymphoedema to be incorporated into the remaining 40 interviews and helped to make sure that items deemed significant by the patients were not left out of the questionnaire rendering it less valid.

Patients were also asked whether similar items had the same meanings or different meanings e.g. discomfort and uncomfortable. Patients were then asked the meanings of each item. This information was used to develop definitions explaining the meaning of the item, in words familiar to patients with breast lymphoedema to reduce any misunderstanding when completing the questionnaire. The use of definitions helps to ensure each patient is interpreting the question the same way when completing the BLYSS questionnaire so that scores can be compared between patients.

3.1.3 Item reduction

At this stage, the pool of items identified from the item elicitation questionnaire was examined. Those items that were unclear, of questionable relevance or seen as duplication compared with other items e.g. swelling and bigger or hardness and solid, were deleted.

All remaining items were screened against the following criteria determined a priori. Items that affected ≥ 60% of the patients were retained. In addition the items must have affected ≥50% of the patients at least once per week and ≥50% of the patients must have considered the item at least slightly important. The justification for retaining ≥60% and ≥50% of items was to have a suitable number of items for the questionnaire (100), sufficient for content validity. This also ensured those items that were infrequently reported, considered not important and/or irrelevant to the majority of participants were not included. This also limited respondent burden or fatigue by reducing an excessive number of items which may not be important to patients. Those items that satisfied all three criteria were included in the first draft of the questionnaire. Nine items were retained as shown in Chapter Four, Results, page 55.

Consideration of the items retained suggested that the circumstances during which some items were experienced (rest, activity or during the night) may alter the way they impact on the patient with breast lymphoedema. This phenomenon is widely recognised in other conditions, for example, patients with osteoarthritis often report being stiffer when they wake in the morning than later in the day. Although not identified in the literature review or with the interviews with the clinicians, we had the opportunity to explore this with patients.

To investigate this further, 20 patients who, during the interviews, had expressed their interest in any further participation in the study were recontacted on the telephone and verbal permission was granted to further discuss these and other issues. For those patients who were willing to be involved, a time suitable for discussion was made. All patients contacted were willing to participate.

Patients were asked whether the symptoms (as shown in Appendix 13, page 171) occurred at rest, during activity and/or night. Only the prevalence of such situations

were asked, as neither the literature review, the clinician interviews nor patient interviews had identified these situations impacting breast lymphoedema. During the same conversation, patients were also asked whether diagnostic ultrasound or summer heat had any impact on their breast lymphoedema. The results of these conversations are presented in Chapter Four, Results, page 55.

These patients were also asked to define the symptoms as described in Appendix 13, page 171. This was done, as despite being able to clearly differentiate whether items had similar or different meanings, patients could not consistently define these terms. This method had the benefit of ensuring each patient was interpreting the question the same way so that scores of the questionnaire could be compared between patients.

During these interviews two additional items, diagnostic ultrasound and summer heat were also identified by patients as exacerbating breast lymphoedema. These two items were included in the BLYSS questionnaire.

3.1.4 Questionnaire formatting

Several questionnaires were reviewed to provide a conceptual basis for the BLYSS instrument. Questionnaires reviewed included the WOMAC Osteoarthritis Index (140), the Functional Assessment of Cancer Therapy-Breast (FACT-B) Scale (104), the Functional Assessment of Cancer Therapy-General (FACT-G) Scale (141), the Breast Project Questionnaire (142), the Incontinence Screening Questionnaire (110), the Functional Assessment of Cancer Therapy-Anaemia (FACT-An) Measurement System (97), the Breast Related Symptom Questionnaire (143), The Lymphoedema and Breast Cancer questionnaire (144), the Clinical Chronic Obstructive Pulmonary Disease (COPD) Questionnaire (106), The Chronic Respiratory Questionnaire (CRQ)- Self Administered- Standardised Activities (145) and the Memorial Symptom Assessment Scale (109).

The wording, layout and formatting of the BLYSS questionnaire underwent numerous considerations and alterations. Eleven items formed the basis of the instrument. The items were divided into three sections; i) the first section was symptom based, ii) the second section contained an item associated with the

psychological impact of breast lymphoedema and iii) the third section contained items including investigations and the impact of summer heat on breast lymphoedema.

Seven response options were initially chosen for the questionnaire. Both Juniper et al (100) and Guyatt et al (96) suggest that a seven to ten response option is reasonable. However seven response options required quite small text to fit on the page and looked overwhelming. As there is little agreement in the literature in regards to the optimal number of response options (61,96,100,112) and the main justification for using a larger number of response categories is that fewer categories are less sensitive to real differences (112), the response options were reduced to five.
A landscape format, consisting of two pages and 11 questions was adopted to display the questionnaire in an easy-to-read presentation (see Appendix 14, page 172). There are five response options in the first and second sections and six in the third section.

3.1.5 Scoring of the BLYSS questionnaire

The standard procedure for scoring questionnaires consists of summing the responses to the questions or to one or more subsets and subsequently standardising or otherwise transforming these sums (146). This is the simplest and most commonly employed approach (147). However there are impediments of a single score for the BLYSS questionnaire encompassing the different recall periods and the conceptual differences in each domain. Based on the identified conceptual differences within the BLYSS, four scores were created (BLYSS I-IV):

BLYSS I- “Appearance and Experience” is the score for the first domain, which are those signs and symptoms to be associated with breast lymphoedema. The scores range from zero to four, resulting in a range of responses from zero to 28.

BLYSS II- “Memory” is the score pertaining to the second domain. This domain asks if the symptoms of breast lymphoedema are a reminder of the breast cancer experience. The scores range from zero to four, resulting in a range of responses from zero to four.

BLYSS III- “Assessments” is the score for the first two items in the third domain. These two items question whether investigations are now more uncomfortable as a result of breast lymphoedema. The scores range from zero to five, resulting in a range of responses from zero to 10.

BLYSS IV-“Weather” is the score for the third item in the third domain. This item asks if summer exacerbates the patient’s breast lymphoedema. The scores range from zero to five, resulting in a range of responses from zero to five.

The scoring sheet to assist clinicians score the BLYSS questionnaire can be viewed in Appendix 15, page 174.

3.1.6 Pilot testing

Having created the questionnaire, the final step in Part A was to pilot test it on a small group of clinicians and patients and to check the applicability, comprehensiveness, relevancy, any ambiguities associated with the instructions and questions, to modify the questionnaire where required and to gain final agreement (95). Both groups were consulted, clinicians providing feedback regarding the relevancy and feasibility of the BLYSS questionnaire in a health care environment, while patient feedback added validity. These two components were integral to the design of the questionnaire.

3.1.6.1 Recruitment

Additional feedback was achieved by recruiting another sample of five clinicians and ten patients (who had previously been treated either at Royal Perth Hospital or in the private sector for breast lymphoedema) in the same manner as earlier in Part A of the study (Appendices 16, 17, 18 and 19, pages 175, 177, 178 and 180).

3.1.6.1 (i) Clinicians

Discussion was divided between the content and structure of the questionnaire (Appendix 20, page 181). A panel of five clinicians who had not been involved with item elicitation were asked to comment on the relevance of the items (including inclusion of non-mentioned items and exclusion of items within the questionnaire), and whether the questionnaire was comprehensive (61,96,100,112). All of the above

were explored in length. The clinicians were also asked to pass judgement and explain the rationale for their comments on the format of the questionnaire, encompassing the questionnaire's length, structure, and the size of the text.

3.1.6.1 (ii)Patients

Demographic and clinical information was first gained from the patients. This used the same document in the first section of Part A, as seen in Appendix 11, page 151. Where the patient was unsure or unable to answer any medically related questions, the medical notes were accessed, if available.

Patients were asked to complete the new questionnaire and then, in an unstructured open ended interview (Appendix 20, page 181), to provide feedback about the clarity of the questionnaire, the relevance of the questions and any inclusions or exclusions to the questionnaire that they considered important and why. Patients were asked to comment on what they perceived the question to be asking, what they meant by their answer and the wording of the questions (112). They were also asked for feedback about the layout, text size and the length of the instrument. The questionnaire was revised according to the feedback received.

The BLYSS questionnaire was pilot tested again, on another sample of five patients only. Clinicians were not asked to participate in the second round of pilot testing due to consistency in responses in the first round, as further discussed in Chapter Four, Results, page 55. The same procedure as previously described was used, collecting demographic and clinical information, having the patients complete the questionnaire and discuss the content and structure of the questionnaire in open ended unstructured interviews. No further refinements were required after the second pilot testing.

3.2 Part B: Instrument evaluation

The purpose of Part B of this project was to evaluate the reliability and validity of the BLYSS questionnaire developed in Part A of the project. This was accomplished by administering the questionnaire to another 31 patients who had previously been treated for breast lymphoedema. Construct validity was assessed by correlating the results from the BLYSS questionnaire with other qualitative scoring tools; the

modified Harris scale (Appendix 21, page 185), with the original Harris scale (2) shown in Appendix 22, page 186 and the GHQ-12 (1) (Appendix 23, page 187) using Spearman's correlation coefficients. Reliability of BLYSS was calculated using ICC's.

3.2.1 Ethical considerations

Ethical considerations for this part of the study were essentially the same as in Part A. There were however, two additional ethical issues in this part of the study. The first relates to use of the GHQ-12 tool (Appendix 23, page 187). This tool can detect affective disorders but does not attempt to give a specific diagnosis (1). Therefore any patient who scored within a range suggestive of an affective disorder (1) was offered appropriate services. Eleven patients scored within this range and these results are discussed in the Chapter Four, Results, page 55. These patients were offered counselling or psychological services.

The second consideration was that observation of both breasts by clinicians was required as part of the validation process. This level of exposure is standard for patients being assessed and/or treated for breast lymphoedema and within the scope of practice in both the Breast Clinic and Physiotherapy Department at Royal Perth Hospital. The need to undress for this part of the study was explained to patients prior to signing the consent form.

3.2.2 Patients and recruitment

Thirty-one patients were recruited from among patients at the Physiotherapy Department and Breast Clinic at Royal Perth Hospital, Western Australia, the Occupational Therapy Department at Sir Charles Gairdner Hospital, Western Australia and the private sector (see Appendices 24 and 25, pages 188 and 190). Inclusion criteria were breast lymphoedema secondary to treatment for breast cancer (ductal and invasive only). For this group a diagnosis of breast lymphoedema was defined on the location, nature, timing and discounted potential differential diagnoses (refer to Chapter Five, Defining Breast Lymphoedema, page 77 and Appendices 26 and 27, pages 191 and 194). Exclusion criteria were the same as for Part A.

Patients were recruited in two ways. Hospital patients were posted an invitation to participate (see Appendices 24 and 25, pages 188 and 190) following the same procedures used in Part A of the study. Patients recruited by private lymphoedema practioners were informed of the study and, with permission, contact details of interested patients were forwarded to the researcher. Interested patients were telephoned to explain the purpose and procedures of the study, and information and consent forms (see Appendices 24 and 25, pages 188 and 190) were posted to those who remained interested. The same procedure used for hospital recruits with reservations, was also used for these patients.

3.2.3 Procedure

Patients attended the Breast Clinic at Royal Perth Hospital. Written consent was obtained and the same clinical and demographic information was collected as in Part A of the study (see Appendix 11, page 151). Patients then completed the BLYSS questionnaire and the GHQ-12. The GHQ-12 is a self-administered test that takes four minutes to complete and focuses on the inability to carry out normal functions and any distressing phenomena (1,148). The GHQ-12 has been shown to be reliable (0.73) on test retest evaluation, has a split half value of 0.83, specificity of 78.5 and is sensitive to change (93.5) (1). Time taken to complete the BLYSS questionnaire was recorded.

The appearance of breast lymphoedema was independently assessed by a clinical nurse specialist and a senior physiotherapist from the Breast Clinic at Royal Perth Hospital, using a modified version of the scale proposed by Harris (shown in Appendix 21, page 185). This four category scoring system first described by Harris et al in 1979, as shown in Appendix 22, page 186 is widely used in breast cancer treatment related studies (149,150). The Harris scale is a subjective method of evaluating the cosmetic outcome of BCT, based on observer evaluation of the treated breast, classifying it into one of four scores: excellent- treated breast nearly identical to untreated breast; good- treated breast slightly different than untreated; fair- treated breast clearly different from untreated but not seriously distorted; poor- treated breast seriously distorted (2,149). Assessors were blind to the other assessor's responses. The researcher did not view the appearance of the patients' breast lymphoedema, and therefore unable to assist, determine or influence scoring by the assessors.

After review by the nurse and physiotherapist, each patient was given another copy of the BLYSS questionnaire and asked to complete it 24 hours later, and return it to the investigator in the replied paid envelope provided. A 24 hour interval was selected to minimise recall bias, without introducing a high risk of change in condition during the interval. Patients were offered a telephone call the following day, as a reminder to complete the second BLYSS questionnaire.

3.2.4 Data analysis

3.2.4.1 Reliability

Data were analysed using Statistical Package for the Social Sciences version 18.0 for Mac. Reliability of BLYSS questionnaire was calculated from the initial (test) and follow up (re-test) completion of the BLYSS questionnaire using ICC's. Duplicate administration in a sample of this size was sufficient to determine a reliability coefficient of 0.8 at alpha = 0.055 and beta = 0.02 (151).

3.2.4.2 Validity

The BLYSS questionnaire addressed face, content, discriminant, criterion, convergent and construct validity. Face and content validity were established by the design of the questionnaire and involvement of both clinicians and patients. This is further discussed in Chapter Four, Results, page 55. The results from the BLYSS questionnaire were correlated with qualitative scoring of the modified Harris scale to determine discriminant validity. The correlations between the BLYSS and GHQ-12 scores were analysed to establish criterion and convergent validity. Construct validity was established based on the content of the questionnaire and if there was a positive correlation between the BLYSS and the GHQ-12.

Chapter 4.0
Results

The development of the BLYSS questionnaire was undertaken in response to the need for a clinically useful instrument aiming to capture all relevant clinical dimensions of breast lymphoedema. The objective was to identify items that reflected the areas affected patients considered important and incorporate them into a valid and reliable questionnaire that was simple and convenient to administer. The approach was designed to both maximise the chances of constructing a useful instrument and to vigorously test its validity and reliability (96). This chapter describes the results of Part A (instrument development) and Part B (evaluation of the BLYSS questionnaire).

4.1 Part A: Instrument development

This first stage involved gathering items to be considered for inclusion in the questionnaire. Based on this objective the initial pool of questions was generated from three sources; i) relevant published material, ii) clinicians who treat patients with breast lymphoedema and iii) patients who have previously been treated for medically diagnosed breast lymphoedema.

4.1.1 Generating a pool of questions

4.1.1.1 Literature review

One hundred and sixty-six articles were identified from the literature review, using the search items described in Table 3.1, Chapter 3 Methodology, page 37. These articles were filtered to include only those articles that described BCT for breast cancer including breast lymphoedema and/or breast oedema, complications of all aspects of BCT treatment (especially chronically), characteristics associated with breast lymphoedema or breast oedema, assessment and treatment of these complications. Items that were mentioned in more than two articles were retained, including such terms as swelling, fibrosis, discomfort and distress. Sixty-six items reported to be associated with breast lymphoedema were identified from the literature. Any items that were, or appeared to be, repetitious or duplicative were reduced to one item (for example larger, bigger, fuller or engorged were considered synonymous with swelling). These items were then grouped into five domains; signs,

symptoms, physical dysfunction, psychosocial factors and functionality, seen in Table 4.1, page 57.

4.1.1.2 Clinician interviews

Of the ten clinicians invited to participate in Part A of the study, eight were willing to be involved. Two clinicians from each of the following professions were represented: breast surgery (consultant medical staff), occupational therapy, physiotherapy and radiation oncology (consultant medical staff). They had worked in their respective professions for a mean (SD) of 16.2 (9.3) years (range 7–33 years) and treated a mean of 486.2 (347.9) patients per year, of which 116.4 (134.6) patients had breast lymphoedema.

All of the clinicians identified breast lymphoedema as a problem, both clinically and for patients. They reported that differential diagnosis could be difficult due to the absence of definitive diagnostic criteria and lack of objective assessment tools. Clinicians used their own rating scales to classify the severity of breast lymphoedema as mild, moderate or significant. Their severity ratings were based on the appearance of the breast and how badly it affected the patient, either physically and/or psychologically. Clinicians reported that specific therapy was not usually recommended for mild breast lymphoedema. However, if the condition was considered moderate to significant, patients would be referred to services such as physiotherapy and psychology for treatment.

Clinicians' responses about breast lymphoedema were associated with how often they treated these patients. Those who did not routinely review patients with breast lymphoedema reported a low prevalence, whereas those who routinely treated patients with breast lymphoedema reported breast lymphoedema as a significant side effect of breast cancer treatment. This was further explored by asking clinicians whether the incidence of breast lymphoedema had changed, particularly as a result of BCT. Responses varied from increased (25%), no change (37.5%), not sure (25%), to a decrease (12.5%) in the incidence of breast lymphoedema.

Table 4.1 Items identified in the literature to be associated with breast lymphoedema

Symptoms

- Altered body image
- Breast size discrepancy
- Discomfort
- Fatigue
- Hypersensitivity
- Increased breast size/increase breast weight
- Numbness
- Distortion in shape
- Heaviness

Signs

- Atrophy/loss
- Erythema
- Fibrosis
- Increased density/firmness
- Induration
- Lymphoedema of the arm
- Non- pitting
- Oedema
- Peau de orange
- Pigmentation
- Pitting
- Retraction
- Telangiectasis
- Thickened skin

Physical dysfunction

- Change in appearance
- Change in fit of jewellery (rings)
- Indentations from the brassieres
- Limitations in arm range of motion
- Skin appears shiny
- Skin appears tight
- Skin has fewer creases
- Marking of brassieres

Psychosocial

- Anxiety/social anxiety
- Avoids looking in the mirror when undressing
- Constant reminder of the breast cancer experience
- Fear
- Fear of recurrence
- Feels ashamed of body
- Feels less feminine
- Feels self conscious about physical appearance
- Psychological distress
- Uneasy about future health

Functionality

- Inability to return to activities of daily living, as prior to breast lymphoedema
- Inability to return to paid occupational activities, as prior to breast lymphoedema
- Inability to return to social activities, as prior to breast lymphoedema
- Arm functioning interferes with daily activities
- Arm functioning interferes with social activities
- Difficulties involving clothing
- Difficulties involving underwear
- Difficultly sleeping
- Discomfort in brassieres
- Functional changes
- Reduced function
- The breast affects the frequency of having sex
- The breast affects the partner’s enjoyment of sex
- The breast affects the partner’s interest in sex
- The breast affects the patient’s enjoyment of sex
- The breast affects the patient’s interest in sex
- The breast interferes with daily activities
- The breast interferes with social activities
- Told by specialist that their breast swelling should resolve (over months to years)

Clinicians reported that breast lymphoedema was a problem when mammograms were required. The swelling and discomfort associated with breast lymphoedema has the potential to limit the amount of breast compression possible during imaging, affecting the quality of the mammogram. As a result some patients with breast lymphoedema had ultrasonography as well as mammography as part of the review process. The responses of the clinicians to the open ended questions about the signs and symptoms they considered were associated with breast lymphoedema and how many clinicians identified each item can be viewed in Table 4. 2, page 59.

Although all items were screened for prevalence, frequency and importance, only the four highest ranking items (as described as important to clinicians and patients) are discussed here. Clinicians reported the frequency of swelling ranging between daily (three clinicians) to constant (three clinicians). One clinician did not answer this question and the other reported that swelling fluctuated between daily and constant. In regards to the importance of swelling to patients, clinicians rated this as ranging from somewhat to very important to patients, and in regards to how important swelling was to clinicians, five clinicians considered swelling to be a very important item.

Discomfort was reported to occur constantly to weekly in patients with breast lymphoedema. Four clinicians considered discomfort as very important and rated it between somewhat and very important to patients. Five clinicians reported heaviness to occur daily in patients with breast lymphoedema. They considered this item as very important whilst they interpreted it to be somewhat to very important to patients. Three clinicians reported constant redness in patients with breast lymphoedema. This item was rated by clinicians as somewhat to very important to patients and as very important by six clinicians.

The next step in generating the pool of items was to integrate the responses from clinicians to the closed ended questions and the items identified in the literature review. All items in Table 4.2, page 59 were included at this stage. Where items contained the main word e.g. anxious or self-conscious but were in different derivatives (anxiety, feels conscious, self conscious of appearance), the main word

Table 4.2 Identified items and between-clinician responses to items considered to be associated with breast lymphoedema (N=8)

Symptom	Agreement within the group
Swelling	8
Discomfort	6
Heaviness	6
Redness	2
Fibrosis	2
Pain	2
Peau de orange	2
Tightness	2
Tenderness	1
Hardness	1
Indentations from brassieres	1
Fear of recurrence	1
Uncomfortable	1
Pinkness	1
Aesthetics	1
Physical reminder of breast cancer	1
Breast changes	1
Hypersensitivity	1
Restriction in glenohumeral joint Range of motion	1
Breast rubs or catches on brassieres	1
Ache	1
Distress	1
Warmth	1

was retained. The items were allocated to five domains which can be seen in the patient elicitation questionnaire (Appendix 12, page 155).

4.1.1.3 Patient interviews

Eighty patients were sent invitation letters to participate and 29 patients responded agreeing to be involved. Six patients returned the consent form declining to be involved and three telephoned to discuss their participation as they no longer felt that they had breast lymphoedema. Forty two patients did not reply to round one of the mail out. On the second mail out, 51 patients from the original mail out were sent invitation letters and the target of 50 patients was achieved.

Patients with breast lymphoedema were predominantly postmenopausal (74%) with a mean age of 57.9 years at diagnosis of breast cancer (Tables 4.3 and 4.4, pages 61 and 62). With respect to treatment, 96% of patients had a wide local excision and 42% of patients had a grade II axillary clearance. The tumour was located in the right breast in 60% of patients and in the upper outer breast quadrant in 58% of patients. Histopathology for the majority of patients was a ductal (82%) grade II (56%) carcinoma without lymph node invasion (68%) that was positive for the hormone oestrogen (43%).

Thirty-six (72%) of the patients experienced postoperative complications. Infection occurred in 24 (48%) patients, seroma in 18 (36%) patients and haematoma in four (8%) patients. Although the total of combined complications was greater than the 36 identified patients, some patients had one or more post operative complications.

Patients were predominantly right hand dominant (92%), pensioners (56%) and born in Australia (44%). Most patients were married (66%) and gave birth to an average of two children, with five patients nulliparous. The highest level of education of 50% of patients was less than or equivalent to an intermediate certificate from secondary school (Table 4.5, page 63).

4.1.2 Item elicitation interviews

Patients who reported experiencing an item were asked further questions regarding the frequency and importance of that item to them. Five response options for how often the item occurred ranged from “constantly” to “less than or monthly”. There were five response options for the importance of each item to the patient. Patients could choose from “not important” to “extremely important”.

The first ten interviews were examined to see if there were any unexpected items associated with breast lymphoedema identified by patients. During this examination it became apparent that patients perceived mammography as an event that exacerbated breast lymphoedema. Therefore this item was incorporated into the interviews, and subsequent patients were asked if it was a problem for them.

Table 4.3 Characteristics of interview patients (N=50)

Characteristics	Mean (SD)	Range
Time since surgery (years)	5.4 (2.6)	1—11
Age at diagnosis (years)	57.9 (9.06)	33—82
Tumour size- first (mm)	18.7 (8.9)	1—35
Second (mm)	12.4 (6.3)	3—20
Age during interviews (years)	62.5 (8.5)	45—85
Duration of breast lymphoedema (years)	3.7 (2.5)	0.1—9.0

Patients were asked the similarities, or differences of items and meanings of each item. From the ten initial interviews, it became apparent that patients could clearly discriminate the meanings of different items but they could not adequately or consistently describe them. It was decided that patients would continue to be asked the similarities and differences between items and the meaning of each item. Once questionnaire items were determined, definitions of these items would be incorporated into the questionnaire. The remainder of the group was interviewed incorporating those additional items identified from the first ten interviews.

Results were tabulated with prevalence, frequency and importance of each item (Table 4.6, page 64) to facilitate screening against the previously determined item retention criteria (affected ≥ 60% of the women at all; affected ≥50% of the women occurring at least once per week; and ≥50% of the women must have considered the item at least slightly important).

The nine items retained were swelling, discomfort, heaviness, uncomfortable, hardness, discomfort in the breast when wearing a brassiere, indentations on the breast from the brassiere, breast lymphoedema is a reminder of breast cancer and mammograms were more uncomfortable now.

Although not identified in the literature review, or clinician or patient interviews, during data collection the investigators questioned whether the items identified from the first round of interviews occurred during different scenarios (at rest, activity and at night). As a result 20 patients were recontacted and verbal permission was granted

Table 4.4 Tumour, surgical, histopathological and treatment characteristics of interview patients (N=50)

Features	Numbers (%)
Tumour location	
Right breast	30 (60%)
Left breast	20 (40%)
Position of Tumour (quadrant)	
Upper inner	7 (14%)
Upper outer	29 (58%)
Upper inner/outer	1 (2%)
Lower inner	4 (8%)
Lower outer	7 (14%)
Central	1 (2%)
Axillary tail	1 (2%)
Surgical procedure	
Wide local excision	48 (96%)
Other	2 (4%)
Adjuvant treatments	
Chemotherapy	23 (46%)
Radiotherapy	50 (100%)
Hormonal therapy	38 (76%)
Tumour Grade	
First tumour	
I	10 (20%)
II	28 (56%)
III	12 (24%)
Second tumour	
I	1 (2%)
II	3 (6%)
III	1 (2%)
Third tumours	
I	1 (2%)
Histological Type	
Ductal	41 (82%)
Lobular	4 (8%)
Mixed ductal and lobular	2 (4%)
Special types	3 (6%)
Type of axillary surgery	
Axillary clearance-grade I	1 (2%)
Axillary clearance-grade II	21 (42%)
Axillary clearance-grade III	2 (4%)
Sentinel node biopsy	9 (18%)
Sentinel node biopsy progressing to axillary clearance	11 (22%)
Unknown	6 (12%)
Lymph node involvement	
Positive	16 (32%)
Negative	34 (68%)
Hormonal status	
Oestrogen positive	38 (76%)

Table 4.5 Demographic characteristics of patients (N=50)

Features	Numbers (%)
Hand Dominance	
Right hand	46 (92%)
Left hand	4 (8%)
Country of Birth	
Australia	22 (44%)
United Kingdom	19 (38%)
Other countries	4 (8%)
New Zealand	3 (6%)
Other European countries	1 (2%)
Malaysia	1 (2%)
Marital Status	
Single	4 (8%)
Married	33 (66%)
De Facto	1 (2%)
Divorced	6 (12%)
Widowed	6 (12%)
Child Bearing	
Nulliparous	5 (10%)
One child	6 (12%)
Two children	17 (34%)
Three children	16 (32%)
Four children	5 (10%)
Five children	1 (2%)
Breast Fed	
None	20 (40%)
One child	4 (8%)
Two children	11 (22%)
Three children	12 (24%)
Four children	3 (6%)
Education	
No school certificate	2 (4%)
School/Intermediate certificate	23 (46%)
High school/Leaving certificate	5 (10%)
Trade/Apprenticeship	1 (2%)
Certificate/Diploma	11 (22%)
University degree	6 (12%)
Postgraduate degree	2 (4%)
Primary Employment	
Pensioner	28 (56%)
Full time work	6 (12%)
Unemployed	4 (8%)
Home duties	4 (8%)
Part time work	4 (8%)
Student	4 (8%)
Voluntary work	2 (4%)
Secondary Employment	
Voluntary work	3 (6%)
Pensioner	2 (4%)
Full time work	2 (4%)
Part time work	2 (4%)

Table 4.6 Prevalence, frequency, importance and inclusion of questionnaire items

Variable	Prevalence (%)	Frequency Overall	Importance Overall	Include
Signs				
Swelling	34 (68%)	32 (64%)	25 (50%)	Yes
Discomfort	31 (62%)	25 (50%)	31 (62%)	Yes
Heaviness	34 (68%)	34 (68%)	34 (68%)	Yes
Pain	27 (54%)	27 (54%)	27 (54%)	No
Hypersensitivity	27 (54%)	22 (44%)	21 (42%)	No
Tenderness	28 (56%)	28 (56%)	27 (54%)	No
Uncomfortable	30 (60%)	30 (60%)	30 (60%)	Yes
Ache	19 (38%)	20 (40%)	20 (40%)	No
Redness	14 (28%)	13(26%)	14(28%)	No
Symptoms				
Hardness	31 (62%)	31 (62%)	31 (62%	Yes
Peau orange	15 (30%)	15 (30%)	15 (30%)	No
Warmth	24 (48%)	21 (42%)	23 (46%)	No
Thickness	16 (32%)	15 (30%)	15 (30%	No
Pinkness	15 (30%	12 (24%)	13 (26%)	No
Heat	25 (50%)	23 (46%)	24 (48%)	No
Physical dysfunction				
Indentations	30 (60%)	30 (60%)	30 (60%)	Yes
Glenohumeral joint range of motion	12 (24%)	12 (24%)	12 (24%)	No
Reaching	18 (36%)	18 (36%)	18 (36%)	No
Taking brassieres on/off	13 (26%)	13 (26%)	13 (26%)	No
Hardness	31 (62%)	31 (62%)	31 (62%)	Yes
Appearance	10 (20%)	10 (20%)	10 (20%)	No
Fear of recurrence	22 (44%)	21 (42%)	22 (44%)	No
Psychosocial				
Reminder	37 (74%)	35 (70%)	34 (68%)	Yes
Anxious	15 (30%)	14 (28%)	15 (30%)	No
Fear	10 (20%)	10 (20%)	10 (20%)	No
Depressed	13 (26%)	12 (24%)	12 (24%)	No
Frustrated	21 (42%)	20 (40%)	20 (40%)	No
Embarrassed	10 (20%)	10 (20%)	10 (20%)	No
Self- conscious	14 (28%)	13 (26%)	13 (26%)	No
Affects clothing	19 (38%)	17 (34%)	18 (36%)	No
Tired	9 (18%)	9 (18%)	9 (18%)	No
Relationship with family	9 (18%)	9 (18%)	9 (18%)	No
Relationship with friends	0 (0%)	0 (0%)	0 (0%)	No
Functionality				
Difficulty wearing a brassiere	18 (36%)	18 (36%)	18 (36%)	No
Difficulty sleeping	22 (44%)	22 (44%)	21 (42%)	No
Discomfort in brassieres	30 (60%)	30 (60%)	30 (60%)	Yes
Affects activities of daily living	19 (38%)	18 (36%)	18 (36%)	No
Affects work	7 (14%)	10 (20%)	10 (20%)	No
Affects sport	8 (16%)	12 (24%)	11 (22%)	No
Affects intimacy	15 (30%)	21 (42%)	20 (40%)	No

Table 4.7 Items and the frequency of occurrence during different scenarios (N=20)

Item	Scenario		
	Rest (%)	Activity (%)	Nocturnal (%)
Swelling	19 (95%)	17 (85%)	17 (85%)
Discomfort	18 (90%)	16 (80%)	18 (90%)
Heaviness	17 (85%)	15(75%)	17 (85%)
Uncomfortable	18 (90%)	17 (85%)	19 (95%)
Hardness	14 (70%)	14 (70%)	14 (70%)
Indents from brassieres	10 (50%)	14 (70%)	7 (35%)
Discomfort in brassieres	10 (50%)	15 (75%)	7 (35%)
Reminder of breast cancer	17 (75%)	15 (75%)	15 (75%)

to further discuss these and other issues. The results of further exploration of different scenarios on the items, is illustrated in Table 4.7. As it was not expected that these scenarios would influence the prevalence or frequency of items, patients were only asked of its presence. As is illustrated in Table 4.7 a similarity in presence for the majority of the items during various scenarios can be seen. Only the indentations from the brassiere and discomfort in the brassiere occurred in half the patients (10/50%) at rest.

Indentations from the brassiere and discomfort in the brassiere occurred in seven patients (35%) nocturnally. This result would not be considered unexpected however as patients would not routinely wear a brassiere to bed. As the prevalence for the remaining items ranged from 75% to 95% for the three scenarios, it was decided not to incorporate any of these situational qualifiers in the questionnaire.

Patients were also asked whether they had ultrasound as a routine part of their investigations for breast lymphoedema and/or as part of ongoing investigations. Ten (50%) of the patients had routine ultrasound and seven of these patients (35%) said that ultrasound was more uncomfortable since developing breast lymphoedema.

During the interviews one patient volunteered that her breast lymphoedema was worse in summer. The potential effect of weather or the seasons on breast lymphoedema had not been considered, as this had not been identified in the literature, by clinicians or other patients. Consequently patients in the subsequent

interviews were asked if there was a season that more affected their breast lymphoedema. Of the twelve patients who were asked the above question, eight (66%) responded that summer exacerbated their symptoms of breast lymphoedema. As a result both ultrasound and summer heat were added to the questionnaire items.

These patients were also asked to define eight of the questionnaire items (swelling, discomfort, heaviness, uncomfortable, hardness, indentations from the brassiere, discomfort when wearing a brassiere and breast lymphoedema is a reminder of breast cancer). Operational definitions were then based on the majority consensus of patients' responses to these items.

Discomfort and uncomfortable were identified by the interviewed patients as items associated with breast lymphoedema. However it is questionable whether these two items have the same or different meanings to patients. Patients who responded positively to experiencing both discomfort and uncomfortable, were asked further questions using the same format as previously described.

Twelve patients reported these items had the same meaning and 11 patients reported that these items had different meanings. As this did not constitute an obvious difference, further analysis was undertaken. The absolute values and averages were examined and as 14 of the 18 responses met the criteria of frequency it was decided to retain both candidate items.

4.1.3 Questionnaire formatting

Fourteen reviews were undertaken to standardise and harmonise questionnaire wording and response options. This required several attempts due to the conceptually different dimensions identified in the earlier processes of Part A.

Alternative templates of the questionnaire were considered using established questionnaires as examples. Revisions were made to the formatting of the BLYSS questionnaire until the final stage was considered acceptable for pilot testing.

4.1.4 Pilot testing

The questionnaire was initially pilot tested by five clinicians and nine patients. Cognitive interviews were conducted with these volunteers with a focus on content and structure of the questionnaire.

4.1.4.1 Clinicians

All clinicians agreed to participate reviewing the BLYSS questionnaire. Clinicians included two physiotherapists, a breast physician, a radiation oncologist and a masseuse. They had worked in their respective professions for a mean (SD) of 14 (8.9) years (range 4–25 years) and treated 179 (88.1) breast cancer patients per year (range 100-300 patients), of which 16 (13.4) of these patients (range 6-40 patients) had breast lymphoedema.

4.1.4.1.1 BLYSS questionnaire content

All clinicians agreed that the content was relevant to the topic. Feedback included that the items were specific, the items described what they thought the common signs and symptoms of breast lymphoedema were and it was relevant not only to the clinician but also to the patient.

Clinicians were asked whether any other items should be included or any item should be excluded in the questionnaire. Four clinicians identified other factors to be included in the battery of items. Discussion was entered into with all clinicians regarding the process of recruitment and selection of items contained within the BLYSS questionnaire. Several clinicians expressed a “doubling up” of items in the questionnaire, such as Items 2 (discomfort), 4 (uncomfortable) and 6 (discomfort when wearing a brassieres). Despite the perceived similarity of these items, patients had expressed distinct differences between them so they were retained.

Clinicians were asked their thoughts about the definitions attached to each item. They agreed the definitions were important as they would improve consistency in the patients’ interpretation of the meaning of items. Two clinicians suggested that the response options should also be defined. Another clinician pointed out that it was not clear if the descriptors (none to extreme) were related to the severity or frequency of each item.

4.1.4.1.2 BLYSS questionnaire structure

The structure and the layout of the BLYSS questionnaire was explored with clinicians. All of the clinicians agreed that the size of the text and the length of the questionnaire were appropriate. Other comments included that the alternate shading enhanced the clarity of the instrument. Clinicians thought the purpose of the BLYSS questionnaire needed improved explanation.

Clinicians were invited to provide any further comments. One commented that Item 7 (how severe are any indentations on the breast from the brassiere?) should be grouped with the rest of the items in the first box. The ultrasound item was suggested to be excluded, as a consequence maybe that patients would want an ultrasound to provide a diagnosis and/or the cause of the breast lymphoedema.
Another suggested that mammograms are not uncomfortable when performed by an experienced professional. One clinician described the questionnaire as purely subjective.

4.1.4.2 Patients

Five patients who had previously been treated for breast lymphoedema were invited to participate in this part of the cognitive debriefing of the BLYSS questionnaire. Four of these patients were willing to pilot test the questionnaire.

Demographic and clinical information was collected on these patients. Table 4.8, page 69 illustrates some of the characteristics of this group. Patients were mainly postmenopausal and who had undergone a wide local excision and axillary clearance, predominantly in the right breast for the surgical management of breast cancer. Although the four patients had differing tumour locations by breast histopathology, all patients had grade III ductal carcinomas in situ. Lymph node status was positive for two patients, and the tumour of one patient was positive for both the hormones oestrogen and progesterone. Three patients had been treated with chemotherapy and all patients had received radiotherapy. Three patients experienced postoperative complications including seroma, cording and haematoma.

All patients were right hand dominant and half of the group were born in Australia. Three of the patients were married. All of the patients had reproduced and had breast

Table 4.8 Characteristics of pilot test patients (N=4)

Characteristics	Range
Time since surgery (years)	2—3
Age at diagnosis (years)	47—58
Age during interviews (years)	50—60
Tumour size (mm)	4—20
Duration of breast lymphoedema (years)	0.3-1.6

fed their infants. Half of the patients had graduated from University and three patients had some form of paid employment.

4.1.4.2.1 Content

All patients reported that the content of the instrument was relevant and that the questionnaire was understandable, facilitated by the definitions within the questionnaire. Four patients stated that the descriptors (none to extreme) were sufficient to answer the questions. Two patients reported completing other questionnaires (including the Pain Scale) and described words being easier to make a choice than numbers.

All patients agreed that the items in the questionnaire represented those items they associated with breast lymphoedema. One patient reported that it was not obvious if the questions were being asked about the frequency and/or the severity of breast lymphoedema. None of the patients suggested any additional items for inclusion. One patient proposed removing item six (discomfort when wearing a brassiere), as this maybe due to a variety of situations, not just breast lymphoedema.

4.1.4.2.2 Structure

All patients liked the configuration of the instrument as it was simple to read, comprehend and answer. All patients reported that the text size and length of the questionnaire were appropriate. One patient suggested modifying page one of the questionnaire so that all of the first seven items were on this page.

4.1.4.3 Revision of the questionnaire and further pilot testing

The BLYSS was modified based on comments provided by clinicians and patients. Amendments included clarification of the purpose of the BLYSS questionnaire in the

introduction and reformatting of the instrument to accommodate the first seven items onto the first page of the questionnaire.

4.1.4.3.1 Second round of pilot testing

Five patients were invited and agreed to provide feedback on the revised BLYSS questionnaire. These patients were recruited using the same process and criteria as in previous parts of Part A of the study. Discussion followed the same format as in the first round of cognitive debriefing of the BLYSS questionnaire.

Characteristics of the second cognitive debriefing patients can be viewed in Table 4.9, page 71. All of the participants were postmenopausal and had undergone a wide local excision in a part of the upper outer breast quadrant as part of the surgical treatment of breast cancer. Of this group, three patients had a sentinel node biopsy progressing to a grade II axillary clearance. Three patients had based on histopathology a grade II ductal breast carcinoma located in the right breast, positive for the hormone oestrogen. Three of this group had developed seroma and infection as postoperative complications. All patients received radiotherapy and three patients took hormonal therapy as part of the adjuvant treatment for breast cancer.

4.1.4.3.2 Content

All five patients reported that the content of the questionnaire was relevant to the topic. They did not think that any of the items should be excluded from the questionnaire. Patients did not volunteer any other items for inclusion in the questionnaire.

All patients considered the explanations associated with each item removed any ambiguity that could be associated with the meanings of the items. Patients also reported that the descriptors (none to extreme) were sufficient to answer the questions. Comments included that the range of choices was sufficient and that circling a word would provoke more of a response than choosing a number or crossing a line. One patient described that having to choose a word response gives the person filling in the questionnaire more of an idea what the question is asking. One patient described experience with questionnaires previously and identified completing pain scale questionnaires. This patient reported familiarity with

Table 4.9 Characteristics of second cognitive debriefing patients (N=5)

Characteristics	Range
Time since surgery (years)	1—4
Age at diagnosis (years)	49—68
Age during interviews (years)	50—72
Tumour size (mm)	5.7—37
Duration of breast lymphoedema (years)	0.5—4

answering a questionnaire and alternative ways of answering a questionnaire.

4.1.4.3.3 Structure

All patients identified the alternative shading of items as an attractive feature of the BLYSS questionnaire. One patient reported that this made the questionnaire easier to read. Other remarks included that the BLYSS questionnaire was clear and understandable in this format. Patients described the layout of the questionnaire as simple. Patients went onto report that this made the instrument easy to complete and made the instructions very easy to follow.

Patients were asked what could be improved with the layout of the BLYSS questionnaire. Only one patient suggested greater balance between the items section and the responses, and suggested expansion of the items section. Patients stated the size of the text and length of the questionnaire was appropriate. All patients reported that questionnaires of four pages or more started to become time-consuming, responses became less accurate due to length and doubted the value of the questionnaire.

Patients were invited to provide additional comments with regards to the BLYSS questionnaire. Three patients took this opportunity. Comments included that the questionnaire was succinct and the length was appropriate.

The ambiguity with response answers, identified in the first pilot testing seemed to have been removed by making clear in the introduction that the questionnaire was a symptom severity-based questionnaire. Consistent comments in both sections implied that no further adjustments of the BLYSS questionnaire were required.

4.2 Part B: Instrument evaluation

The reliability and validity of the instrument was assessed in this part of the study. Thirty-one patients were recruited to participate in Part B using the same process as previously described in Part A. Thirty patients completed both the initial BLYSS questionnaire (test) and the follow up BLYSS questionnaire (retest). This group was predominantly postmenopausal (60%). Histopathologically the breast cancer tumours of the majority of these patients was grade II (53%) ductal carcinomas (80%) that were positive for the hormones oestrogen (87%) and progesterone (50%). Seventeen (57%) of the patients experienced post operative complications, with infection occurring in 12 (48%) of patients. Demographic and histopathological details can be seen in Tables 4.10, 4.11 and 4.12, pages 73, 74 and 75.

4.2.1 Reliability of the BLYSS questionnaire

Test re-test reliability of the BLYSS questionnaire was ICC=0.948 (95% CI=0.894 to 0.975). This ICC score indicates that the score is excellent and that the BLYSS questionnaire is considered to be reliable (129).

4.2.2 Validity of the BLYSS questionnaire

4.2.2.1 Convergent validity

There were significant correlations between the BLYSS and GHQ-12 scores (Spearman's rho=0.58; p=0.001 between the first administration of the BLYSS questionnaire and GHQ-12; and Spearman's rho=0.50; p=0.005 between the second administration of the BLYSS questionnaire and GHQ-12).

4.2.2.2 Discriminant validity

There were poor correlations between the BLYSS questionnaire and both clinicians' modified Harris scores. For the first clinician the statistics were Spearman's rho=0.15; p=0.043 between the first administration BLYSS questionnaire and the modified Harris scores; and Spearman's rho=0.23; p=0.22 between the second administration of the BLYSS questionnaire and the modified Harris scores. For the second clinician, the statistics were Spearman's rho=0.31; p= 0.1 between the first administration of BLYSS questionnaire and the modified Harris scores; and Spearmans' rho=0.16; p=0.39 between the second administration of the BLYSS

Table 4.10 Characteristics of patients in Part B (N=30)

Characteristics	Range
Time since surgery (years)	0—21
Age at diagnosis (years)	468—912
Age during interviews (years)	46—82
Tumour size (mm)	1.9—35
Duration of breast lymphoedema (years)	0.25—14

questionnaire and the modified Harris scores.

4.2.3 Other measures

4.2.3.1 Time to complete the BLYSS questionnaire

Patients were timed to determine the approximate length of time to complete the BLYSS questionnaire. On average it took the 30 patients 2 minutes and 14 seconds (standard deviation of 0.72) to complete the questionnaire. The time to complete the BLYSS questionnaire ranged from 0.53 seconds to 3 minutes and 41 seconds.

4.2.3.2 Inter-tester reliability using the Modified Harris score

There was a significant association between the two clinicians' modified Harris scores (Kappa coefficient 0.593; 23/30 or percentage agreement 77%).

4.2.3.3 GHQ-12

Patients also completed the GHQ-12. Seventeen (56.3%) patients scored within a range that suggested no psychological component of ill health. Five patients (16.3%) recorded a score that was considered borderline of a psychological component of ill health and eight (26.3%) scored within a range indicating a high likelihood of a psychological component of ill health.

Of the 13 patients who recorded borderline to high scores, (potential) causes were explored with these patients. The five patients who scored between 2 and 3 were asked to identify any reasons that may have contributed to their score. Four patients could not identify any factors that may have contributed to a borderline response. One patient was able to identify potential factors, including feeling worse than normal (which may have attributable to a breast cancer treatment related hormonal

Table 4.11 Tumour, surgical, histopathological, treatment and characteristics of patients in Part B of the study (N=30)

Features	Numbers (%)
Tumour location	
Right breast	14 (47%)
Left breast	16 (53%)
Position of Tumour (quadrant)	
Upper inner	2 (6.5%)
Upper outer	14 (46.5%)
Upper inner/outer	2 (6.5%)
Lower inner	5 (16.5%)
Lower outer	3 (10%)
Lower inner/outer	1 (3%)
Not documented	3 (10%)
Surgical procedure	
Wide local excision	29 (97%)
Other	1 (3%)
Adjuvant treatments	
Chemotherapy	15 (50%)
Radiotherapy	29 (97%)
Hormonal therapy	24 (80%)
Tumour Grade	
I	6 (20%)
II	16 (53%)
III	5 (17%)
Unknown	3 (10%)
Histological Type	
Ductal	24 (80%)
Special types	2 (7%)
Not reported	4 (13%)
Type of axillary surgery	
Axillary clearance-grade II	6 (20%)
Axillary clearance-grade III	2 (7%)
Sentinel node biopsy	7 (23%)
Sentinel node biopsy progressing to axillary clearance	9 (30%)
Not performed	1 (3%)
Unknown	5 (1%)
Lymph node involvement	
Positive	14 (47%)
Negative	16 (53%)
Hormonal status	
Oestrogen positive	26 (87%)

Table 4.12 Demographic characteristics of patients in Part B of the study (N=30)

Features	Numbers (%)
Hand Dominance	
Right hand	28 (93%)
Left hand	2 (7%)
Country of Birth	
Australia	22 (73.3%)
United Kingdom	6 (20%)
New Zealand	1 (3.3%)
South Africa	1 (3.3%)
Marital Status	
Married	23 (77%)
Widowed	5 (17%)
Single	1 (3%)
Divorced	1 (3%)
Child Bearing	
Nulliparous	3 (10%)
One child	5 (17%)
Two children	13 (43%)
Three children	5 (17%)
Four children	4 (13%)
Education	
School/Intermediate certificate	22 (73%)
High school/Leaving certificate	4 (13%)
Trade/Apprenticeship	1 (3%)
Certificate/Diploma	9 (30%)
University degree	3 (10%)
Postgraduate degree	1 (3%)
Breast Fed	
One child	5 (17%)
Two children	8 (27%)
Three children	5 (17%)
Four children	2 (7%)
Primary Employment	
Pensioner	11 (37%)
Home duties	7 (23%)
Part time work	6 (20%)
Fulltime work	4 (13%)
Student	1 (3%)
Unable to work	1(3%)
Secondary Employment	
Voluntary work	6 (20%)
Pensioner	1 (3%)
Part time work	1 (3%)
Home duties	1 (3%)
Tertiary Employment	
Part time work	2 (7%)

drug, having a current cold or a recent birthday), that may have contributed to a borderline response. This patient declined any form of psychological assistance that was offered.

Five of the eight patients, who recorded a score of 4 or more on the GHQ-12, were able to identify current situations that may have reflected this score. This included family situations (members with a diagnosis of metastatic breast cancer and being a carer for a partner deteriorating both physically and cognitively), breast cancer treatment related issues (the side effects associated with hormonal therapy) and other non-breast cancer related health issues (chronic back pain requiring surgery).

Three of the eight patients were not able to identify any factors that may have contributed to their score. However one patient had a past medical history of depression that could have influenced these results.

All of these patients were offered access to a variety of services to assist with these psychological situations. Seven of the eight patients declined services, citing being able to access their own avenues or resources to assist with their current psychological situations. One patient accepted information and a pamphlet for access to the Western Australian Breast Cancer Psychology Service.

Chapter 5.0
Defining breast lymphoedema

5.1 Introduction

At the time of this study, there was no widely accepted definition of breast lymphoedema either in the literature or used by clinicians in Western Australia. Because of the difficulty in evaluating the literature due to the wide range and variance between definitions (if a definition was supplied), a group of experts in the area of lymphoedema was formed, with the purpose of developing a consensus definition for breast lymphoedema.

5.2 Literature review

5.2.1 Definitions

Objective, accurate and reliable measures and standardised clinical definitions are essential to the generation of evidence, and the development of practice guidelines fundamental for evidence-based practice (152). However, little attention has been paid to defining disease in clinical medicine (153). Although it has been argued that patients can be treated without one, the importance to patients, clinicians and society cannot be argued (153). The true prevalence and incidence of breast lymphoedema has been difficult to elucidate, and is likely to be under-estimated due to the lack of consensus pertaining to a clinical definition (38,152). The necessity "to describe precisely how the disease is defined" (154)(p300) has been reiterated by other authors. Other researchers have continued to explore this theme. Although the impact of lymphoedema is extensive, it is largely unrecognised and under diagnosed, partly because of a lack of uniformity in diagnostic criteria (144). These inconsistencies in the scientific literature consequently lead to confusion surrounding clinical practice in the prevention and management (155) of breast lymphoedema.

In 2009 Norman and colleagues revisited this discussion, stating that the inconsistencies in measuring and defining lymphoedema still remained a barrier to research and reporting (156), as results cannot be generalised since study populations may differ. Although the conclusions of this research were limited to lymphoedema of the arm and hand, the authors did acknowledge that breast lymphoedema was not

assessed (156). When provided, the terminology used to define breast lymphoedema is inconsistent (7,8,31). As a result, the lack of this understanding hinders patient care (157).

It has been identified that information regarding the assessment and treatment of breast lymphoedema is lacking (41). The lack of a definition for this condition maybe be contributing, and compounding these matters.

A definition that is consistent, bone fide and agreed to allows for assessments within and between groups (154). “Whilst definitions are essential to determine the consistency of measurement, lymphoedema is rarely defined in precise terms” (154)(p300). However, establishing a definition of breast lymphoedema, will facilitate uniformity in identifying patients with breast lymphoedema, and will be advantageous in clinical and research settings (32).

5.2.2 Consensus techniques

Consensus methods provide a means of synthesising information from a wide range of sources, frequently via insights provided by appropriate experts. They are particularly useful where purely quantitative methods are inappropriate or impossible. The three most commonly known consensus methods are the Delphi technique, the nominal group technique and the consensus development conference (158). The resources to orchestrate the consensus development conference were beyond this project, and is beyond that of most researchers (158). The Delphi technique and the nominal group technique involve measuring and developing consensus (158). Both approaches have been used in medical, nursing and allied health.

5.2.2.1 The Delphi technique

The Delphi technique uses group facilitation to achieve agreement of the opinion of experts in the field, typically through a series of sequential structured questionnaires in rounds (158-160). The process allows respondents to be exposed to the anonymous opinion of their peers. It enables researchers with limited resources to contact a large group of experts cheaply (via mail or electronic mail) with a self

administered questionnaire with few geographical barriers (158). Table 5.1, page 80 illustrates the areas for reporting using the Delphi technique.

5.2.2.2 The Nominal group technique

The Nominal Group Technique originated in the 1960's with the aim of facilitating effective group decision making in regards to social psychological research (161). As with the Delphi technique, this technique also uses experts, has at least two rounds of balloting but also includes face to face meetings from the beginning to identify issues associated with the topic to reach consensus (163). This method can be adapted and a modified nominal group technique involves only one meeting (163).

There are similarities in both techniques. These include the generation of a large number of ideas, avoidance of a single train of thought, brainstorming to help explore the concept, encouragement of equal expert input, highly structured processes, avoidance of quick decision making, high degree of task completion and measurement of the relative importance of generated ideas (158,161).

However significant differences exist as well. The nominal group technique involves a face to face meeting (usually of one to two hours length), whereas the Delphi technique does not (158, 161). The nominal group technique provides immediate feedback to participants, the Delphi Technique does not (158,161).

A predominantly Delphi technique was used in this part of the project as this technique has demonstrated its value in previous health studies (158-160) and it integrates qualitative and quantitative approaches. However due to time limitations associated with a Masters degree, the desire to apply the definition to the project, and the economic constraints of the project, this initiative did not start with a questionnaire asking experts what should constitute a definition of breast lymphoedema. The components were provided to experts, who were asked to express their opinions of the merits of these components. In light of the time and economic constraints, a face to face meeting was not feasible.

Table 5.1 Areas for reporting on the Delphi technique

Research problem	Clearly defined
Research rationale	Topic and method justification
Literature review	Topic under study
Methodology	Data collection: clear explanation of the Delphi method employed Rounds: number employed, outline of each Sample: experts selection process and characteristics described in details Reliability and validity issues identified Statistical interpretation: guidelines for the reader Ethical responsibilities: towards "expert" sample and research research community
Data Analysis	Response rate for each round Round 1: presentation of total number of issues generated Round 2: presentation of results indicating the strength of support Further rounds (if applicable): presentation of results
Discussion and conclusions	Issue of consensus Interpretations of consensus gained/not gained Direction of further research leading to conclusions
Appendices	Copy of each round of questionnaire illustrated

(162)(p1009)

5.2.3 Factors for consideration

There are considerations for establishing and determining a consensus group. The success of the consensus group depends upon the combined know-how of the experts (160). The qualifications of the experts and the size of the panel are two fundamental features, as are the meaning of consensus, data analysis, reliability and validity (160).

5.2.3.1 Experts

The most appropriate experts will be those practicing in the area (158), which also provides credibility with the target audience (158). Yet experts should be relatively impartial (160), as those with a direct interest in the area could cause bias (159). Another consideration is that experts ideally should not be chosen on the basis of acquaintance with the researchers, as this too may introduce bias into the process (160).

What constitutes an expert and how to identify one is controversial (159). The selection of experts usually involves non-probability sampling techniques, either purposive sampling or criterion sampling (159). Either technique means that experts

are not randomly selected therefore representativeness is not assured (159). This is also a potential cause of bias (154) as experts are chosen for a selected purpose.

A heterogeneous group of experts should include those with a wide knowledge base (160). This will potentially lead to better performance due to differing perspectives on a problem (leading to a wider range of alternatives) and has the promise of producing a substantially higher proportion of high quality, highly acceptable outcomes than a homogenous group (160).

5.2.3.2 Numbers

The numbers of experts in the group will affect the generation of ideas and the amount of data to be analysed (159). In the Delphi technique there is a wide variation in the panel sizes from 10 to 1685 although this technique does not call for panel sizes to be representative samples for statistical purposes (160). However, time and money constraints associated with projects, maybe more influential and important considerations in regards to the number of participants (160). Intuitively it seems reasonable that the more experts the better because as the number of experts increases (160), so does "the reliability of a composite judgement" (164)(p37).

5.2.3.3 The meaning of consensus

There are no level or firm rules that determine consensus in the Delphi technique (160), nor is there any uniform or consistent way of measuring this. Although the final round will show "convergence of opinion with the dispersion of experts views lessening with each round" (160)(p379).

A clear definition of acceptable levels of consensus (158) must be identified and justified within the methodology. Consensus can be defined in several different ways. Establishing a percentage level is a common way of clarifying the meaning of consensus (159,160), however this percentage can be construed at different levels (160). In one author's review of the literature (160), this inconsistency of the meaning of consensus is evident in some studies. Some studies suggested consensus was implied by the results, other studies reported it was most participants' agreement, others defined consensus based on stability of responses between rounds, or the interpretation of consensus was left to the reader (160).

5.2.4 Data analysis

The Delphi Technique includes qualitative and quantitative methods (159,161) . The first round of the Delphi technique is often qualitative (159). Following rounds are then assessed to determine convergency and change of participants' opinions (159).

Scrutiny of statements can be summarised by using the median (158,159), modes and means (159), and levels of dispersion using interquartile ranges and standard deviations (158,159). Some authors have used a very precise methodological quantitative analysis involving ranking and scoring on a nine point scale, where scores represented levels of total disagreement through to levels of total agreement (158).

5.2.5 Reliability and validity

There is no evidence for the reliability of the Delphi technique (159) however aspects of validity can be assessed. Face validity can be determined by how consensus was achieved and the rigor of this process will determine its scientific quality (96,131). Content validity may be established using experts with knowledge and interest in the topic (159). Predictive and concurrent validity of a Delphi technique can be evaluated by comparing findings with data from alternative sources (160). Concurrent validity can also be helped to be developed by successive rounds using the instrument developed (159).

5.3 Methodology

Initially the literature was searched for information related to breast lymphoedema in breast cancer patients, the use of the term and whether and how this was defined. The literature was also reviewed for standards for what should be included in a definition.

Databases searched included Medline, AMED (Allied and Complimentary Medicine), PsycINFO, Health and Psychosocial instruments and the Ovid Nursing. Given the success with Google Scholar earlier in the project, this was also searched. As identified in other parts of this thesis, the literature review identified that uniformity in the use and terminology of breast lymphoedema is limited. As a pre-

existing definition could not be used, it was decided to create a definition for breast lymphoedema (112).

Experts working in the field of lymphoedema were invited to participate in a discussion group (Table 5.2, page 84). These people were known to the researcher through professional affiliations and collaborations. At the commencement of this project there was no widely accepted definition of breast lymphoedema. During a discussion at the 7th ALA Conference held in Fremantle, Western Australia in 2008, this was identified as a potential limitation of the study. Therefore a complimentary study was introduced to the project with the aim of developing a definition of breast lymphoedema. As this was not part of the original project, being able to access a large number participants, less known to the researcher was not feasible. The limitation of this approach does have implications for the generalisability of the definition adopted. Experts were contacted via electronic mail, explaining why they specifically had been approached, the aims, requirements and expected outcomes of the project. The purpose of this project (as an adjunct to a Masters degree) was also discussed. Participation was requested of the experts and it was explained that all contact would be via electronic mail (email) due to logistics, time and budgetary constraints. They were reassured that participation in the project was entirely voluntary and choosing not to participate would not affect any future professional interactions or affiliations. If experts wanted to be involved in the study, a reply email was requested. If no response was indicated by the expert, no further contact was pursued. Experts were directed to contact the researcher in regards to any questions or concerns about the project, either by email or telephone.

In the first round of discussion, 12 issues were generated and presented as suggestions for the requirements for a definition of breast lymphoedema to panel members. No standards for what should go in a diagnostic definition were revealed during the literature review. However general requirements suggested that a vigorous definition should be based on the nature, location and the timing of breast lymphoedema.

Differentiating true breast lymphoedema is a process of identification of a possible cause of lymphatic vessel or node damage (in this case potentially surgery and/or

Table 5.2 Experts who participated in the breast lymphoedema consensus definition group

Expert	Position and affiliation
Dr. Sandi Hayes	Senior Research Fellow, School of Public Health, Queensland University of Technology, Australia
Dr. Monika Janda	Senior Research Fellow, School of Public Health, Queensland University of Technology, Australia
Louise Koelmeyer	Senior Occupational Therapist, Westmead Breast Cancer Institute, Westmead Hospital, New South Wales, Australia
Dr. Helen Mackie	ALA Medical Adviser, Australia
Mr. Alex Munnoch	Consultant Plastic Surgeon, Ninewells Hospital, Dundee, Scotland
Professor Neil Piller	Director Lymphoedema Assessment Clinic, Department of Surgery, School of Medicine, Flinders University, South Australia, Australia
Dr. Leigh Ward	Reader in Nutritional Biochemistry, Department of Biochemistry, University of Queensland, Australia

radiotherapy for treatment of breast cancer treatment), and elimination of other systemic or local causes (165). An initial document containing other criteria including location, nature, timing, differential diagnosis and risk factors for developing breast lymphoedema was sent to experts for their contribution. For each section, criteria derived from the literature review were provided, as a starting point for discussion amongst the group. For example in regards to location of the breast tissue, a description of the position of the breast, with references, was provided. Using a dichotomous scale experts were asked whether they agreed or disagreed with the statements, and to provide their rationale for this. Results were then collated. As there is no widely recognised level of consensus required, it was decided that a minimum of 80% agreement from the group would be required for further consideration of inclusion in the definition. Anonymous responses from the group were fed back to the experts, along with the rationale as to why certain decisions and choices had been made and the consensus document was changed to reflect these

suggestions. This process continued for three rounds until all experts were satisfied with the content of the definition for breast lymphoedema.

5.4 Results

Thirty- seven articles on breast oedema and/or breast lymphoedema were identified from the literature review. Table 5.3, page 86, identifies those authors that define and do not define breast lymphoedema and breast oedema. Although these articles were not shown to the panel of experts, it identified the inconsistency in regards to definitions. Reviewing these articles informed the development of the criteria provided to the panel during the first round of data collection. Seven experts were contacted. All (as shown in Table 5.2, page 84) accepted the invitation to participate in the consensus group.

5.4.1 Data collection

5.4.1.1 Round one

5.4.1.1.1 Experts comments

An initial document was emailed to each of the expert panel members who provided feedback including verification of provided material, ideas for further development or components that required clarification. Analysis involved identifying whether an expert agreed or disagreed with statements in each section, by reviewing the comments they provided. The responses for round one are summarised in Table 5.4, page 87. One hundred per cent agreement was achieved during this round.

5.4.1.1.2 Location

Three experts questioned whether the discussion of breast lymphoedema, included chest wall lymphoedema following mastectomy. Another expert questioned naming the breast a round eminence where the breast has been modified or tissue removed. An expert suggested components of definitions should include the breast quadrant/s involved. This expert's proposal was to term the breast quadrants as lateral superior, lateral inferior, medial superior and medial inferior. This idea was supported by another two experts. No expert reported that the criteria in this section were not of value to the definition.

Table 5.3 Authors that defined and did not define breast lymphoedema and breast oedema

Characteristic	Author/s
Defined breast lymphoedema	Kirshbaum 2000 (31), King et al 2001 (64), Falagas et al 2005 (67), Lawenda et al 2009 (41), Fu et al 2009 (35), Degnim et al (60)
No definition of breast lymphoedema	Mertz et al 1998 (49)
Defined both breast lymphoedema and oedema	Clarke et al 1982 (3), Mondry et al 2002 (5), Goffman et al 2004 (7), Ronka et al 2004 (8), Stevenson et al 2005 (56), Jahr et al 2008 (43)
No definition of either breast lymphoedema or breast oedema	Sarin et al 1993 (77), Loprinzi et al 1996 (47), Meek 1998 (4), Majeski et al 2000 (50)
Defined breast oedema	Carl et al 2001 (90), Fehlauer et al 2003 (23), Moffatt et al 2003 (57), Kwak et al 2005 (65), Jeffs 2006 (42), Wratten et al 2007 (59)
No definition of breast oedema	Habibollahi et al 1988 (44), Senofsky et al 1991 (45), Mendelson 1992 (46), Carl et al 1998 (48), Martlew 2000 (51), Wratten et al 2000 (52), Kurtz 2002 (26), Lopez et al 2002 (30), Wratten et al 2002 (53), Zippel et al 2003 (6), Back et al 2004 (15), Parbhoo 2006 (40), Williams 2006 (54), Linnitt et al 2007 (55)

5.4.1.1.3 Nature

The experts provided points for consideration in this section. These included description of skin and tissue quality using the terms pitting, fibrotic, indurated and/or painful. The staging of lymphoedema created by the International Society of Lymphology (ISL)(166) was also provided as a consideration and can be viewed (Table 5.5, page 88).

Table 5.4 Summary of experts' comments in round one.

Expert	Opinion	Comment
1	Agree	Discussion of breast lymphoedema, included chest wall lymphoedema following mastectomy
2	Agree	Discussion of breast lymphoedema, included chest wall lymphoedema following mastectomy
3	Agree	Discussion of breast lymphoedema, included chest wall lymphoedema following mastectomy
4	Agree	Discussion of breast lymphoedema and questioned naming the breast a round eminence where the breast has been modified or tissue removed
5	Agree	Discussion of breast lymphoedema, suggesting inclusion of the breast quadrant/s involved
6	Agree	Agreed with expert 5 for inclusion of breast quadrant/s involved
7	Agree	Agreed with expert 5 for inclusion of breast quadrant/s involved

5.4.1.1.4 Timing

During discussion of the diagnosis of breast lymphoedema at the 2008 ALA Conference, it was suggested by an audience member that a definitive diagnosis of breast lymphoedema could not be made until breast swelling had been present for a minimum of three years. Five of the seven experts questioned the need to have breast considered this to be extreme and questioned its basis. The relevance of the time after breast surgery and the completion of radiotherapy were also queried. One expert questioned the need to have breast lymphoedema for a minimum of three years as a criterion for the definition. The panel considered this to be extreme and questioned its basis. The relevance of the time after breast surgery and the completion of radiotherapy were also queried. One expert suggested this was an unsound recommendation, as earlier detection can result in more favourable outcomes.

One expert pointed out the need to be clear about distinguishing between timing related to development of breast lymphoedema, and timing with respect to how long someone has had breast lymphoedema. This expert thought that there was a general consensus that normal post-operative or post-radiotherapy swelling is resolved within three months. The expert suggested encompassing this concept with this, even if only on the basis that there is nothing better to go by. Whilst wanting to ensure a diagnosis

Table 5.5 International Society of Lymphology lymphoedema staging

Stage	Definition
Stage 0 or Ia	A subclinical state where swelling is not evident despite impaired lymph transport. This stage may exist for months or years before oedema becomes evident
Stage I	This represents early onset of the condition where there is accumulation of tissue fluid that subsides with limb elevation. The oedema may be pitting at this stage
Stage II	Elevation alone rarely reduces swelling and pitting is manifest. ISL late stage II- there may or may not be pitting as tissue fibrosis is more evident
Stage III	The tissue is hard (fibrotic) and pitting is absent. Skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits and warty overgrowths

(166)(p53)

of breast lymphoedema as opposed to other conditions, alternative causes could be ruled out using other diagnostic tools. This expert also discussed the issue about whether someone has acute (meaning transient or short-term) lymphoedema, compared with chronic lymphoedema (which is persistent – could be stable persistent or fluctuating, but persistent). Accepting the theory that swelling from an event (e.g. surgery) goes within three months, Moffat's definition of persistent "lymphoedema of greater than three months duration" (57)(p732) may be appropriate.

5.4.1.1.5 Differential diagnosis

This section achieved consensus by the group. One expert suggested lying on the same side continually to be included in this section.

5.4.2 Responses and recommendations

5.4.2.1 Location

In response to whether breast lymphoedema included chest wall lymphoedema following mastectomy, it was clarified that this definition at present was restricted to those female patients who had BCT for breast cancer treatment. As a result at this stage the definition would also not include other areas such as the axilla, lateral chest wall, inferior clavicle, superior clavicle or the arm.

One expert questioned naming the breast a round eminence as removal of breast tissue could potentially change breast shape. Although it is acknowledged that the appearance and structure of the breast may be altered or changed as a result of breast cancer treatment and breast lymphoedema, the anatomical location will still be on the anterior chest wall and there is a need to clearly identify the organ that is being discussed and defined. Changes in the shape of the breast in the location section were made to reflect these suggestions.

The terms for breast quadrants provided uniformity and consistency when describing locations on a breast. This suggestion was adopted as it is anatomically based. Therefore, these descriptors should be recognisable across different health professions working with women with breast lymphoedema.

5.4.2.2 Nature

Experts were asked to consider using the terms for breast quadrants, the descriptions of skin and tissue quality, the lymphoedema staging created by the ISL and/or both. There were several reasons for this suggestion. There is repetition of the terms pitting and fibrosis in the descriptions of skin and tissue quality and the lymphoedema staging created by the ISL. Although induration and pain may be important items associated with breast lymphoedema, there are many items identified in the literature associated with breast lymphoedema. As explained by one expert “the information derived from studies needs to be put in the context of study design, and comments about the strength of the study need to be described”. Another expert pointed out that detectable swelling may be a comparatively late development.

The ISL staging is a familiar and established grading system in the assessment of lymphoedema, in the lymphology community. Therefore it was suggested to the group, as a basis for assessment of grading for breast lymphoedema.

5.4.2.3 Timing

Rationale for the basis of the three year suggestion was that if breast oedema was still present, differential causes of breast oedema could be disregarded. Regardless of what timeframe was decided upon by the group, experts were reassured by the author

there was no implication that if a patient had breast oedema/lymphoedema, they would not be denied any sort of lymphoedema management.

All of the above suggestions were incorporated in the document as risk factors associated with the development of breast lymphoedema. These risk factors were identified from the literature review and included suggestions from experts. A list of risk factors was included in the second document for comment by the experts. The second revised version was distributed among experts.

5.4.3 Round two

5.4.3.1 Experts comments

All experts (100%) expressed their support for information in this section.

5.4.3.1.1 Location

One expert interpreted the base of the breast as being the bottom of the breast as opposed to the top and questioned whether this is what was being described. Two experts suggested a diagram to supplement the breast quadrant Table. One expert questioned the effect of aging on the breast and another whether this only applied to a female breast (as breast cancer is seen in males). Other than these comments experts expressed their support for information in this section.

5.4.3.1.2 Nature

General consensus of agreement was achieved within this section.

5.4.3.1.3 Timing

General consensus of agreement was achieved within this section.

5.4.3.1.4 Differential diagnosis

One expert suggested that in this section it may be useful, depending on the context that the definition would be used, to provide a brief summary detailing the differential diagnoses. Other experts of the group supported this.

5.4.3.1.5 Risk factors

There was also discussion about whether a section on risk factors for breast lymphoedema should be included in the definition. A list of these factors, with references was provided to the experts to review. One expert suggested considering breast scar direction and breast scar length to be considered as a potential risk factor. However another expert responded to this comment by suggesting these scars (the breast incision and the node dissection scar) were two individual factors to be considered separately. Experts' comments can be seen in Table 5.6, page 92.

5.4.3.2 Responses and recommendations

5.4.3.2.1 Location

As a result of the feedback, a diagram to supplement the breast quadrant terms was added. The effect of aging on the breast was included as part of the definition and a statement that the definition was only applicable to female breast lymphoedema was added.

5.4.3.2.2 Nature

One expert queried if other items (such as heaviness, tightness and hardness) should be included in this section. Although heaviness, tightness and hardness may be items associated with breast lymphoedema, there are many items identified in the literature associated with breast lymphoedema. One expert clearly explained that information derived from studies needs to be put in the context of study design and comments about the strength of the study need to be described. Therefore at this time, based upon study design and strength, these items were not included.

5.4.3.2.3 Timing

Based on the comments provided by experts in this section it was suggested that breast lymphoedema consists of breast swelling that persists greater than or equal to three months post surgery and/or radiotherapy.

5.4.3.2.4 Differential diagnosis

Definitions were provided for the differential diagnoses and were included as an appendix to the main document. This can be seen in Appendix 27, page 194.

Table 5.6 Summary of experts' comments in round two

Expert	Opinion	Comment
1	Agree	Discussion of breast lymphoedema, included risk factors for breast lymphoedema
2	Agree	Discussion of breast lymphoedema, included the effect of aging on the breast
3	Agree	Discussion of breast lymphoedema, included risk factors for breast lymphoedema
4	Agree	Discussion of breast lymphoedema, included description of breast location, differential diagnosis and risk factors for breast lymphoedema
5	Agree	Discussion of breast lymphoedema, included rationale for timing section and limitations risk factors for breast lymphoedema
6	Agree	Discussion of breast lymphoedema, included discussion of genders of breast cancer patients
7	Agree	No comments provided

5.4.3.2.5 Risk factors

Four experts provided feedback in this section. A concern of one expert, with listing the risk factors, was that the information derived from studies was not put in the context of study design (including how breast lymphoedema was defined). This expert suggested making some comment about the strength of the study design that informs in regards to risk factors, to help recognise whether these are facts or possibilities. Other experts conferred that without describing study designs, it would be very difficult to determine the strengths and weakness of the research that identified risk factors.

The references that supported the risk factors listed were either low (observational studies) or very low (any other evidence) level evidence. None of the risk factors are diagnostic, nor are risk factors themselves diagnostic. Therefore there is a need to be careful how to incorporate risk factors into the definition. Consequently, risk factors for developing breast lymphoedema, were removed from the definition.

5.4.3.3 Round three

5.4.3.3.1 Experts comments

All experts (100%) agreed to this version of the consensus document. The consensus document for defining breast lymphoedema is seen in Appendices 26 and 27, pages 191 and 194.

5.5 Discussion

Currently there are no objective measures used for breast lymphoedema. Although there are treatment modalities that appear to be effective, any research involving these modalities will be limited, if a definition for breast lymphoedema is not developed. There were no requirements that a definition should be a clinical diagnosis or involve laboratory tests.

This exercise aimed to establish consensus among a group of experts in the field of lymphoedema to provide a definition for breast lymphoedema (167). Despite the literature demonstrating the need for lymphoedema to be clearly defined (38,152,154), this has not yet been translated into breast lymphoedema research. As a result, the absence of a generally accepted definition for this condition makes research projects difficult to compare and constrains application of findings to clinical practice.

Where high quality research evidence is unable to answer clinical questions, recommendations from scientific consensus evidence is advocated due to its structured procedures involve (163,168). These methods are increasingly important (163) and are being used to define key aspects of health care (164). Studies using the Delphi technique have been published in the medical, allied health and nursing literature (168). Consensus groups have been criticised as a method that does not provide high level evidence (169), which is understandable in light of the dominant paradigm. Nevertheless, consensus methods are argued to lead to guidelines that are more clinically useful, than guidelines based purely on systematic review of the evidence (163). Consensus techniques are familiar, have previously been and continue to be used in the lymphoedema community. The document “Best Practice for the Management of Lymphoedema” (34) was created by consensus techniques. However which techniques and how this was done is not described in the document.

Although a questionnaire was not circulated to experts at the commencement of the process, the first round was still structured, required open responses from the experts, and allowed them to discuss issues raised, and elaborate on their views, therefore increasing the diversity of data collected (160,162). This allowed the experts

relatively free scope to elaborate on breast lymphoedema. The qualitative analysis of the experts' comments provided basis to construct subsequent rounds (160, 162).

As recommended in the literature experts were informed where their responses sat in relation to other experts in the group and the overall picture (164). This feedback gave the opportunity to revise responses that had been identified as important elements contributing towards consensus (169).

Major themes for defining breast lymphoedema were identified from the literature. This approach has been used by other authors, as it provides a point of reference for the experts, and limits the randomness of an open ended dialogue (170). Being quantitative in design, subsequent rounds were analysed using rating or ranking techniques (160) and central tendencies and levels of dispersion about collected opinion (167). The technique is described as part of data analysis for consensus techniques, as it enables experts to compare their responses in relation to that of the group (162).

It has been described that "by their very nature, definitions are neither true nor false, only more or less useful" (112)(p41). This project has commenced development of a definition of breast lymphoedema. The acceptance and application of this definition is to be seen, but it addresses a need in the area of breast lymphoedema. Justification of how this process was undertaken (112), and how this project was started has been documented. Although consensus techniques are designed to capture collective knowledge they are also vulnerable to collective ignorance (164). In view of these issues, definition of breast lymphoedema developed in this project should be considered as making the best use of available information, and it does not necessarily mean that the correct answer has been found.

In practice, the process of clarification continues as data is analysed (112), and it is envisaged that this will continue as more is learnt about breast lymphoedema. "Clarification is not a once-and-for-all process; it is an ongoing process of interaction between analysing data and clarifying concepts" (112)(p45). "As a result of analysing data, we are often in a better position to say what we mean by a concept, than before we began" (112)(p 45).

The current breast lymphoedema definition is a working definition which was used in this project (112). It provided a focus for this and potential future research (112). This will enable researchers and clinicians to draw conclusions as to whether the research is applicable to their patients, clinical practice and research.

There is no consensus in the literature for defining timelines of post operative breast oedema, or breast lymphoedema as a result of breast cancer treatment. However, some authors have identified post operative and radiotherapy events within timeframes (3,8), and have further defined oedema as early onset (developing within the first two months after surgery and/or radiotherapy), and late onset occurring about 20 months after surgery and/or radiotherapy. Other authors have categorised the oedema response into acute (less than six months after radiotherapy) and late (from six months to several years after radiotherapy)(172,173), or have defined chronic oedema as greater than three months duration (57). It has been recognised by these authors that lymphoedema may occur in the late oedema response (172,173). One of these authors also acknowledges that chronic oedema is synonymous with chronic lymphoedema (57).

Discussion continues on this issue regarding whether a patient has acute (meaning transient or short-term) lymphoedema, compared with chronic lymphoedema (which is persistent – could be stable persistent or fluctuating, but persistent). Therefore accepting the theory that swelling from an event (e.g., surgery or radiotherapy) should be resolved within three months, the definition of persistent "lymphoedema of greater than or equal to three months" (57)(p732) was considered most appropriate by the group.

To ensure breast lymphoedema is the condition being addressed, as opposed to other differential diagnostic conditions, other causes could be ruled out using appropriate diagnostic tools. The list of differential diagnoses and the associated definitions assist in this process.

5.5.1 Strengths and limitations

The Delphi technique allows the generation of consensus opinion to begin to answer clinical questions unanswered by research (163), by drawing on the opinion of a group of experts over a series of rounds interspersed with feedback, to gain the most reliable consensus (163). Strengths of the project design include the clarity of the purpose of the consensus group and the high degree of methodological precision and research rigor including insight into the process of the methodology, sequential data collection and analysis (160, 162,163).

A potential limitation of this project concerns the panel of experts. The limited number of experts, their relationship to the author and the lack of random selection could potentially introduce bias to the project, and limit generalisability. However, the panel members represented the diversity of professions working in the field of lymphoedema. The experts are also recognised for their contributions and achievements in this field, therefore providing credibility to not only the group but the outcomes proposed by the group.

5.6 Conclusion

There is an urgent need for a definition of breast lymphoedema. This will facilitate uniformity in identifying patients with breast lymphoedema that will be both advantageous in clinical and research settings (32). In this part of the study a working definition was established using expert opinion in a three-round Delphi exercise, and based on the location, nature, timing and exclusion of differential diagnoses. This definition has immediate application in research and clinical settings. The success of this definition (172) will require a broader consensus and more widespread uptake among those working with breast lymphoedema (157).

Chapter 6.0
Discussion

The development of the BLYSS questionnaire was undertaken to measure health status in women with breast lymphoedema. Breast lymphoedema is a recognised complication of BCT and rates have been reported at 6-80% (3-8). However a lack of standard diagnostic criteria and a definition for breast lymphoedema make comparing research difficult and hampers evaluation of the effectiveness of treatment and translation to clinical practice. This project has addressed two issues critical to the forward progression of research around breast lymphoedema. In particular, a working definition for breast lymphoedema was constructed using a consensus technique, and a patient self-reported health status questionnaire was developed. The approach to questionnaire development was designed to not only maximise the chances of developing a useful questionnaire that struck a balance between patients' needs such as containing items considered important to patients with breast lymphoedema, clinicians' needs that it be simple and convenient to administer and scientific needs for validity and reliability to be determined.

6.1 Breast cancer and breast lymphoedema

Breast cancer is the most common cancer affecting Australian women (9), with one in nine Australian women diagnosed with breast cancer before the age of 85 years (174). As breast cancer treatments become more effective and patients' survival longer, the importance of morbidity is increased (30). The categorisation of possible side effects such as breast lymphoedema according to scoring systems like the BLYSS questionnaire will facilitate monitoring the quality of care (30).

For women with early diagnosed breast cancer, the current paradigm of treatment is BCT. This treatment option not only gives women survival outcomes equivalent to mastectomy (14,16,17), but salvages the breast. Lymphoedema, as a result breast cancer treatment, is recognised as one of the most significant survivorship issues and is reported to have significant consequences including physical, functional, quality of life and financial (175). Lymphoedema has been referred to as the dreaded sequela of

breast cancer treament (35) and some consider it to be worse than the cancer itself (35).

In patients treated with breast conservation, breast lymphoedema is reported to be a more frequently seen complication than arm lymphoedema (4,7,39,40). As approximately 15,400 Australian women are expected to be diagnosed with breast cancer by 2015 (10), an increase in breast cancer survivors and those living with the burden of breast lymphoedema, is probable.

Advances in surgical and adjuvant treatments for breast cancer, such as sentinel node biopsy, targeted intraoperative radiotherapy and brachytherapy (176), have the potential to reduce the likelihood of developing lymphoedema. Regardless, secondary lymphoedema can still occur after less invasive surgical procedures, such as wide local excision and/or sentinel node biopsy (176). As a result effective outcome measures are required to monitor the frequency and severity of breast lymphoedematous changes.

Targeted radiotherapy offers a single high dose of radiation to the tumour bed performed in the operating theatre (176). However, as this technique is relatively new, longer monitoring is required before the effects of this treatment on the risks and severity of breast lymphoedema can be determined (176). Valid and reliable measuring procedures, definitions and reporting criteria for breast lymphoedema are critical for monitoring these changes and ultimately determining whether the risk and severity of breast lymphoedema are reduced.

Despite recognition that breast lymphoedema is occurring more frequently (39), it is often an overlooked side effect of breast cancer treatment (41) and the resulting problems are minimised (43). Factors related to the lack of knowledge regarding breast lymphoedema include the historical focus on upper limb lymphoedema and in regards to this, predominantly on acute treatment and lack of a definition (144, 177). Not only does the lack of a definition and reporting criteria make interpretation of lymphoedema of the breast difficult, it may misinform clinicians, researchers and patients regarding the actual incidence and risk factors for breast lymphoedema.

It has been stated that the cause of breast lymphoedema is less well known than its signs and symptoms (8). This statement however, is open to question. Despite defining breast oedema and breast lymphoedema, like many other authors (4,5,43,50), Ronka et al (8) alternates between the terms breast oedema and breast lymphoedema.

One of these authors does recognise that the incidence of breast lymphoedema does vary depending on how it is defined (4). Some researchers have differentially defined breast oedema and breast lymphoedema (8), whilst others have not (4,47,49,50). As these are two different conditions, it is difficult to determine what condition is being assessed, and although lymphoedema occasionally becomes apparent immediately after surgery, it most often appears after a latent period (35,175,176).

In reference to signs and symptoms, it is not explained in the literature, how they have been attributed to breast lymphoedema. It is unclear whether they are anecdotal findings, based on clinicians' and/or patients' reports or if they have been extrapolated from research in the upper limb and applied to breast lymphoedema (7,31,42,56). Methodological evaluation of modern oncoplastic and radiotherapeutic techniques require standardised instruments to measure outcomes (177). As the ability to measure breast lymphoedema is difficult, most studies have used the dichotomous choices of present or not (15). As a result, thorough documentation of the severity of breast oedema is not possible from these data (15). For studies in other conditions, authors have chosen response categories other than dichotomous choices, as it gives further knowledge into the severity of patients' conditions (110). It has been stated that diffuse breast lymphoedema is the most obvious symptom up to one year after radiotherapy, with close to zero incidence in the second year of post treatment review (178). These authors also reported that evidence based results regarding "other possible risk factors for lymphoedema of the breast should be able to be obtained from the meta-analysis of large randomised studies (such as the NSABP-B-06, Milano III, Ontario, Uppsalla-Orebro, and Scottish trials) evaluating the outcome of breast conserving surgery with and without radiotherapy" (174)(p240). Nevertheless, a search of Ovid Medline and Google Scholar failed to find any published results from those studies (the NSABP-B-06, Milano III, Ontario,

Uppsalla-Orebro, and Scottish trials) in regards to risk factors for breast lymphoedema and BCT, inclusive or exclusive of radiotherapy.

There are still few simple objective methods for evaluating post treatment symptoms, especially in the breast (8), which may be due to the complexities in valid and reliable breast measurements (144). Technologies such as MRI, the Breast Symmetry Index and Bioimpedance spectroscopy may have a role in the diagnosis of breast lymphoedema, however, access to these technologies may not be readily available and/or expensive. Other modalities such as cosmetic and functional scales and the Breast Retraction Assessment (73) are not routinely used, perhaps as the validity and reliability of these scales has not been determined, or because of a lack of awareness, or availability. Water displacement and brassiere size have also been considered as objective measurements but they too have limitations due to the logistics of water displacement and the imprecision of brassiere size for use as an objective outcome measure of breast size.

Due to limitations in assessment of breast lymphoedema, other assessment options needed to be considered. The literature identifies that there is no disease specific questionnaire available to measure health status in patients (37) with breast lymphoedema. This could also be contributing to the lack of research in patients with breast lymphoedema. Changes in signs and symptoms over time may suggest breast lymphoedematous changes (144). Due to the unique symptoms and problems of patients with breast lymphoedema and the reported increased occurrence (39), it was important to create a health status questionnaire designed especially for this group (37). The primary aim of this project was to create a questionnaire to measure the health status in women with breast lymphoedema.

At the commencement of this project there was no widely accepted definition of breast lymphoedema. During discussion at the 7th ALA Conference held in Fremantle Western Australia in 2008, this was identified as a potential limitation of the study. Therefore a complementary study was introduced to the project with the aim of developing a definition of breast lymphoedema. The development of a definition of breast lymphoedema gave a clear understanding of what constituted a definition of

this condition applied in the study. This component of the project is described and discussed in Chapter 5, Defining Breast Lymphoedema, page 77.

6.2 BLYSS questionnaire development and validation

Measurements of health status provide important information about the humanistic and economic benefits of clinical medicine (179), however data collected using questionnaires may not be considered as robust as more objective outcome measures (179). Regardless, questionnaires are important resources for the evaluation of patient care and the effectiveness of patient treatment programmes (95).

The BLYSS questionnaire is a comprehensive, multidimensional measure of health status that provides an understanding of the impact of breast lymphoedema. A questionnaire design was chosen as an assessment tool as the impact of breast lymphoedema is not just about measuring the size and shape of the lymphoedematous breast, but includes other factors about how a woman feels and how this condition affects activities of daily living, including functional aspects associated with the wearing of a brassiere. The BLYSS questionnaire incorporated those domains (appearance and experience, memory, assessments and weather) identified as important by patients with breast lymphoedema as a result of breast cancer treatment (180).

Due to the unique symptoms and problems of patients with breast lymphoedema and the reported increased occurrence (39), it was important to create a health status questionnaire designed especially for this group (37). Sophisticated and complex approaches to questionnaire development can result in valid and reliable questionnaires that are suitable as outcome measures for clinical trials (94). The methods used to develop the BLYSS questionnaire addressed those considerations identified in the literature as important in the development of patient self reported questionnaire. An example of this is the use of an item elicitation questionnaire that provided the structure to further explore the dimensionality of symptoms experienced and identified by patients (140). Although this type of questionnaire development required more substantial resources than improvised measure development (96), the methods used ensured that the BLYSS questionnaire addressed issues that patients

considered important, and as well as those issues important to clinicians, such as reliability, validity, clinical credibility and feasibility.

Part A of the study identified that patients had previously been exposed to and completed questionnaires/scales. During pilot testing two patients reported completing other questionnaires. These patients described how the word options in the BLYSS questionnaire made it easier to make a choice than numbers such as in the Pain Scale. All of the patients in the pilot testing phase reported that the content of the instrument was relevant and that the questionnaire was understandable, facilitated by the definitions within the questionnaire. This acceptability to patients (121) may be advantageous in regards to completing the BLYSS questionnaire, making the BLYSS questionnaire ideal for use in clinical practice (120).

As our interviews with women with breast lymphoedema began with open-ended questions about how breast lymphoedema affected their lives we do not believe our use of an item elicitation questionnaire introduced bias into their responses. When more detail was required about the identified item, the item elicitation questionnaire provided a resource for the investigator to encourage further responses and discussion by referring to the concepts and items identified from the literature and/or from clinical experience. The item elicitation questionnaire permitted probing into all of the characteristics and properties associated with that item.
It is also important to note that women did identify items that related to image and psycho-social issues, however these were not considered important enough by sufficient numbers of the women to warrant inclusion in the final questionnaire.

The justification for retaining ≥60% and ≥50% of items also may have resulted in a narrower focus. Yet the aim was to have a suitable number of items for the questionnaire (100), sufficient for content validity. The priori ensured those items that were infrequently reported, considered not important and/or irrelevant to the majority of participants were not included. This approach also limited respondent burden or fatigue by reducing an excessive number of items which may not be important to patients.

A different methodological approach taken during the initial stages with women may

have generated different results. A different approach could have involved using Rasch analysis. However this approach is not without its controversies including the need for a high degree of software insight, a large number of observations and an infinite data set with unidimensionality (117-119). If there are lots of items and refinement of items during Rasch analysis, questionnaires maybe very reliable but they are also much less valid and this analysis has strong assumptions not easily matched by the observations (119).

6.2.1 Reliability of the BLYSS questionnaire

6.2.1.1 Test- retest method

The test-retest method (61,121), which evaluates whether a questionnaire is capable of measuring a variable with consistency (61,121,128), involves comparing scores of the same patient on two separate occasions (121,129). The assumption is that there is no change in scores, if there is no substantial change in health status of the patient being measured between tests (129). However the time interval between tests needs to be considered carefully (61). There is no exact agreement on a suitable time interval (121). Whichever interval is used it needs to be far enough apart to avoid fatigue, learning or memory effects, but close enough to avoid genuine changes in the underlying dimension of health (61,121). Consequently the most appropriate interval will depend on the nature of the questionnaire and the constructs that it measures, as well as the population for which the questionnaire is designed. There is considerable variation described in the literature. Some authors have used a two hour test-retest interval (181) and some a median time interval of three weeks (37). It was considered that breast lymphoedema was not so labile that the breast lymphoedema would be likely to change significantly in 24 hours. Also the logistics of longer follow up were taken into account. Considering these principles, a 24 hour interval was used to determine reliability of the BLYSS questionnaire.

6.2.2 Validity

The BLYSS questionnaire signifies a validated measure of the overall effect of breast lymphoedema on a breast cancer patient's life. As aspects of validity are key attributes of a well designed questionnaire, aspects of validity were considered an important inclusion in the BLYSS questionnaire development (61,112). The BLYSS

questionnaire has addressed face, content, construct, discriminant, convergent and criterion validity issues.

6.2.2.1 Face and content validity

Together face and content validity address whether the items clearly assess the intended subject matter and whether the range is adequately covered (121). However as face validity is the weakest form of measurement validity (61) and neither face nor content validity can be readily measured statistically, the questionnaire itself needs to be reviewed (121).

The design approach used to create the BLYSS questionnaire; the clarity of how the questionnaire was developed and how the rigor of this process maximised the chances of constructing a useful questionnaire which then established face and content validity, in itself allows an informed opinion of the merit of these approaches (96). These approaches ensured the BLYSS questionnaire of its scientific quality (96,131).

The design, development and validation of the BLYSS questionnaire has married three concepts integral to development of a health status measure; patient participation, scientific value and clinician acceptability. It is generally agreed that patient opinion needs to be taken into account when developing a health status measure (182). Although knowledgeable about an illness, experts cannot substitute completely for the direct experience that patients have of health problems (121). Several studies have shown the disparity between patients', doctors' and relatives' ratings of the patients' quality of life (132). Using measures that are not patient centered may not cover domains important to patients and therefore may not be valid measures (128,132,133). If such measures do not capture the lived experience of the disease they are unlikely to be responsive to change after treatment (135). This has implications for interpreting the validity of the measure, determining the effectiveness of interventions and consequently the relative quality of service and the allocation of resources (132).

Face validity of the BLYSS questionnaire was established by generating an item elicitation questionnaire. The item elicitation questionnaire was based on a review of

the literature, interviews with clinicians and structured interviews with affected women.

Content validity was concluded after a panel of expert clinicians who diagnose and treat breast lymphoedema reviewed and determined that the items within the instrument satisfied the content domain. Items in the BLYSS questionnaire were established by generating an item elicitation questionnaire based on a review of the literature, interviews with clinicians and structured interviews with affected women. Consultation with clinicians and patients has also been the approach during the design phase of the content of other questionnaires, to ensure capitalising content validity, including all appropriate concerns and items fully applicable to these specific groups of patients (108,111).

6.2.2.2 Construct validity

Construct validity is whether a questionnaire is able to measure an abstract concept (61,112). It has been described as the most rigorous approach to establishing validity (113) but it can be difficult to determine whether a questionnaire is actually measuring the intended concept. Again the questionnaire itself needs to be assessed. The BLYSS questionnaire addresses four separate aspects of breast lymphoedema-appearance and experience, memory, investigations and the weather. The scope and assortment of items contained in the BLYSS questionnaire contributes to the credence that the BLYSS questionnaire represents a meaningful approximation to breast lymphoedema.

Discriminant and convergent validity were considered in the validation of the BLYSS questionnaire. These forms of validity were examined by considering the associations between the BLYSS questionnaire and two other forms of assessment, the modified Harris score and the GHQ-12.

6.2.2.2a Discriminant validity

The cosmetic result of BCT is an important outcome and one that is conceptually different from health status. Therefore cosmetic outcome was selected as the variable to examine discriminant validity. In view of its subjective nature, grading the cosmetic outcome of BCT is difficult. One method that is considered useful (80) and

is widely used in breast cancer research as measure of breast aesthetics (150), is the four-point Harris score. This has previously been used in validity studies of the breast symmetry index (81) and the Breast Cancer Conservative Treatment Cosmetic software (82, 150).

A modified version of the Harris score was used in this project. Words in the original Harris score (as shown in Appendix 22, page 186) were added and changed to be the same as the BLYSS questionnaire.

Despite reports of disparity in regards to comparison of observer ratings for the cosmetic outcomes after breast conserving therapy (74,76,80), the inter-rater agreement between assessors using the modified Harris score in this study showed high agreement. This may be due to the assessors' extensive experience and skills, as it is documented that previous experience in BCT treatment should be a prerequisite for evaluation of aesthetic result (79).

Correlations between the BLYSS questionnaire scores and the clinicians' modified Harris scores were poor. This provided evidence of discriminant validity as the BLYSS questionnaire and the modified Harris score are measures of different traits (61).

6.2.2.2b Convergent validity

Although the serious emotional and psychological effects of breast lymphoedema are addressed in the literature (35,55), these consequences have not been explored by using previously established psychological tools. The GHQ-12 is a widely used measure of mental health. Although it is typically used as a one-dimensional tool it has been shown to be multidimensional addressing three factors; anxiety and depression, social dysfunction and loss of confidence (183). These factors reflect feelings and experiences expressed by women with breast cancer. Although the underlying phenomenon measured by the GHQ-12 is not identical to that measured by the BLYSS questionnaire, it does address a number of similar constructs. Furthermore, the GHQ-12 has established validity, reliability and good internal consistency (184). Not only is this the shortest of the three types of GHQ (taking four minutes to complete) and is recommended for research use (184), the GHQ-12 has

been used in other studies of patients with breast cancer (1,68). Consequently it was selected as an appropriate comparator to examine convergent validity.

The significant correlation between the BLYSS questionnaire and GHQ-12 scores (see Chapter Four, Results, page 55) provide evidence of convergent validity of the BLYSS questionnaire and indicate that the BLYSS questionnaire is measuring some, but not all of the aspects of health indicated by the GHQ-12. If the association was too strong it would suggest that both questionnaires were measuring almost the same entity and therefore there would be no need for the BLYSS questionnaire, as the GHQ-12 could be used. These findings considered in the light of the poor correlations between the Harris score and the BLYSS questionnaire (discriminant validity) also help to define "health status" as measured by the BLYSS (61).

6.2.2.2c Criterion validity

Criterion validity reflects whether a questionnaire is valid insofar as its results correspond to those of a criterion standard, or another measure generally accepted as more accurate or an established "gold standard" (61,112,121). This is difficult to establish for the BLYSS questionnaire as there is no perfect criterion available to be used for comparison.

6.3 Strengths and weaknesses

To date the BLYSS questionnaire is the only questionnaire to specifically measure the health status of women with breast lymphoedema. The methodology employed in this project underpinned the development of a valid questionnaire. This project has provided the template for a definition for breast lymphoedema that can be used for future deliberation. This format of developing a definition of breast lymphoedema and then a condition-specific outcome measure increases confidence in the validity of the BLYSS questionnaire to be considered as the primary measure of outcome in subsequent studies (96).

Eighty-nine women with breast lymphoedema participated in this study. While these numbers may be considered small for studies of questionnaire design, (61,96,100,112) they are typical for studies of breast lymphoedema (43). Reasons

such as the lack of a definition for breast lymphoedema, unclear incidence and prevalence of the condition and/or a lack of standardised diagnostic criteria may be account for small sample sizes associated with breast lymphoedema studies. The development and validation of established questionnaires were reviewed to identify any further strengths and weaknesses of this study (104-106,111). No further information was able to be retrieved using this process.

Strengths of the project design included the clarity of the purpose of the project, creation of a definition of breast lymphoedema to be applied in the study and the high degree of methodological precision and research rigor throughout all aspects of the project. The BLYSS questionnaire considers multiple dimensions of breast lymphoedema, including physical, emotional, investigational and weather, whilst basing item content on the literature, clinicians and patients' perspective. Inclusion of different aspects of breast lymphoedema has been identified as not only furthering knowledge of the physical aspects of lymphoedema, but also cognitive and affective components related to this disease (144).

A potential limitation of this project is the definition of breast lymphoedema. As the definition was created whilst the project was underway, it was only applied to Part B of the project. However retrospective examination of the characteristics of the participants in Part A of the studies showed that 57 of the 59 patients (97%) would have met this criteria of breast lymphoedema. Timing and differential diagnosis were the only two items in the definition where two of the patients did not meet the selection criteria.

A limitation of the definition of breast lymphoedema may be the panel of experts. The limited number of experts, their relationship to the author and the lack of random selection could potentially introduce bias to the project, and limit generalisability. Nevertheless the panel of experts that participated in the consensus group to define breast lymphoedema work in the field of lymphoedema, are recognised for their contributions and achievements in this field, and therefore provide credibility to not only the group, but the outcomes proposed by the group. However the ultimate success of this definition (172) does require a broader consensus and more widespread uptake among those working with breast lymphoedema (157).

Important characteristics of useful questionnaires are that they are psychometrically robust, whilst also being brief enough to be of practical use in clinical settings (98, 185). Although reported in the literature that questionnaires are not widely used in lymphoedema related research (33), this may be because there are no questionnaires specifically developed for breast lymphoedema, let alone psychometrically evaluated. Therefore one aim of the project was to establish the reliability and validity of the BLYSS questionnaire. The BLYSS questionnaire was also designed for ease of administration and respondent and administrative burden is minimal. These issues are germane to evaluating comparative treatments (97). The value of an accurate health status assessment such as the BLYSS questionnaire is that gives an immediate insight into an individual patient's current status, making it a useful outcome tool (97). The capacity of the BLYSS to indicate a patient's current status has been evaluated comparing the results of BLYSS with those of the GHQ-12 and a modified Harris scale. The responsiveness of the BLYSS has not yet been tested, as that was beyond the scope of this current project. Indeed the demonstration of responsiveness, requires the availability of an effective treatment delivering clinically discernible improvements. Nevertheless, the demonstrable reliability and validity of the BLYSS questionnaire are encouraging and are a prerequisite for embarking on future studies of questionnaire responsiveness.

6.4 Future development of the BLYSS questionnaire

6.4.1 Determining the responsiveness of the BLYSS questionnaire.

This could be investigated by introducing the BLYSS questionnaire as a pre-post-manual lymphatic drainage treatment assessment protocol for patients to run parallel with other questionnaires such as the Short Form 36 questionnaire (186) and a global improvement scale. It is anticipated that patients receiving treatment would respond favourably enabling responsiveness to be assessed.

6.4.2 Validity assessment of the breast lymphoedema definition

The definition created for breast lymphoedema could also provide a basis for future development. The definition created could be delivered to a wider audience, either nationally and/or or internationally. This could follow the approach used in the thesis or a different approach, such as what is suggested in the literature. The validity of the

created definition of breast lymphoedema could be assessed by comparing against clinicians' classifications of breast lymphoedema according to their current practices.

Chapter 7.0
Conclusion

Although the incidence and prevalence of breast cancer have increased, survival rates have increased. Such interventions as screening and awareness programmes, new and further refined treatments have contributed to this increased survival. Whereas mastectomy was the traditionally prescribed treatment option, BCT now gives equitable survival chances, with women still retaining their breast. A consequence of more women surviving breast cancer, is the development of breast lymphoedema. This condition is a common, important and distressing phenomenon, with physical, psychosocial and functional consequences.

However information regarding breast lymphoedema is difficult to collate, due to a lack of standard measuring procedures, reporting criteria, and a definition for breast lymphoedema. This is a significant impediment when evaluating the effectiveness of treatments for breast lymphoedema.

These limitations also impact on the diagnosis of breast lymphoedema. Breast lymphoedema is difficult to diagnose as its presentation can mimic many other conditions; two of the major concern being breast cancer recurrence (in a primary, secondary or inflammatory context), and infection. At the present time a diagnosis of breast lymphoedema, in a patient with features of the condition, is often made by excluding any competing alternative diagnoses.

In recognition of the lack of a definition for breast lymphoedema, a consensus group was established to create a definition. Although applicable to this study, this definition could be applied in clinical practice. The definition now provides a template for further discussion and further works, and supports the need identified in the literature.

The emergence of BCT, with reported and anecdotal increased rates of breast lymphoedema, encouraged this study. Using a standardised approach and utilising an extensive literature review and key informants (both clinical specialists and patients

with breast lymphoedema), a prototype BLYSS questionnaire was developed. Through a re-iterative process, the validity, reliability and feasibility of the BLYSS questionnaire were evaluated.

The end result was a sophisticated, valid, reliable and feasible patient reported outcome measure for the evaluation of patients with breast lymphoedema. The BLYSS questionnaire needs to be disseminated will need continued use and testing for ongoing validation. However the demonstratable reliability and validity of the BLYSS questionnaire are not only encouraging, but are necessary requirements before embarking on the further development of the BLYSS questionnaire, and evaluation of its responsiveness, in an appropriate interventional setting.

The results of this project add to the body of information on breast lymphoedema. The BLYSS questionnaire and the definition will be useful for any clinician treating breast lymphoedema. Both will also be useful as a condition specific outcome measure in research projects, and in clinical practice applications.

References

1. Goldberg D, Williams P. A users guide to the General Health Questionnaire (GHQ). London: GL Assessment Limited; 2006.

2. Harris JR, Levene MB, Svensson G, Hellman S. Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. Int J Radiat Oncol Biol Phys. 1979 Feb;5(2):257-61.

3. Clarke D, Martinez A, Cox RS, Goffinet DR. Breast edema following staging axillary node dissection in patients with breast carcinoma treated by radical radiotherapy. Cancer. 1982 Jun 1;49(11):2295-9.

4. Meek AG. Breast radiotherapy and lymphedema. Cancer. 1998 Dec 15;83(12)Supp l:2788-97.

5. Mondry TE, Johnstone PAS. Manual lymphatic drainage for lymphedema limited to the breast. J Surg Oncol. 2002 01;81(2):101-4.

6. Zippel D, Siegelmann-Danieli N, Ayalon S, Kaufman B, Pfeffer R, Zvi Papa M. Delayed breast cellulitis following breast conserving operation. Eur J Surg Oncol. 2003 May;29(4):327-30.

7. Goffman TE, Laronga C, Wilson L Elkins D. Lymphedema of the arm and breast in irradiated breast cancer patients: risks in an era of dramatically changing axillary surgery. Breast J. 2004 Sep-Oct;10(5):405-11.

8. Ronka RH, Pamilo MS, von Smitten KAJ, Leidenius MHK. Breast lymphedema after breast conserving treatment. Acta Oncol. 2004;43(6):551-7.

9. Devoogdt N, Christiaens M-R, Geraerts I, Truijen S, Smeets A, Leunen K, Neven P, Van Kampen M. Effect of manual lymph drainage in addition to guidelines and exercise therapy on arm lymphoedema related to breast cancer: randomised controlled trial. BMJ. 2011;343:d5326.

10. NBOCC. Breast cancer statistics [homepage on the Internet]. c2011 [updated 2 011 Jan 18; cited 2011 20 Jan]. Available from: www.nbocc.org.au/breast-cancer/breast-cancer statistics.

11. Yang C-Y, Tsai J-C, Huang Y-C, Lin C-C. Effects of a home-based walking program on perceived symptom and mood status in postoperative breast cancer women receiving adjuvant chemotherapy. J Adv Nurs. 2011;67(1):158-68.

12. Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, Nur U, Tracey E, Coory M, Hatcher J, McGahan CE, Turner D, Marrett L, Gjerstorff ML, Johannesen TB, Adolfsso J, Lambe M, Lawrence G, Meechan D, Morris EJ, Middleton R, Steward J, Richards MA. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the international cancer benchmarking partnership): An analysis of population-based cancer registry data. Lancet. 2011;377(9760):127-38.

13. Craft PS, Buckingham JM, Dahlstrom JE, Beckmann KR, Zhang Y, Stuart-Harris R, Jacob G, Roder D, Tait N. Variation in the management of early breast cancer in rural and metropolitan centres: Implications for the organisation of rural cancer services. Breast. 2010 Oct;19(5):396-401.

14. Fougo JL, Senra FS, Araújo C, Dias T, Afonso M, Leal C, Dinis-Ribeiro M. Validating the MSKCC nomogram and a clinical decision rule in the prediction of non-sentinel node metastases in a Portuguese population of breast cancer patients. Breast. 2011 Apr;20(2):134-40.

15. Back MF, Guerrieri M, Wratten C, Steigler A. Impact of radiation therapy on acute toxicity in breast conservation therapy for early breast cancer. Clin Oncol. 2004;16: 12-6.

16. Delaney G. Recent advances in the use of radiotherapy to treat early breast cancer. Curr Opin Obstet Gynecol. 2005;17(1):27-33.

17. Collette S, Collette L, Budiharto T, Horiot JC, Poortmans PM, Struikmans H, Van den Bogaert W, Fourquet A, Jager JJ, Hoogenraad W, Mueller RP, Kurtz J, Morgan DAL, Dubois JB, Salamon E, Mirimanoff R, Bolla M, Van der Hulst M, Warlam-Rodenhuis CC, Bartelink H. Predictors of the risk of fibrosis at 10 years after breast conserving therapy for early breast cancer - A study based on the EORTC trial 22881-10882 'boost versus no boost'. Eur J Cancer Clin Oncol. 2008;44(17):2587-99.

18. Sneeuw KCA, Aaronson NK, Yarnold JR, Broderick M, Regan J, Ross G, Goddard A. Cosmetic and functional outcomes of breast conserving treatment for early stage breast cancer. 2. Relationship with psychosocial functioning. Radiother Oncol. 1992;25(3):160-6.

19. O'Sullivan B, Levin W. Late radiation-related fibrosis: Pathogenesis, manifestations, and current management. Semin Radiat Oncol. 2003;13(3):274-89.

20. Johansson S, Svensson H, Denekamp J. Dose response and latency for radiation-induced fibrosis, edema, and neuropathy in breast cancer patients. Int J Radiat Oncol Biol Phys. 2002 01; 52(5):1207-19.

21. Bourgeois JF, Gourgou S, Kramar A, Lagarde JM, Gall Y, Guillot B. Radiation-induced skin fibrosis after treatment of breast cancer: profilometric analysis. Skin Res Techol. 2003;9(1):39-42.

22. Davis AM, Dische S, Gerber L, Saunders M, Leung SF, O'Sullivan B. Measuring postirradiation subcutaneous soft-tissue fibrosis: State-of-the-art and future directions. Semin Radiat Oncol. 2003;13(3):203-13.

23. Fehlauer F, Tribius S, Holler U, Rades D, Kuhlmey A, Bajrovic A, Alberti W. Long-term radiation sequelae after breast-conserving therapy in women with early-stage breast cancer: an observational study using the LENT-SOMA scoring system. Int J Radiat Oncol Biol Phys. 2003 Mar 1;55(3):651-8.

24. Winchester DP, Cox JD. Standards for breast conservation treatment. **CA** Cancer J Clin 1992;42:134-62.

25. Lopez E, Guerrero R, Nunez MI, del Moral R, Villalobos M, Martinez-Galan J, Valenzuela MT, Munoz-Gamez JA, Oliver FJ, Martin-Oliva D, Ruiz de Almodovar JM. Early and late skin reactions to radiotherapy for breast cancer and their correlation with radiation-induced DNA damage in lymphocytes. Breast Cancer Res Treat. 2005;7(5):R690-8.

26. Kurtz J. The curative role of radiotherapy in the treatment of operable breast cancer. Eur J Cancer. 2002 Oct;38(15):1961-74.

27. Herskind C, Johansen J, Bentzen SM, Overgaard M, Overgaard J, Bamberg M Rodemann HP. Fibroblast differentiation in subcutaneous fibrosis after postmastectomy radiotherapy. Acta Oncol. 2000;39(3):383-8.

28. Bentzen SM, Dische, S. Morbidity related to axillary irradiation in the treatment of breast cancer. Acta Oncol. 2000;39(3):337-47.

29. Perbeck L, Celebioglu F, Svensson L, Danielson R. Lymph circulation in the breast after radiotherapy and breast conservation. Lymphology. 2006 Mar;39(1):33-40.

30. Lopez E, Nunez MI, Guerrero MR, Del Moral R, Luna JDD, Rodriguez MDM, Valenzuela MT, Villalobos M, Ruiz de Almodovar JM. Breast cancer acute radiotherapy morbidity evaluated by different scoring systems. Breast Cancer Res Treat. 2002;73(2):127-34.

31. Kirshbaum M. Breast lymphoedema. In: Twycross R, Jones K, Todd J, editors. Lymphoedema. London. Radcliffe Medical Press; 2000.

32. Ward LC. Early detection of lymphoedema: Is BIS ready for prime time as the gold standard. Proceedings of the 22nd International Congress of Lymphology Conference; 2009 Sept 21-25; Sydney, Australia. Sydney; 2009; p.90.

33. Cheville AL, McGarvey CL, Petrek JA, Russo SA, Thiadens SR, Taylor ME. The grading of lymphedema in oncology clinical trials. Semin Radiat Oncol. 2003 Jul;13(3):214-25.

34. Lymphoedema Framework. Best practice for the Management of Lymphoedema. International Consensus. London: MEP Ltd; 2006. Chapter 4, Treatment decisions; p.15-23.

35. Fu MR, Ridner SH, Armer J. Post-breast cancer. Lymphedema: part 1. Am J Nurs. 2009 Jul;109(7):48-54; quiz 5.

36. Kristjanson L. Quality of Life in Lymphoedema. Proceedings of the 5th Australasian Lymphology Association Conference; 2004 Mar 26-28; Brisbane, Australia. Brisbane; 2004; p.51-3.

37. Klernäs P, Kristjanson LJ, Johansson K. Assessment of quality of life in lymphedema patients: validity and reliability of the Swedish version of the Lymphedema Quality of Life Inventory (LQOLI). Lymphology. 2010;43(3):135.

38. Norman SA, Miller LT, Erikson HB, Norman MF, McCorkle R. Development and validation of a telephone questionnaire to characterize lymphedema in women treated for breast cancer. Phys Ther. 2001;81(6):1192-205.

39. Olszewski WL. Lymph circulation in the breast after radiotherapy and breast conservation. Lymphology. 2006 Dec;39(4):201.

40. Parbhoo S. Lymphoedema in young patients with breast cancer. Breast. 2006 Dec;15Supp 2:S61-S4.

41. Lawenda BD, Mondry TE, Johnstone PAS. Lymphedema: A primer on the identification and management of a chronic condition in oncologic treatment. CA Cancer J Clin. 2009 Jan-Feb;59(1):8-24.

42. Jeffs E. Treating breast cancer-related lymphoedema at the London Haven: Clinical audit results. Eur J Oncol Nurs. 2006 Feb;10(1):71-9.

43. Jahr S, Schoppe B, Reisshauer A. Effect of treatment with low-intensity and extremely low-frequency electrostatic fields (deep oscillation) on breast tissue and pain in patients with secondary breast lymphoedema. J Rehabil Med. 2008;40(8):645-50.

44. Habibollahi F, Hayles HMO, Mayles WPM, Winter PJ, Tong D, Fentiman IS, Chaudary MA, Hayward JL. Assessment of skin dose and its relation to cosmesis in the conservative treatment of early breast cancer. Int J Radiat Oncol Biol Phys. 1988;14(2):291-6.

45. Senofsky GM, Moffat FL, Davis K, Masri MM, Clark KC, Robinson DS, Sabates B, Ketcham AS. Total axillary lymphadenectomy in the management of breast cancer. Arch Surg. 1991;126(11):1336-42.

46. Mendelson EB. Evaluation of the postoperative breast. Radiol Clin North Am. 1992;30(1):107-38.

47. Loprinzi CL, Okuno SH, Pisansky TM, Sterioff S, Gaffey TA, Morton R. Postsurgical changes of the breast that mimic inflammatory breast carcinoma. Mayo Clin Proc. 1996;71(6):552-5.

48. Carl UM, Hartmann, KA. Hyperbaric oxygen treatment for symptomatic breast edema after radiation therapy. Undersea Hyperb Med. 1998;25(4):233-4.

49. Mertz KR et al. Breast cellulitis following breast conservation therapy: A novel complication of medical progress. Clin Infect Dis. 1998;26(2):481-6.

50. Majeski J, Austin RM, Fitzgerald RH, Mondry TE, Johnstone PAS. Cutaneous angiosarcoma in an irradiated breast after breast conservation therapy for cancer: Association with chronic breast lymphedema. J Surg Oncol. 2000;74(3):208-13.

51. Martlew B. Seroma and other factors influencing the development of breast edema following breast cancer treatment. Proceedings of the British Lymphology Society conference; 2000 Oct 9-10; Birmingham, UK.

52. Wratten C, Kilmurray J, Wright S, O'Brien PC, Back M, Hamilton CS, Denham JW. Pilot study of high-frequency ultrasound to assess cutaneous oedema in the conservatively managed breast. Int J Cancer. 2000;90(5):295-301.

53. Wratten C, Kilmurray J, Wright S, O'Brien P, Back M, Hamilton C, Denham J. A study of high frequency ultrasound to assess cutaneous oedema in conservatively managed breast. Front Radiat Ther Oncol. 2002;37:121-7.

54. Williams A. Breast and trunk oedema after treatment for breast cancer. J Lymphoedema. 2006;1(1):32-9.

55. Linnitt N, Young H. The complexities of managing breast oedema. Bri J Community Nurs. 2007 Nov;12(11):513-7.

56. Stevenson O, Bedlow A, Harries S, Carr R Charles-Holmes R. Delayed breast cellulitis: a bacterial infection or a skin response to lymphoedema? Br J Dermatol. 2005;153Supp 1:48-9.

57. Moffatt CJ, Franks PJ, Doherty DC, Williams AF, Badger C, Jeffs E, Bosanquet N,Mortimer PS. Lymphoedema: An underestimated health problem. QJM. 2003 01;96(10):731-8.

58. Pezner RD, Patterson MP, Hill LR. Breast edema in patients treated conservatively for stage I and II breast cancer. Int J Radiat Oncol Biol Phys. 1985;11(10):1765-8.

59. Wratten CR, O'Brien PC, Hamilton CS, Bill D, Kilmurray J Denham JW. Breast edema in patients undergoing breast-conserving treatment for breast cancer: Assessment via high frequency ultrasound. Breast J. 2007 May;13(3):266-73.

60. Degnim AC, Miller J, Hoskin TL, Boughey JC, Loprinzi M, Thomsen K, Maloney S, Baddour LM, Cheville AL. A prospective study of breast lymphoedema: frequency, symptoms, and quality of life. Breast Cancer Res Treat. 2012;134:915-22.

61. Portney LG, Watkins MP. Foundations of clinical research: applications to practice. Stamford: Appleton and Lange; 1993.

62. Shuttleworth M. Observational study. [homepage on the Internet]. c2012 [cited 2009 16 Mar]. Available from: http://www.experiment-resources.com/observational-study.

63. Constable R et al. Ethnography, Observational Research, and Narrative Inquiry. Writing@CSU. [homepage on the Internet]. c2005 [cited 2011 Mar 16]. Available from: http://www.writing.colostate.edu/guides/research/observe/index.cfm.

64. King R, Duncan L, Shupp DL, Googe PB. Postsurgical dermal lymphedema clinically mimicking inflammatory breast carcinoma. Arch Dermatol. 2001;137(7):969-70.

65. Kwak JY, Kim EK, Chung, SY, You JK, Oh KK, Lee YH, Kwon TH, Jung HK. Unilateral breast edema: Spectrum of etiologies and imaging appearances. Yonsei Med J. 2005 28;46(1):1-7.

66. Mortimer P. Acute inflammatory episodes. In: Twycross R, Jones K, Todd J, editors. Lymphoedema. London. Radcliffe Medical Press; 2000.

67. Falagas ME, Vergidis PI. Narrative review: diseases that masquerade as infectious cellulitis. Ann Intern Med. 2005 Jan 4;142(1):47-55.

68. Ibbotson T, Maguire P, Selby P, Priestman T, Wallace L. Screening for anxiety and depression in cancer patients: the effects of disease and treatment. Eur J Cancer. 1994;30A(1):37-40.

69. Fu MR, Rosedale M. Breast cancer survivors' experiences of lymphedema-related symptoms. J Pain Symptom Manage. 2009 Dec;38(6):849-59.

70. Moseley A, Piller N. Reliability of bioimpedance spectroscopy and tonometry after breast conserving cancer treatment. Lymphat Res Biol. 2008 01;6(2):85-7.

71. Caruso MK, Guillot TS, Nguyen T, Greenway FL. The cost effectiveness of three different measures of breast volume. Aesthetic Plast Surg. 2006 Jan-Feb;30(1):16-20.

72. Pezner RD, Patterson MP, Hill LR. Breast retraction assessment: Multiple variable analysis of factors responsible for cosmetic retraction in patients treated conservatively for stage I or II breast carcinoma. Acta Radiol Oncol. 1985;24(4):327-30.

73. Pezner RD, Patterson MP, Hill LR. Breast retraction assessment: An objective evaluation of cosmetic results of patients treated conservatively for breast cancer. Int J Radiat Oncol Biol Phys. 1985;11(3):575-8.

74. Pezner RD, Lipsett JA, Vora NL, Desai KR. Limited usefulness of observer-based cosmesis scales employed to evaluate patients treated conservatively for breast cancer. Int J Radiat Oncol Biol Phys. 1985;11(6):1117-9.

75. Van Limbergen E, Van Der Schueren E, Van Tongelen K. Cosmetic evaluation of breast conserving treatment for mammary cancer. 1. Proposal of a quantitative scoring system. Radiother Oncol. 1989;16(3):159-67.

76. Sneeuw KCA, Aaronson NK, Yarnold JR, Broderick M, Regan J, Ross G, Goddard A. Cosmetic and functional outcomes of breast conserving treatment for early stage breast cancer. 1. Comparison of patients' ratings, observers' ratings and objective assessments. Radiother Oncol. 1992;25(3):153-9.

77. Sarin R, Dinshaw KA, Shrivastava SK, Sharma V, Deore SM. Therapeutic factors influencing the cosmetic outcome and late complications in the conservative management of early breast cancer. Int J Radiat Oncol Biol Phys. 1993;27(2):285-92.

78. Johansen J, Overgaard J, Rose C, Engelholm SA, Gadeberg CC, Kjaer M, Kamby C, Juul-Christensen J, Blichert-Toft M, Overgaard M. Cosmetic outcome and breast morbidity in breast-conserving treatment - Results from the Danish DBCG-82TM national randomized trial in breast cancer. Acta Oncol. 2002;41(4):369-80.

79. Cardoso MJ, Santos AC, Cardoso J, Barros H, Cardoso De Oliveira M. Choosing observers for evaluation of aesthetic results in breast cancer conservative treatment. Int J Radiat Oncol Biol Phys. 2005 01;61(3):879-81.

80. Zgajnar J. Digital evaluation of breast cosmesis after breast-conserving treatment: End of the beginning. Breast. 2007 Oct;16(5):441-2.

81. Fitzal F, Krois W, Trischler H, Wutzel L, Riedl O, Kühbelböck U, Wintersteiner B, Cardoso MJ, Dubsky P, Gnant M, Jakesz R, Wild T. The use of a breast symmetry index for objective evaluation of breast cosmesis. Breast. 2007 Aug;16(4):429-35.

82. Cardoso MJ, Cardoso J, Amaral N, Azevedo I, Barreau L, Bernardo M, Christie D, Costa S, Fitzal F, Fougo JL, Johansen J, Macmillan D, Mano MP, Regolo L, Rosa J, Teixeira L, Vrieling C. Turning subjective into objective: The BCCT.core software for evaluation of cosmetic results in breast cancer conservative treatment. Breast. 2007 Oct;16(5):456-61.

83. Bulstrode N, Bellamy E, Shrotria S. Breast volume assessment: Comparing five different techniques. Breast. 2001;10(2):117-23.

84. Wright MCM. Graphical analysis of bra size calculation procedures. International Journal of Clothing Science and Technology. 2002;14(1):41-5.

85. Zheng R, Yu W, Fan J. Development of a new Chinese bra sizing system based on breast anthropometric measurements. Int J of Ind Ergon. 2007;37(8):697-705.

86. Coulthard A, Potterton AJ. Pitfalls of breast MRI. Br J Radiol. 2000 Jun;73(870):665-71.

87. Ralleigh G, Walker AE, Hall-Craggs MA, Lakhani SR, Saunders C. MR imaging of the skin and nipple of the breast: Differentiation between tumour recurrence and post-treatment change. Eur Radiol. 2001;11(9):1651-8.

88. Morakkabati N, Leutner CC, Schmiedel A, Schild HH, Kuhl CK. Breast MR Imaging during or Soon after Radiation Therapy. Radiology. 2003 Dec;229(3):893-901.

89. Padhani AR, Yarnold J, Regan J, Husband JE. Dynamic MRI of breast hardness following radiation treatment. J Magn Reson Imaging. 2003 01;17(4):427-34.

90. Carl UM, Feldmeier JJ, Schmitt G, Hartmann KA. Hyperbaric oxygen therapy for late sequelae in women receiving radiation after breast-conserving surgery. Int J Radiat Oncol Biol Phys. 2001 Mar 15;49(4):1029-31.

91. Krishnamurthy R, Whitman GJ, Stelling CB, Kushwaha AC. Mammographic findings after breast conservation therapy. Radiographics. 1999 Oct;19 Spec No:S53-62; quiz S262-3.

92. Warszawski A, Rottinger EM, Vogel R, Warszawski N. 20 MHz ultrasonic imaging for quantitative assessment and documentation of early and late postradiation skin reactions in breast cancer patients. Radiother Oncol. 1998 Jun;47(3):241-7.

93. Michael S, Charikleia S, Konstantinos K. Lymphedema and breast cancer: a review of the literature. Breast Cancer. 2011;18(3):174-80.

94. Stone DH. Design a questionnaire. Br Med J. 1993;307(6914):1264-6.

95. Jackson CJ, Furnham A. Designing and analysing questionnaires and surveys: A manual for health professionals and administrators. London: Whurr Publishers; 2000. Chapter 1, The basic rationale; p.3-62.

96. Guyatt GH, Bombardier C, Tugwell PX. Measuring disease-specific quality of life in clinical trials. Can Med Assoc J. 1986;134(8):889-95.

97. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage. 1997 Feb;13(2):63-74.

98. Aaronson N. Methodologic Issues in Assessing the Quality of Life of Cancer Patients. Cancer. 1991;67:844-50.

99. Selby PJ, Chapman JA, Etazadi-Amoli J, Dalley D, Boyd NF. The development of a method for assessing the quality of life of cancer patients. Br J Cancer. 1984;50(1):13-22.

100. Juniper EF, Guyatt GH, Jaeschke R. How to Develop and Validate a New Health- Related Quality of Life Instrument. In: Spilker B, editor. Quality of Life and Pharmacoeconomics in Clinical Trials. 2nd ed. Philadelphia. Lippincott-Raven; 1996.

101. Bellamy N, Campbell J, Haraoui B, Gerecz-Simon E, Buchbinder R, Hobby K, MacDermid JC. Dimensionality and clinical importance of pain and disability in hand osteoarthritis: Development of the Australian/Canadian (AUSCAN) osteoarthritis hand index. Osteoarthritis Cartilage. 2002 01;10(11):855-62.

102. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999;14(4):902-7.

103. Levine MN, Guyatt GH, Gent M, De Pauw S, Goodyear MD, Hryniuk WM, Arnold A, Findlay B, Skillings JR, Bramwell VH, Levin L, Bush H, Abu-Zahra H, Kotalik J. Quality of life in stage II breast cancer: An instrument for clinical trials. J Clin Oncol. 1988;6(12):1798-810.

104. Brady MJ, Cella DF, Mo F, Bonomi AE, Tulsky DS, Lloyd SR, Deasy S, Cobleigh M, Shiomoto G. Reliability and validity of the functional assessment of cancer therapy- breast quality-of-life instrument. J Clin Oncol. 1997 Mar;15(3):974-86.

105. Cella DF, Nowinski, CJ. Measuring quality of life in chronic illness: the functional assessment of chronic illness therapy measurement system. Arch Phys Med Rehabil. 2002;83(12)Supp 2:S10-7.

106. Van der Molen T, Willemse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. Health Qual Life Outcomes. 2003;1:13.

107. Damato S, Bonatti C, Frigo V, Pappagallo S, Raccanelli R, Rampoldi C, Rodeo F. Validation of the Clinical COPD questionnaire in Italian language. Health Qual Life Outcomes. 2005;3:9.

108. Schipper H, Clinch J, McMurray A, Levitt M. Measuring the quality of life of cancer patients: The functional living index-cancer: Development and validation. J Clin Oncol. 1984;2(5):472-83.

109. Portenoy RK, Thaler HT, Kornblith AB, McCarthy Lepore J, Friedlander-Klar H, Kiyasu E, Sobel K, Coyle N, Kemeny N, Norton L, Scher H. The Memorial Symptom Assessment Scale: An instrument for the evaluation of symptom prevalence, characteristics and distress. Euro J Cancer. 1994;30A(9):1326-36.

110. Gunthorpe W, Brown W, Redman, S. The development and evaluation of an incontinence screening questionnaire for female primary care. Neurourol Urodyn. 2000;19(5):595-607.

111. Cormier JN, Ross MI, Gershenwald JE, Lee JE, Mansfield PF, Camacho LH, Kim K, Webster K, Cella D, Palmer JL. Prospective assessment of the reliability, validity, and sensitivity to change of the Functional Assessment of Cancer Therapy-Melanoma questionnaire. Cancer. 2008 May 15;112(10):2249-57.

112. De Vaus DA. Surveys in social research. 5th ed. London: Routledge; 2002.

113. Guyatt GH, Jaeschke R, Feeny DH, Patrick DL. Measurements in Clinical Trials: Choosing the Right Approach. In: Spilker B, editor. Quality of Life and Pharmacoeconomics in Clinical Trials. 2nd ed. Philadelphia. Lippincott-Raven; 1996.

114. Bellamy N. WOMAC Osteoarthritis Index. User Guide IX; Brisbane; 2009.

115. Carpenter C, Suto M. Qualitative research for occupational and physical therapists: a practical guide. Oxford: Blackwell; 2008. Chapter 5, Involving participants and data collection methods; p.77-97.

116. Bellamy N, Campbell J, Haraoui B, Gerecz-Simon E, Buchbinder R, Hobby K, MacDermid JC. Clinimetric properties of the AUSCAN osteoarthritis hand index: An evaluation of reliability, validity and responsiveness. Osteoarthritis Cartilage. 2002 01;10(11):863-9.

117. Patel AS, Siegert RJ, Creamer D, Larkin G, Maher TM, Renzoni EA, Wells AU, Higginson IJ, Birring SS. The development and validation of the King's Sarcoidosis Questionnaire for the assessment of health status. Thorax. 2013;68:57-65.

118. Kriener S. Rasch models: validity, sufficiency and – in principle- objectivity [Internet]. 2013 Mar 21 [cited 2013 Jun 13]. Available from: www.bmj.com/346/bmj.f232/rr/637148.

119. Ghaemi H. Is Rasch without drawback? A reanalysis of Rasch model limitations [Internet]. 2013 [cited 2013 May 21]. Available from: www.mjltm.com/index.php?option=content&t=co&i=23.

120. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. Med Care. 1989 Mar;27Supp 3:S217-32.

121. Fitzpatrick R, Davey C, Buxton MJ, Jones DR. Evaluating patient-based outcome measures for use in clinical trials. Health technology assessment (Winchester, England). 1998;2(14):i-iv, 1-74.

122. Guyatt GH, Naylor D, Juniper E, Heyland DK, Jaeschke R, Cook DJ. Users' guides to the medical literature: XII. How to use articles about health-related quality of life. JAMA. 1997;277(15):1232-7.

123. Fitzpatrick R, Davey C, Buxton MJ, Jones DR. Evaluating patient-based outcome measures for use in clinical trials. Health technology assessment (Winchester, England). 1998;2(14):i-iv, 1-74. Box 3, Different types of instruments and examples; p.8.

124. Garratt A, Schmidt L, Mackintosh A, Fitzpatrick R. Quality of life measurement: bibliographic study of patient assessed health outcome measures. BMJ. 2002 Jun 15;324(7351):1417-21.

125. Bowling A. Measuring disease: A review of disease specific quality of life measurement scales. Philadelphia: Open University Press; 1995. Chapter 1, Health-related quality of life: A discussion of the concept, its use and measurement; p.12-16.

126. McDowell I, Newell, C. Measuring health: a guide to rating scales and questionnaires. 3rd ed. Oxford: Oxford University Press; 2006. Chapter 10, General health status and quality of life; p.522.

127. Husted JA, Cook RJ, Farewell VT, Gladman DD. Methods for assessing responsiveness: A critical review and recommendations. J Clin Epidemiol. 2000 May;53(5):459-68.

128. Carr AJ. Margaret Holroyd Prize Essay. A patient-centred approach to evaluation and treatment in rheumatoid arthritis: the development of a clinical tool to measure patient-perceived handicap. Br J Rheumatol. 1996 Oct;35(10):921-32.

129. Thoma A, Sprague S, Veltri K, Duku E, Furlong W. Methodology and measurement properties of health-related quality of life instruments: A prospective study of patients undergoing breast reduction surgery. Health Qual Life Outcomes. 2005;3(44).

130. Guyatt GH, Walter S, Norman G. Measuring change over time: Assessing the usefulness of evaluative instruments. J Chronic Dis. 1987;40(2):171-8.

131. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. J Clin Epidemiol. 1991;44(11):1271-8.

132. Carr A, Higginson, I. Are quality of life measures patient centred? Br Med J. 2001 Jun 2;322(7298):1357-60.

133. Haywood KL, Garratt AM, Jordan KP, Healey EL, Packham JC. Evaluation of ankylosing spondylitis quality of life (EASi-QoL): Reliability and validity of a new patient-reported outcome measure. J Rheumatol. 2010 Oct;37(10):2100-9.

134. Ehrich EW, Davies GM, Watson DJ, Bolognese JA, Seidenberg BC, Bellamy N. Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities Osteoarthritis Index questionnaire and global assessments in patients with osteoarthritis. J Rheumatol. 2000;27(11):2635-41.

135. Bellamy N, Wilson C, Hendrikz, J. Population-based normative values for the Western Ontario and McMaster (WOMAC) osteoarthritis index and the Australian/Canadian (AUSCAN) hand osteoarthritis index functional subscales. Inflammopharmacology. 2010 Feb;18(1):1-8.

136. Bellamy N, Wilson C, Hendrikz, J. Population-Based Normative Values for the Australian/Canadian (AUSCAN) Hand Osteoarthritis Index: Part 1. Semin Arthritis Rheum. 2011 Oct;41(2):139-48.

137. Bellamy N, Wilson C, Hendrikz, J. Population-Based Normative Values for the Australian/Canadian (AUSCAN) Hand Osteoarthritis Index: Part 2. Semin Arthritis Rheum. 2011 Oct;41(2):149-56.

138. Feinstein A. The Theory and Evaluation of Sensibility. In: Feinstein A, editor. Clinimetrics. New Haven. Yale University Press; 1987.

139. Greene JG. Constructing a standard climacteric scale. Maturitas. 1998 20;29(1):25-31.

140. Bellamy N, Buchanan WW. A preliminary evaluation of the dimensionality and clinical importance of pain and disability in osteoarthritis of the hip and knee. Clin Rheumatol. 1986 Jun;5(2):231-41.

141. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993 Mar;11(3):570-9.

142. Nicholson RM, Leinster S, Sassoon EM. A comparison of the cosmetic and psychological outcome of breast reconstruction, breast conserving surgery and mastectomy without reconstruction. Breast. 2007 Aug;16(4):396-410.

143. Kerrigan CL, Collins ED, Striplin D, Kim HM, Wilkins E, Cunningham B, Lowery J. The health burden of breast hypertrophy. Plast Reconstr Surg. 2001;108(6):1591.

144. Armer JM, Elise Radina M, Porock D, Culbertson SD. Predicting breast cancer-related lymphedema using self-reported symptoms. Nurs Res. 2003;52(6):370-9.

145. Schünemann HJ, Puhan M, Goldstein R, Jaeschke R, Guyatt GH. Measurement properties and interpretability of the Chronic Respiratory Disease Questionnaire (CRQ). COPD: Journal of Chronic Obstructive Pulmonary Disease Jan 2005, 2(1): 81–89.

146. Hofstee W, Ten Berge J, Hendriks A. How to score questionnaires. Pers Individ Dif. 1998 Nov;25(5):897-909.

147. Bellamy N. Weighting and Aggregation. In: Bellamy N, editor. WOMAC Osteoarthritis Index User Guide 1X; Brisbane; 2009. p. 9-11.

148. Gallagher J, Parle M, Cairns D. Appraisal and psychological distress six months after diagnosis of breast cancer. Br J Health Psychol. 2002 Sep;7(3):365-76.

149. Cardoso MJ, Cardoso J, Santos AC, Barros H, Cardoso de Oliveira, M. Interobserver agreement and consensus over the esthetic evaluation of conservative treatment for breast cancer. Breast. 2006 Feb;15(1):52-7.

150. Preuss J, Lester L, Saunders C. BCCT.core - Can a computer program be used for the assessment of aesthetic outcome after breast reconstructive surgery? Beast. 2012 Aug;21(4):597-600.

151. Donner A, Eliasziw M. Sample size requirements for reliability studies. Stat Med. 1987;6(4):441-8.

152. Cormier JN. Capitalising on the momentum through collaboration. J Lymphoedema. 2009;4(1):8-9.

153. Temple LK, McLeod RS, Gallinger S, Wright JG. Defining disease in the genomics era. Science. 2001 Aug 3;293(5531):807-8.

154. Williams AF, Franks PJ, Moffatt CJ. Lymphoedema: estimating the size of the problem. Palliat Med. 2005;19(4):300-13.

155. Hayes S. Review of Research Evidence on Secondary Lymphoedema: Incidence, Prevention, Risk Factors and Treatment. Surry Hills (NSW): National Breast and Ovarian Cancer Centre (AUS); 2008.

156. Norman SA, Localio AR, Potashnik SL, Simoes Torpey HA, Kallan MJ, Weber AL, Miller LT, DeMichele A, Solin LJ. Lymphedema in breast cancer survivors: Incidence, degree, time course, treatment, and symptoms. J Clin Unco. 2009 20;27 (3):390-7.

157. Thijs RD, Wieling W, Kaufmann H, Gert van Dijk, J. Defining and classifying syncope. Clin Auton Res. 2004;14Supp 1:i4-i8.

158. Jones J, Hunter D. Qualitative Research: Consensus methods for medical and health services research. BMJ. 1995;311(7001):376-80.

159. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs. 2000;32(4):1008-15.

160. Powell C. The Delphi technique: myths and realities. J Adv Nurs. 2003;41(4):376-82.

161. Potter M, Gordon S, Hamer P. The Nominal Group Technique: A useful consensus methodology in physiotherapy research. New Zealand Journal of Physiotherapy. 2004 Nov;32(3):126-30.

162. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs. 2000;32(4):1008-15. Figure 1, Areas for reporting on the Delphi survey technique; p. 1009.

163. Jackson A, Hettinga DM, Mead J, Mercer C. Using consensus methods in developing clinical guidelines for exercise in managing persistent low back pain. Physiotherapy. 2009 Dec;95(4):302-13.

164. Murphy MK, Black N, Lamping D, McKee M, Sanderson C, Askham J, Marteau T. Consensus development methods, and their use in clinical guideline development. Health Technol Assess. 1998;2(3):i-iv, 1-88.

165. Konecne SM, Perdomo M. Lymphedema in the elderly: A special needs population. Top Geriatr Rehabil. 2004 Apr;20(2):98-113.

166. International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2009 Consensus Document of the International Society of Lymphology. Lymphology. 2009 Jun;42(2):51-60.

167. Stevinson C, Preston N, Todd C, Cancer Experiences Collaborative. Defining priorities in prognostication research: results of a consensus workshop. Palliat Med. 2010 Jul;24(5):462-8.

168. Searle RD, Howell SJ, Bennett MI. Diagnosing postoperative neuropathic pain: a Delphi survey. Br J Awash. 2012;109(2):240-4.

169. Holey EA, Feeley JL, Dixon J, Whittaker VJ. An exploration of the use of simple statistics to measure consensus and stability in Delphi studies. BMC Med Res Methodol. 2007;7:52.

170. Minkman M, Ahaus K, Fabbricotti I, Nabitz U, Huijsman R. A quality management model for integrated care: results of a Delphi and Concept Mapping study. Int J Qual Health Care. 2009;21(1):66-75.

171. Keeney SBAM, Hasson F, McKenna H. Consulting the oracle: the lessons from using the Delphi technique in nursing research. J Adv Nurs.2006:53(2):205-12.

172. Tokarek R, Bernstein EF, Sullivan F, Uitto J, Mitchell JB. Effect of therapeutic radiation on wound healing. Clin Dermatol. 1994 Jan-Mar;12(1):57-70.

173. Riekki R. Late dermal effects of breast cancer radiotherapy [PhD thesis]. Oulu (Finland): University of Oulu; 2006.

174. Cancer Australia. Breast cancer statistics. [homepage on the Internet]. c2012 [updated 2011 Jan 18; cited 2012 9 Mar]. Available from: http://www.canceraustralia.gov.au/breast cancer/breast cancer statistics.

175. Murdaca G, Cagnati P, Gulli R, Spanò F, Puppo F, Campisi C, Boccardo F. Current Views on Diagnostic Approach and Treatment of Lymphedema. Am J Med. 2012;125(2):134-40.

176. Fu MR, Ridner SH, Armer J. Post-breast cancer lymphedema: part 2. Am J Nurs. 2009 Aug;109(8):34-41; quiz 2.

177. Heil J, Carolus A, Dahlkamp J, Golatta M, Domschke C, Schuetz F, Blumenstein M, Rauch G, Sohn C. Objective assessment of aesthetic outcome after breast conserving therapy: subjective third party panel rating and objective BCCT.core software evaluation. Breast. 2012 Feb;21(1):61-5.

178. Polgar C, Orosz, Z, Fodor, J. Is postirradiation angiosarcoma of the breast so rare and does breast lymphedema contribute to its development? J Surg Oncol. 2001;76(3):239-40.

179. Feinstein AR. Benefits and obstacles for development of health status assessment measures in clinical settings. Med Care. 1992 May;30(5)Supp l:MS50-6.

180. Sprangers MAG. Quality-of-life assessment in oncology - Achievements and challenges. Acta Oncol. 2002;41(3):229-37.

181. Armer JM, Stewart BR. A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. Lymphat Res Biol. 2005;3(4):208-17.

182. Hoving JL, O'Leary EF, Niere KR, Green S, Buchbinder R. Validity of the neck disability index, Northwick Park neck pain questionnaire, and problem elicitation technique for measuring disability associated with whiplash-associated disorders. Pain. 2003 Apr;102(3):273-81.

183. Gao F, Luo N, Thumboo J, Fones C, Li S, Cheung Y. Does the 12-item General Health Questionnaire contain multiple factors and do we need them? Health Qual Life Outcomes. 2004;2:63.

184. Sie AS, Spruijt L, van Zelst-Stams WA, Mensenkamp AR, Ligtenberg MJ, Brunner HG, Prins JB, Hoogerbrugge N. DNA-testing for BRCA1/2 prior to genetic counselling in patients with breast cancer: design of an intervention study, DNA-direct. BMC Womens Health. 2012;12:12.

185. Cella DF. The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Scale: Summary of development and validation. Evanston: Centre on Outcomes, Research and Education (CORE), Evanston Northwestern Healthcare and Northwestern University; 2003.

186. Ware JE. SF-36 Health survey update. Spine. 2000;25(24): 3130-39.

187. Breast. In: Standring S, editor. Gray's Anatomy: the Anatomical Basis of Clinical Practice 39th ed. Edinburgh. Elsevier Churchill Livingstone; 2005.

188. Mosby's Dictionary of Medicine, Nursing and Health Professions. 2nd ed. Sydney: Elsevier; 2010. Breast cancer; p.242-43.

189. Carlson RW. Surveillance of patients following primary therapy. In: Harris JR, Lippman ME, Kent Osborne C, Morrow M, editors. Diseases of the Breast. 4th ed. Philadelphia. Lippincott Williams & Wilkins; 2010.

190. Merajver SD, Niesta MD, Sabel MS. Inflammatory breast cancer. In: Harris JR, Lippman ME, Kent Osborne C, Morrow M, editors. Diseases of the Breast. 4th ed. Philadelphia. Lippincott Williams & Wilkins; 2010.

191. Esteva FJ, Gutierrez C. Nonepithelial malignancies of the breast. In: Harris JR, Lippman ME, Kent Osborne C, Morrow M, editors. Diseases of the Breast. 4th ed. Philadelphia. Lippincott Williams & Wilkins; 2010.

192. Cameron RB, Loehrer PJ, Thomas Jnr CR. Neoplasms of the mediastinum. In: DeVita VT, Lawrence TS, Rosenberg SA, DePinho RA, editors. Cancer: principles and practice of oncology. 9th ed. Philadelphia. Lippincott Williams and Wilkins; 2011.

193. Reszko A, Aasi SZ, Wilson LD, Leffell DJ. Cancer of the skin. In: DeVita VT, Lawrence TS, Rosenberg SA, DePinho RA, editors. Cancer: principles and practice of oncology. 9th ed. Philadelphia. Lippincott Williams and Wilkins; 2011.

194. Francis GS, Sonnenblick EH, Wilson Tang WH, Poole-Wilson P. Pathophysiology of heart failure. In: Fuster V, Walsh R, Harrington R, editors. Hurst's the Heart. 13th ed. New York. McGraw Hill Medical; 2011.

195. Dixon J, Bundred N. Management of disorders of the ductal system and infections. In: Harris JR, Lippman ME, Kent Osborne C, Morrow M, editors. Diseases of the Breast. 4th ed. Philadelphia. Lippincott Williams & Wilkins; 2010.

196. Sumner D. Noninvasive vascular laboratory assessment. In: Sumner D, editor. Vascular Disorders of the Upper Extremity. 3rd ed. New York. Futura; 1998.

197. Morrow M. Benign breast disorders. In: Harris JR, Hellman S, Henderson I, Kinne DW, editors. Breast diseases. 2nd ed. Philadelphia. JB Lippincott Company; 1991.

198. Buchholz TA, Hunt, KK. Breast-Conserving Therapy: Conventional Whole Breast Irradiation. In: Harris JR, Lippman ME, Kent Osborne C, Morrow M, editors. Diseases of the Breast. 4th ed. Philadelphia. Lippincott Williams & Wilkins; 2010.

199. Hall JC. Granulomatous dermatoses. In: Hall JC, editor. Sauer's manual of skin diseases. 9th ed. Philadelphia. Lippincott Williams and Wilkins; 2006.

200. Bleicher RJ. Management of the Palpable Breast Mass. In: Harris JR, Lippman ME, Kent Osborne C, Morrow M, editors. Diseases of the Breast. 4th ed. Philadelphia. Lippincott Williams & Wilkins; 2010.

201. Wojnarowska F, Venning VA. Intradermal immunobullous disease. In: Breathnach S et al, editors. Rook's Textbook of Dermatology. 8th ed. West Sussex. Wiley- Blackwell; 2010.

Chapter 9.0

Appendices

Appendix 1

memorandum

Curtin University of Technology

Office of Research and Development

Human Research Ethics Committee

TELEPHONE 9266 2784
FACSIMILE 9266 3793
EMAIL hrec@curtin.edu.au

To	Associate Professor Kathy Briffa, Physiotherapy
From	A/Professor Stephan Millett, Chairperson, Human Research Ethics Committee
Subject	Protocol Approval **HR 98/2007**
Date	7 February 2008
Copy	Christine Smith, Physiotherapy Graduate Studies Officer, Faculty of Health Sciences

Thank you for your application submitted to the Human Research Ethics Committee (HREC) for the project titled "*The development of the Breast Lymphoedema Severity Symptom (BLYSS) questionnaire*". Your application has been reviewed by the HREC and is **approved**.

- You are authorised to commence your research as stated in your proposal.
- The approval number for your project is **HR 98/2007.** *Please quote this number in any future correspondence.*
- Approval of this project is for a period of twelve months **05-02-2008** to **05-02-2009.** To renew this approval a completed Form B (attached) must be submitted before the expiry date **05-02-2009**
- If you are a Higher Degree by Research student, data collection must not begin before your Application for Candidacy is approved by your Divisional Graduate Studies Committee.
- The following standard statement **must be** included in the information sheet to participants:

  This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 98/2007). The Committee is comprised of members of the public, academics, lawyers, doctors and pastoral carers. Its main role is to protect participants. If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au.

Applicants should note the following:

It is the policy of the HREC to conduct random audits on a percentage of approved projects. These audits may be conducted at any time after the project starts. In cases where the HREC considers that there may be a risk of adverse events, or where participants may be especially vulnerable, the HREC may request the chief investigator to provide an outcomes report, including information on follow-up of participants.

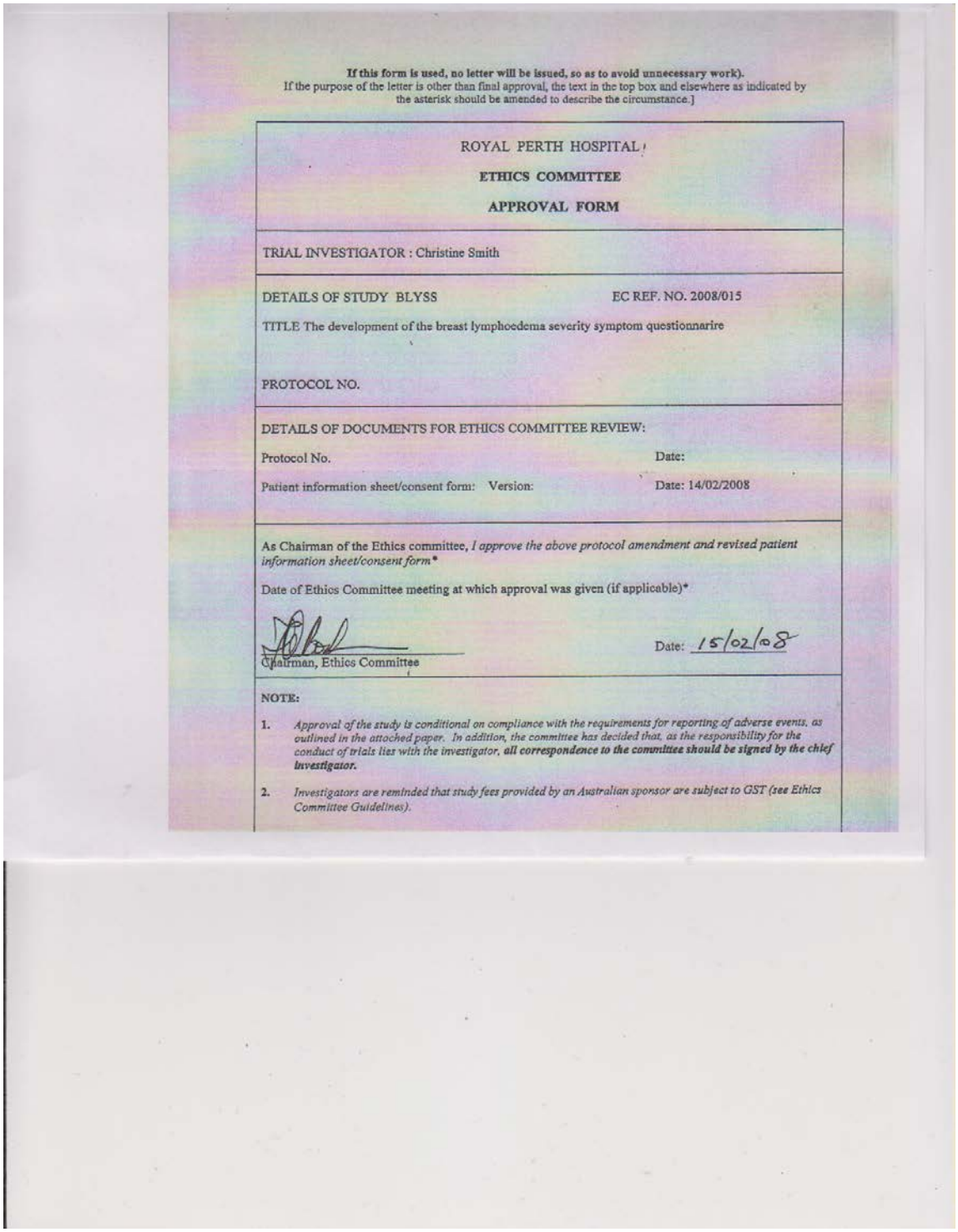
The attached **FORM B** should be completed and returned to the Secretary, HREC, C/- Office of Research & Development:
When the project has finished, or

- If at any time during the twelve months changes/amendments occur, or
- If a serious or unexpected adverse event occurs, or
- 14 days prior to the expiry date if renewal is required.
- An application for renewal may be made with a Form B three years running, after which a new application form (Form A), providing comprehensive details, must be submitted.

Regards,

A/Professor Stephan Millett
Chairperson
Human Research Ethics Committee

Appendix 2



If this form is used, no letter will be issued, so as to avoid unnecessary work).
If the purpose of the letter is other than final approval, the text in the top box and elsewhere as indicated by the asterisk should be amended to describe the circumstance.]

ROYAL PERTH HOSPITAL

ETHICS COMMITTEE

APPROVAL FORM

TRIAL INVESTIGATOR : Christine Smith

DETAILS OF STUDY BLYSS EC REF. NO. 2008/015

TITLE The development of the breast lymphoedema severity symptom questionnarire

PROTOCOL NO.

DETAILS OF DOCUMENTS FOR ETHICS COMMITTEE REVIEW:

Protocol No. Date:

Patient information sheet/consent form: Version: Date: 14/02/2008

As Chairman of the Ethics committee, *I approve the above protocol amendment and revised patient information sheet/consent form**

Date of Ethics Committee meeting at which approval was given (if applicable)*

Chairman, Ethics Committee

Date: 15/02/08

NOTE:

1. *Approval of the study is conditional on compliance with the requirements for reporting of adverse events, as outlined in the attached paper. In addition, the committee has decided that, as the responsibility for the conduct of trials lies with the investigator,* ***all correspondence to the committee should be signed by the chief investigator.***
2. *Investigators are reminded that study fees provided by an Australian sponsor are subject to GST (see Ethics Committee Guidelines).*

Appendix 3

Government of **Western Australia**
Department of **Health**
Ethics Ref: 2010-035
Ext 2999

Sir Charles
Gairdner Hospital

17 June 2010

Ms Hillary Palladino
Occupational Therapy
Lower Ground Floor G Block
Sir Charles Gairdner Hospital
Hospital Ave
NEDLANDS WA 6009

Ms Christine Smith
Physiotherapy
Royal Perth Hospital
PO Box X2213
PERTH WA 6847

Dear Ms Palladino

APPLICATION TO CONDUCT HUMAN RESEARCH AT SCGH:
TRIAL No: 2010-035
TRIAL TITLE: The Development of the Breast Lymphoedema Severity Symptom Questionnaire (BLYSS)

On behalf of the Sir Charles Gairdner Group Executive I give approval to conduct your research project at Sir Charles Gairdner Hospital based on the favourable reviews provided to me by the Research Governance Unit and the Sir Charles Gairdner Group Human Research Ethics Committee. This approval is granted until 30 June 2012, and on the basis of compliance with all requirements laid out in your application and with the provision of reports as required by the RGU and approving HREC in giving their favourable opinion (attached).

The responsibility for the conduct of this study remains with you as the Principal Investigator. You must notify the Research Governance Unit of any relevant issues arising during the conduct of the study that may affect continued favourable opinions by the hospital or by an HREC.

Please quote Study number 2010-035 on all correspondence associated with this study.

Yours sincerely

SDavis

SUE DAVIS
Acting Executive Director of Nursing Services
Sir Charles Gairdner Group
North Metropolitan Area Health Service

Sir Charles Gairdner Group Human Research Ethics Committee, Level 2 A Block, Hospital Ave, Nedlands, WA 6009
Telephone (08) 9346 2999 Fax (08) 9346 3307 ABN: 13 993 250 709
email HREC.SCGH@health.wa.gov.au Website www.scgh.health.wa.gov.au

Appendix 4

ROYAL PERTH HOSPITAL

18 February 2008

«Name» «Surname»
«Address»
«Suburb»

Dear «Name»,

Breast lymphoedema is a complication for women following breast conservation treatment for breast cancer. In order to monitor the benefits of treatment for breast lymphoedema it is important to be able to measure the severity of the condition and changes that occur with treatment. The aim of this study is to develop a questionnaire, specifically designed for this. Due to your clinical specialisation in treating patients with breast cancer, I am inviting to you participate in this research.
This study has been approved by the Royal Perth Hospital Human Research Ethics Committee and Curtin University Human Research Ethics Committee.

Your role in the trial
If you agree to be involved in this study you will be asked to attend the Physiotherapy Department once for an interview. During the interview you will be asked about the symptoms associated with breast lymphoedema. You will also be asked to rank the symptoms from most important to least important to you. The interview will take approximately an hour. Your responses will be collated with responses from other professionals who volunteer for the study. These responses will then be put to previously treated breast lymphoedema patients to create a questionnaire, specifically for breast lymphoedema. Although notes will be taken during the interview, these will be completely anonymous. The only record of your involvement will be the signed consent form.

Participation in the study is entirely voluntary. You do not have to join the study and choosing not to volunteer will not affect any future physiotherapy service provision.

If you would like to be involved in the study please return the enclosed form in the replied paid envelope and we will contact you to make an appointment for the interview. If you would like to talk to me in regards to any questions or concerns about this project, please ring me on 9224 2076, Monday to Friday, 8am-430pm.

If you are not interested, please do not reply to this letter.
Thank you for taking the time to read this letter and considering helping with this research.

Yours sincerely,

Christine Smith
Senior Physiotherapist
Oncology/Lymphoedema
Royal Perth Hospital

Masters student
Curtin University

Appendix 5

CONSENT TO AGREE TO BE CONTACTED AND PARTICIPATE IN THE DEVELOPMENT OF A BREAST LYMPHOEDEMA QUESTIONNAIRE

I,…… agree/disagree to be contacted and participate in the study described above. I have read and understood the attached Information Sheet and I have retained a copy of the signed document. I have been given the opportunity to ask questions about the study by the investigator. I understand that I may withdraw from the study at any time without affecting any future physiotherapy service provision.

Signed…….. Date…….

Time, day and number to contact you to make an appointment…….

……

Signature of Investigator……. Date…….

Appendix 6

Demographic Information- Professionals

Please answer the following questions. Please tick responses for questions one and two.

1. Gender: □ Male □ Female

2. Profession:
□ Breast physician
□ Breast surgeon
□ Radiation Oncologist
□ Physiotherapist
□ Occupational Therapist
□ Other _____

3. How many years have you been working in your profession?_____

4. How many patients with breast cancer do you treat per year? _____

5. How many patients with breast lymphoedema do you treat per year? _____

Appendix 7

Professional Interviews

(Interviewer to read to professional)

I am Christine Smith, a senior physiotherapist working in Lymphoedema/Oncology at Royal Perth Hospital, Western Australia. I am developing a questionnaire to measure the health status of women with breast lymphoedema, as a result of breast cancer treatment.

As the first step in this process, I am asking clinicians from a variety of professions who currently treat patients with breast lymphoedema to help me to identify items to include in the questionnaire. Clinicians working in the area should be particularly well placed to provide ideas and insights into the condition and its effects on physical, psychological and daily functioning of affected women.

The next step will be to conduct interviews with women who have previously been treated for breast lymphoedema to gather similar information from their perspective. Items you have identified, will be collated with information from the literature to develop an item elicitation questionnaire for patient interviews. The item elicitation questionnaire provides structure to further explore the dimensionality of symptoms associated with breast lymphoedema.

Firstly I am going to ask you to complete this demographic profile.
(Hand to clinician. Once completed, check that all responses are answered. If any questions remain unanswered, check if the professional as to why the question is not answered and correct/modify as necessary).

- Tell me how much of a problem you think breast lymphoedema is?
  - Clinically
  - For the patients?
- Are you commonly seeing patients with breast lymphoedema? If yes, why and if no, why not?
- Is this to do with your position in the progression of treatment, or your specific areas of interest and expertise?
- At what stage of breast cancer treatment do you see breast lymphoedema? Have you noticed a change in incidence/prevalence?
- Do you have any ideas why this might be?
  - Change in overall approach to treatment
  - Better diagnosis of breast lymphoedema

What are the symptoms the patients most commonly complain of?

Which appear to be the symptoms they find most distressing?

What are the symptoms you see as being the most indicative of breast lymphoedema? After symptoms, then ask the signs, physical dysfunction, psychosocial and functionality factors.

(a) _____
(b) _____
(c) _____
(d) _____
(e) _____

For each response e.g. (a)-

- How would you normally assess this with your patient?
- Does (a) vary?
- How severe do you think (a) is? If requires prompt offer not, somewhat, very or extremely. You may have to explain what you mean by severe, and your prompt responses might not be appropriate for some factors.
- How severe do you think (a) is to the patient?
- How frequently does (a) occur? If unable to answer, suggest constant, daily, weekly, fortnightly, less than monthly or monthly.
  How many patients with breast lymphoedema have it?
  Is something that has the propensity to become chronic?

- How important is (a) to you? If requires prompt offer not, somewhat, very or extremely.
- Is it an important diagnostic characteristic? Is it an important prognostic characteristic? Does it indicate the need for specific therapy?
- How important is (a) to the patient? If requires prompt offer not, somewhat, very or extremely. Does it vary between patients? Is it related to other factors like age, cancer prognosis, body image, pain etc…?
- What constraints currently make (a) difficult to assess in breast lymphoedema patients?
- You have not mentioned… (something off the closed ended list). Is this something you associate with breast lymphoedema?

Is there anything else you would like to add?

Thank for you participating in the interview.
Please leave your details with the interviewer, if you would like to know the final outcomes of the BYLSS development.

Appendix 8

ROYAL PERTH HOSPITAL

Dear «Name», 20 June 2008

RE: Breast Lymphoedema Research.

Breast lymphoedema can occur in some women following breast conservation treatment for breast cancer. In order to monitor the benefits of treatment for breast lymphoedema it is important to be able to measure the severity of the condition and changes that occur with treatment. The aim of our study is to develop a questionnaire, specifically designed for this. As you have been treated at Royal Perth Hospital for breast lymphoedema following breast cancer treatment in the past, we are inviting to you participate in our research.
This study has been approved by the Royal Perth Hospital Human Research Ethics Committee and the Human Research Ethics Committee, Curtin University, Western Australia.

Your role in the trial
If you agree to be involved in this study you will be asked to attend the Physiotherapy Department once for an interview. During the interview you will be asked about the symptoms you have experienced associated with your breast lymphoedema. You will also be asked to rank the symptoms from most important to least important to you. The interview will take approximately an hour. Your responses will be collated with responses from other ladies who volunteer for the study to create a questionnaire, specifically for breast lymphoedema. Although notes will be taken during the interview, these will be completely anonymous.
If you live in the country and travelling to Perth is not possible, you maybe able to have a tele-interview. This would involve attending your local hospital for a telephone and television hook up, made from your local hospital, with myself at Royal Perth Hospital.
There will be some re-embursement for the cost of travel and parking to attend the interview at Royal Perth Hospital. Ten dollars ($10) will be provided to you for this.
As Curtin University is providing this money, I will need you to sign a form that says you received this money from me. This form and the signed consent form will be the only records of your involvement.

Participation in the study is entirely voluntary. You do not have to join the study and choosing not to volunteer will not affect any future physiotherapy that you might need.

If you would like to be involved in the study please return the enclosed form in the replied paid envelope and we will contact you to make an appointment for the interview. If you would like to talk to me in regards to any questions or concerns about this project, please ring me on 9224 2076, Monday to Friday, 8am-430pm.

If you are not interested, please do not reply to this letter.
Thank you for taking the time to read this letter and considering helping with this research.

Yours sincerely,

Christine Smith
Senior Physiotherapist
Lymphoedema/Oncology
Royal Perth Hospital

Masters student
Curtin University

Appendix 9

CONSENT TO AGREE TO BE CONTACTED AND PARTICIPATE IN THE DEVELOPMENT OF A BREAST LYMPHOEDEMA QUESTIONNAIRE (PART A)

I,…… agree/disagree to be contacted and participate in the study described above. I have read and understood the attached Information Sheet and I have retained a copy of the signed document. I have been given the opportunity to ask questions about the study by the investigator. I understand that I may withdraw from the study at any time without affecting any future physiotherapy treatment, or the treatment of the condition which is the subject of the study.

Signed…….. Date…….

Time, day and number to contact you to make an appointment…….

……

Signature of Investigator……. Date…….

Appendix 10

ROYAL PERTH HOSPITAL

<Subject's name>
<Subject's address>
<Suburb, Post code> 12 October 2008

Dear <Subject's name>,

Earlier this year you were contacted by myself in regards to participating in an interview in regards to your breast lymphoedema.
Due to a poor response, I am writing to you again. There may have been a problem with you not receiving the initial letter. So far 28 women have agreed to be involved, but 50 women are needed to make this research scientifically sound.
In the past you have been treated for breast lymphoedema due to breast cancer treatment at Royal Perth Hospital.
At that time, the physiotherapist would have explained to you that not much is known about the symptoms of breast lymphoedema.
Now more women are having surgery (only removing part of their breast), followed by radiotherapy to treat breast cancer. Due to this and as more women are surviving from breast cancer, it is important that there is a greater understanding what breast lymphoedema includes.

The Ethics Committee of Royal Perth Hospital has allowed me to access your notes, and to contact you again to ask if you would be interested in being involved in a study. This study involves interviewing you once to find those symptoms of breast lymphoedema. Only your answers to these questions will be recorded, but no other details. If you are not interesting in taking part, there will be no further contact from myself. This will not affect any future physiotherapy that you might need.
Once 50 women are interviewed, a questionnaire will be written. This will be given to another 10 women to check its structure and how clear it reads.
If you would like to be involved in the study, please read the consent form. If you are interested, please sign and send the consent form back in the replied paid envelope. The physiotherapy receptionist will ring you to book an appointment.

If you are not interested, please sign and send the consent form back in the replied paid envelope. I will not contact you again on this matter.
Thank you for taking the time to read this letter and considering helping with this research.
If you would like to talk to me in regards to any questions or concerns about this project, please ring me on 9224 2076, Monday to Friday, 8am-430pm.
Thanks again,

Yours sincerely,

Christine Smith
Senior Physiotherapist
Lymphoedema/Oncology
Royal Perth Hospital

Masters student
Curtin University

CONSENT TO AGREE TO BE CONTACTED AND PARTICIPATE IN THE DEVELOPMENT OF A BREAST LYMPHOEDEMA QUESTIONNAIRE (PART A)

I,…… agree/disagree to be contacted and participate in the study described above. I have read and understood the attached Information Sheet and I have retained a copy of the signed document. I have been given the opportunity to ask questions about the study by the investigator. I understand that I may withdraw from the study at any time without affecting any future physiotherapy treatment, or the treatment of the condition which is the subject of the study.

Signed…….. Date…….

Time, day and number to contact you to make an appointment…….

……

Signature of Investigator……. Date…….

Appendix 11

Clinical and demographic characteristics of interview patients

ID Number: Date of Data Collection / / 2008	
Date of definitive diagnosis	
/ /	
Date of surgery	
/ /	
Age when having surgery	
20-29	
30-39	
40-49	
50-59	
60-69	
70-79	
80-89	
Menopausal state	
1.Premenopausal	
2.Perimenopausal	
3.Postmenopausal	
Surgery	
1.Wide local excision	
2.Other specify	
Staging	
Stage	
T	
N	
M	
Position of incision	
1.Upper inner quadrant	
2.Upper outer quadrant	
3.Lower inner quadrant	
4.Lower outer quadrant	
5.Central	
6.Axillary tail	
Side of tumour	
1.Left	

2.Right	
Pathological tumour size (cm)	
0-0.9	
1.0-1.9	
2.0-2.9	
>3.0	
Unknown	
Tumour grade	
1.1	
2.11	
3.111	
4.Unknown	
Histological type	
1.Ductal	
2.Lobular	
3.Mixed ductal and lobular	
4.Special types	
5.Not reported	
Receptor status	
1.Oestrogen	
2.Progesterone	
3.Unknown	
Node status	
1.Positive	
2.Negative	
3.Unknown	
Axillary surgery	
1.None	
2.Axillary clearance- Grade 1	
Grade 11	
Grade 111	
Sentinel node biopsy	
Unknown	
Adjuvant treatment	
1.None	
2.Neoadjuvant chemotherapy	
3.Chemotherapy	
4.Radiation therapy	

5.Endocrine therapy	
Post operative complications	
1.Seroma	
2.Haematoma	
3.Infection	
4.Cording	
Past medical history	
Medications	
Current Age	
Years	
Dominant side	
1.Left	
2.Right	
3.Unknown	
Country of birth	
1.Australia	
2.Canada	
3.China	
4.Greece	
5.Hong Kong	
6.India	
7.Italy	
8.Malta	
9.Malaysia	
10.Middle East (Turkey, Lebanon)	
11.New Zealand	
12.Other Asia	
13.Other European	
14.Philippines	
15.Poland	
16.UK	
17.US	
18.Vietnam	
19.Other specify	

Indigenous status	
Aboriginal	
Torres Strait Islander	
Marital status	
1.Single	
2.Married	
3.De facto	
4.Divorced	
5.Widow	
Child bearing	
1.Nulliparous	
Number of births specify	
Breast fed	
Unknown	
Level of education	
1.No school certificate or other qualifications	
2.School or intermediate certificate	
3.High school or leaving certificate	
4.Trade/apprenticeship	
5.Certificate/diploma	
6.Undergraduate degree	
7.University degree	
8.Post graduate qualifications	
Employment activity	
1.Student	
2.Unemployed	
3.Home duties	
4.Not able to work	
5.Pension	
6.Voluntary work	
7.Part time work	
8.Full time work	
Occupation-	
Time of breast lymphoedema diagnosis (post surgery)	
Years	
Months	

Appendix 12

Item Elicitation Questionnaire

(Interviewer to read to patient)

I am Christine Smith, a senior physiotherapist working in Lymphoedema/Oncology at Royal Perth Hospital, Western Australia. I am developing a questionnaire to measure the health status of women with breast lymphoedema, as a result of breast cancer treatment.

This step involves conducting interviews with women who have previously been treated for breast lymphoedema, to gather items to include in the questionnaire. Those items that you have identified as being relevant with breast lymphoedema will be collated with information from clinicians and the literature. This will be used to develop the final questionnaire.

Interviewer- Refer to appendix one for the abbreviations used in table one.

If more room is required for the open ended responses, refer to appendix two and three for an additional response tables.

Symptoms

Interviewer to read to patient-

The following questions are interested in how you perceive your breast lymphoedema.

What terms would you most commonly use to describe your symptoms of breast lymphoedema?

Table One

Symptom	Occur.		Frequency					Importance				
	Y	N	C	D	W	F	≤M	N	S	M	V	E
1. Swelling												
2. Discomfort												
3. Heaviness												
4. Pain												
5. Hypersensitive												
6. Tightness												
7. Tenderness												
8. Uncomfortable												
9. Ache												
10.												
11.												
12.												
13.												
14.												
15.												
16.												
17.												

For each symptom, to further explore the dimensionality of that symptom, ask-

1. Is _____ (name the symptom) there constantly or on and off?
   If on and off, how often (using the above scale) is _____ (name the symptom) there?

2. How important is (name the symptom) this to you?

For the responses volunteered by the patient, probe further with the following questions-

1. Why is _____ (name the symptom) important to you?
   _____
   _____
   _____
   _____

2. How does _____ (name the symptom) affect you?
   _____
   _____
   _____
   _____

3. When does _____ (name the symptom) affect you?
   _____
   _____
   _____
   _____

Additional closed ended questions to patient-

Do you consider the following terms to mean the same or do they have different meanings?
For either response ask the patient to explain the similarities or differences of the terms.

Table Two

Terms	Same	Different	Rationale
Swelling and tightness			
Swelling and hardness			
Tightness and hardness			
Discomfort and pain			
Discomfort and tenderness			
Pain and tenderness			
Heaviness and tightness			
Discomfort and uncomfortable			
Discomfort and ache			
Pain and ache			
Uncomfortable and ache			

Signs

Interviewer to read to patient-

What terms would you most commonly use to describe your signs of breast lymphoedema?

Table Three

Sign	Occur.		Frequency					Importance				
	Y	N	C	D	W	F	≤M	N	S	M	V	E
1. Redness												
2. Hardness												
3. Orange peel type skin on the L/O breast												
4. Increased warmth												
5. Thickened skin												
6. Pinkness												
7. Heat												
8.												
9.												
10.												
11.												
12.												

For each sign, to further explore the dimensionality of that sign, ask-

1. Is _____ (name the sign) there constantly or on and off?
   If on and off, how often (using the above scale) is _____ (name the sign) there?

2. How important is this to you?

For the responses volunteered by the patient, probe further with the following questions-

1. Why is _____ (name the sign) important to you?
   _____
   _____
   _____

2. How does _____ (name the sign) affect you?
   _____
   _____
   _____

3. When does _____ (name the sign) affect you?
   _____
   _____
   _____

Additional closed ended questions to patient-

Do you consider the following terms to mean the same or do they have different meanings?
For either response ask the patient to explain the similarities or differences of the terms.

Table Four

Terms	Same	Different	Rationale
Redness and pinkness			
Heat and increased warmth			
Hardness and thickened skin			

Physical limitations

Interviewer to read to patient-
These next questions are interested in how your breast lymphoedema has affected the way you manage activities.

What physical limitations do you have as a result of your breast lymphoedema?

Table Five

Physical Limitation	Occur.		Frequency					Importance				
	Y	N	C	D	W	F	≤M	N	S	M	V	E
1. Indentations of the bra on the L/O breast												
2. Decrease in shoulder movement												
3. Reaching above your shoulder												
4. Putting on/ taking off a bra												
5. Doing housework												
6.												
7.												
8.												
9.												
10.												
11.												
12.												

For each physical limitation, to further explore the dimensionality of that physical limitation, ask-

1. Is _____ (name the physical limitation) there constantly or on and off?
If on and off, how often (using the above scale) is _____ (name the physical limitation) there?

2. How important is this to you?

For the responses volunteered by the patient, probe further with the following questions-

1. Why is _____ (name the physical limitation) important to you?
   _____
   _____
   _____
   _____

2. How does _____ (name the physical limitation) affect you?
   _____
   _____
   _____
   _____

3. When does _____ (name the physical limitation) affect you?
   _____
   _____
   _____
   _____

Emotional

Interviewer to read to patient-
The next questions are interested in how your breast lymphoedema affects your emotional well being. This includes such things as being happy with your life.

What terms would you most commonly use to describe how your breast lymphoedema makes you feel?

Table Six

Emotional	Occur.		Frequency					Importance				
	Y	N	C	D	W	F	≤M	N	S	M	V	E
1. Fear of breast cancer recurrence												
2. Appearance of the breast												
3. Reminder of breast cancer												
4. Distress												
5. Anxious												
6. Fear												
7. Depressed												
8. Frustrated												
9. Embarrassed												
10. Self – conscious												
11. Affects choice of clothing												
12. Tired												
13. Affect relationship with family												
14. Affect relationship with friends												
15.												
16.												

For each emotion, to further explore the dimensionality of that emotion, ask-
1. Is _____ (name the emotion) there constantly or on and off?
If on and off, how often (using the above scale) is _____ (name the emotion) there?
2. How important is this to you?

For the responses volunteered by the patient, probe further with the following questions-

1. Why is _____ (name the emotion) important to you?
   _____
   _____
   _____

2. How does _____ (name the emotion) affect you?
   _____
   _____
   _____

3. When does _____ (name the emotion) affect you?
   _____
   _____
   _____

Additional closed ended questions to patient-

Do you consider the following terms to mean the same or do they have different meanings?
For either response ask the patient to explain the similarities or differences of the terms.

Table Seven

Terms	Same	Different	Rationale
Distress and fear of recurrence			
Feels self conscious about appearance and feels less feminine			
Feels self conscious about appearance and embarrassed			

Social

Interviewer to read to patient-
The next questions are interested in how your breast lymphoedema affects your ability to interact at work, with family and/or friends.

What terms would you most commonly use to describe how your breast lymphoedema affects how you function?

Table Eight

Social	Occur.		Frequency					Importance				
	Y	N	C	D	W	F	≤M	N	S	M	V	E
1. Difficulty wearing a bra												
2. Difficulty sleeping												
3. Discomfort wearing a bra												
4. Affects ability to do ADL's												
5. Affects occupational activities												
6. Affects sporting activities												
7. Affects intimate relationships												
8.												
9.												
10.												
11.												
12.												

For each social response, to further explore the dimensionality of that social response, ask-

1. Is _____ (name the social response) there constantly or on and off?
If on and off, how often (using the above scale) is _____ (name the social response) there?
2. How important is this to you?
For the responses volunteered by the patient, probe further with the following questions-

1. Why is _____ (name the social response) important to you?

_____
_____
_____
_____

2. How does _____ (name the social response) affect you?

_____
_____
_____
_____

3. When does _____ (name the social response) affect you?

_____
_____
_____
_____

Additional closed ended questions to patient-

Do you consider the following terms to mean the same or do they have different meanings?
For either response ask the patient to explain the similarities or differences of the terms.

Table Nine

Terms	Same	Different	Rationale
Discomfort wearing a bra and difficulty wearing a bra			

Is there anything else you would like to add?
Thank you for participating in the development of the BLYSS questionnaire.

Abbreviations Used in the Tables

Frequency-

C- constantly
D- daily
W- weekly
F- fortnightly
≤M- less than and/or monthly

Importance-

N- not
S- slightly
M- moderately
V- very
E- extremely

Additional Table

Group	Occur.		Frequency					Importance				
	Y	N	C	D	W	F	≤M	N	S	M	V	E
1.												
2.												
3.												
4.												
5.												
6.												
7.												
8.												
9.												
10.												
11.												
12.												

Additional Table Two

Terms	Same	Different	Rationale

Probing open ended questions

For the responses volunteered by the patient, probe further with the following questions-

1. Why is _____ (name the group) important to you?
   _____
   _____
   _____
   _____

2. How does _____ (name the group) relate to your breast lymphoedema?
   _____
   _____
   _____
   _____

3. When does _____ (name the group) affect you?
   _____
   _____
   _____
   _____

Appendix 13

Symptomology

Symptom	Rest		Activity		Night	
	Yes	No	Yes	No	Yes	No
1. Swelling						
2. Discomfort						
3. Heaviness						
4. Pain						
5. Hypersensitive						
6. Tightness						
7. Tenderness						
8. Uncomfortable						
9. Ache						

Appendix 14
Breast Lymphoedema Symptoms Severity (BLYSS) Questionnaire

Name: _____ Institution: _____ Date: _____

This questionnaire is designed for women who have breast swelling/lymphoedema as a result of breast cancer treatment. Please grade the severity of the following items in the affected breast. To start, please circle which breast is the swollen/lymphoedematous breast.

LEFT RIGHT

Considering the **last seven days**, circle the response that best describes what you have felt in your affected breast. Choose the answer that best applies to you. Circle only one box for each question.						
1	How severe is any swelling in your breast? For example one breast may look larger than the other and/or feel larger.	None	Mild	Moderate	Severe	Extreme
2	How severe is any discomfort in your breast? Words like ache or mild pain may describe this experience.	None	Mild	Moderate	Severe	Extreme
3	How severe is any heaviness in your breast? Words like a weight and/or dragging down might describe this experience.	None	Mild	Moderate	Severe	Extreme
4	How severe is any uncomfortable feeling in your breast? This could be considered an unpleasant awareness that maybe associated with clothing and/ or positioning.	None	Mild	Moderate	Severe	Extreme
5	How severe is any hardness in your breast? Words like solid, firm to touch and/or a feeling of firmness might describe this.	None	Mild	Moderate	Severe	Extreme
6	How severe is any discomfort in your breast when wearing a bra?	None	Mild	Moderate	Severe	Extreme
7	How severe are any indentations on your breast from the bra?	Not at all	Mild	Moderate	Severe	Extreme

Now please turn over to complete the questionnaire

Breast Lymphoedema Symptoms Severity Questionnaire (BLYSS)

Considering the **last seven days**, circle the response that best describes what you have felt in your affected breast. There are no right or wrong answers. Circle only one box for the question.						
1	How often do your symptoms of breast lymphoedema cause you to remember the breast cancer?	Never	Occasionally	Some days	Every day	Constantly

Considering the **last year**, answer each question by placing a circle around the response that best describes what you have felt in your affected breast during the following events. There are no right or wrong answers. Circle only one box for each question.							
1	Please grade the severity to which mammograms have been more uncomfortable than previously.	Not applicable	Not at all	Mild	Moderate	Severe	Extreme
2	Please grade the severity to which breast ultrasounds have been more uncomfortable than previously.	Not applicable	Not at all	Mild	Moderate	Severe	Extreme
3	Please grade the severity to which the breast lymphoedema is more of a problem in summer/hot weather.	Not applicable	Not at all	Mild	Moderate	Severe	Extreme

Thank you for completing this questionnaire

Appendix 15

How to score the BLYSS

There are four scores of the BLYSS questionnaire (BLYSS I-IV). Due to the differences of each domain, a single score is not suitable. Each domain is explained below.

BLYSS I- "Appearance and Experience" is the score for the first domain, which are those signs and symptoms to be associated with breast lymphoedema. The scores range from 0-4, resulting in a range of responses from 0-28.

BLYSS II- "Memory" is the score pertaining to the second domain. This domain asks if the symptoms of breast lymphoedema are a reminder of the breast cancer experience. The scores range from zero to four, resulting in a range of responses from 0-4.

BLYSS III- "Assessments" is the score for the first two items in the third domain. These two items question whether investigations are now more uncomfortable as a result of breast lymphoedema. The scores range from zero to five, resulting in a range of responses from 0-10.

BLYSS IV-"Weather" is the score for the third item in the third domain. This item asks if summer exacerbates the patient's breast lymphoedema. The scores range from zero to five, resulting in a range of responses from 0-5.

Scoring table for the BLYSS questionnaire

Date	BLYSS 1	BLYSS 11	BLYSS 111	BLYSS 1V

Appendix 16

ROYAL PERTH HOSPITAL

The development of the Breast Lymphoedema Severity Symptom Questionnaire (BLYSS).

Investigator: Christine Smith, Department of Physiotherapy

Trial summary

Breast lymphoedema can develop after the treatment for breast cancer. To date, there are no reliable or valid ways of assessing the symptoms of breast lymphoedema. The aim of this study is to develop a questionnaire, specifically designed for this purpose.

This study has received ethical approval from the Royal Perth Hospital Ethics Committee and the Curtin University Human Research Ethics Committee.

Your role in the trial

If you agree to be involved in this study you will be contacted and ask to attend the physiotherapy department for an interview on one occasion with the research investigator.
During this interview you will be asked to comment on the relevance of the items and whether the questionnaire is comprehensive.

Once the interviews are finished, your responses will be collated with responses from other clinicians and patients to refine the questionnaire, specifically for breast lymphoedema.

How your personal information will be handled

Special arrangements are in place to ensure that your data is handled in strict confidence and in compliance with all privacy laws (in Australia this is the Privacy Act 1988). Your name will not appear on study documents and only duly authorised persons will have access to your data. Your name will also not appear on any publications arising from the study.

Cost of participation in the trial

Participation in the study will be at no cost to you.
If you chose not to participate in the study, this will have no consequences on future physiotherapy service provision.

Further information

There are several sources of additional information:

1. Feel free to ask the interviewer questions about the study.
2. For questions relating to ethical approval, contact the Chairman of the Ethics Committee, A/Professor FM van Brockxmeer, on 9224 2244.

During the study you can telephone Christine Smith (Senior Physiotherapist) during weekdays, 8am-430pm, on 9224 2076 if other questions occur to you.

If after reading this sheet you are interested in enrolling in the study you should now sign the CONSENT FORM. Please put this in the replied envelope provided and post.

Thank you for considering participating in this study.

Appendix 17

CONSENT TO BE CONTACTED AND PARTICIAPTE IN THE DEVELOPMENT OF A BREAST LYMPHOEDEMA QUESTIONNAIRE

I,…… agree/disagree to be contacted and participate in the above study. I have read and understood the attached Information Sheet and I have retained a copy of the signed document. I have been given the opportunity to ask questions about the study by the investigator. I understand that I may withdraw from the study at any time without affecting any future physiotherapy service provision.

Signed…….. Date…….

Time, day and number to contact you to make an appointment…….

……

Signature of Investigator……. Date…….

Appendix 18

ROYAL PERTH HOSPITAL

The development of the Breast Lymphoedema Severity Symptom Questionnaire (BLYSS).

Investigator: Christine Smith, Department of Physiotherapy

Trial summary

Breast lymphoedema can develop after your treatment for breast cancer. To date, there are no reliable or repeatable ways of detecting and monitoring the symptoms of breast lymphoedema. The aim of this study is to develop a questionnaire, specifically designed for this purpose.

This study has received ethical approval from the Royal Perth Hospital Ethics Committee and the Curtin University Human Research Ethics Committee.

Your role in the trial

If you agree to be involved in this study you will be contacted, at a day and time suitable for you. You will be asked to attend the physiotherapy department for an interview on one occasion with the research investigator.
During this interview you will be asked to complete the new questionnaire and then to provide feedback about the clarity of the questionnaire and the relevance of the questions. You will be asked to comment on what you believe the question to be asking, what they meant by your answer and the wording of the question. If necessary, the questionnaire will be revised according to feedback received.

Once the interviews are finished, your responses will be collated with responses from other ladies to refine the questionnaire. If necessary, the questionnaire will be revised according to feedback received.

How your personal information will be handled

Special arrangements are in place to ensure that your data is handled in strict confidence and in compliance with all privacy laws (in Australia this is the Privacy Act 1988). Your

name will not appear on study documents and only duly authorised persons will have access to your data. Your name will also not appear on any publications arising from the study.

Cost of participation in the trial

Participation in the study will be at no cost to you.
If you chose not to participate in the study, this will have no consequences on future physiotherapy treatments.

Further information

There are several sources of additional information:

1. Feel free to ask your physiotherapist questions about the study.
2. For questions relating to ethical approval, contact the Chairman of the Ethics Committee, A/Professor FM van Brockxmeer, on 9224 2244.

During the study you can telephone Christine Smith (Senior Physiotherapist) during weekdays, 8am- 430pm, on 9224 2076 if other questions occur to you.

If after reading this sheet you are interested in enrolling in the study you should now sign the CONSENT FORM. Please put this in the replied envelope provided and post.

Thank you for considering participating in this study.

Appendix 19

CONSENT TO AGREE TO BE CONTACTED AND PARTICIPATE IN THE DEVELOPMENT OF A BREAST LYMPHOEDEMA QUESTIONNAIRE

I,…… agree/disagree to be contacted and participate for the above study. I have read and understood the attached Information Sheet and I have retained a copy of the signed document. I have been given the opportunity to ask questions about the study by the investigator. I understand that I may withdraw from the study at any time without affecting any future physiotherapy treatment, or the treatment of the condition which is the subject of the study.

Signed…….. Date…….

Time, day and number to contact you to make an appointment…….

……

Signature of Investigator……. Date…….

Appendix 20

Pilot testing Interview of the BLYSS Questionnaire

The items within the BLYSS questionnaire are based on a literature review, interviews with clinicians (working in the assessment and treatment of patients with breast oedema/ lymphoedema) and interviews with patients with breast oedema/lymphoedema.

Those items elicited from the literature and clinicians formed the template interviews with patients.
The responses from patients formed the items contained in the BLYSS.

The BLYSS is designed only for women who have developed breast oedema/ lymphoedema as a result treatment for breast cancer.
At this stage, the BLYSS questionnaire is only designed for use in women with unilateral breast oedema/lymphoedema.

Content

Generally, do you think the content is relevant to the topic?

Does the second sentence make sense i.e. which is the lymphoedematous breast?

Do I need to make this clearer e.g. please circle which breast is affected?

Items

As a clinician, are these items representative as those items associated with breast lymphoedema? Yes/No. Please elaborate.

What else could be included? Please elaborate.

Should any of these items be excluded? Please elaborate.

Does the explanation attached to each item make sense to you? Yes/ No

How would you describe –

(1) Swelling-

(2) Discomfort-

(3) Heaviness-

(4) Uncomfortable

(5) Hard-

(6) Discomfort in the breast when wearing a bra-

Are the descriptors (not at all – extremely) sufficient to describe the items?
Yes/No

Structure

What do you like about the layout of the questionnaire?

What could be improved in regards to the layout of the questionnaire?

In regards to the size of the text, is it easy to read? Yes/No.

Are two pages sufficient for the questionnaire? Yes/No.

Additional comments

Appendix 21

Modified Harris Score

1. None- excellent aesthetic result. At first sight no visible therapy related sequelae. Both breasts have similar appearance
2. Mild- treated breast nearly identical to untreated breast.
3. Moderate- treated breast slightly different than untreated.
4. Severe- treated breast clearly different from untreated but not seriously distorted
5. Extreme- treated breast seriously distorted

Appendix 22

Harris Score

1. Excellent- treated breast nearly identical to untreated breast.
2. Good- treated breast slightly different than untreated.
3. Fair- treated breast clearly different from untreated but not seriously distorted
4. Poor- treated breast seriously distorted

(Harris et al 1979)

Appendix 23

GENERAL HEALTH QUESTIONNAIRE

GHQ-12

Please read this carefully:

We should like to know if you have had any medical complaints, and how your health has been in general, *over the past few weeks*. Please answer ALL the questions simply by underlining the answer which you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those you had in the past. It is important that you try to answer ALL the questions.

Thank you very much for your co-operation.

HAVE YOU RECENTLY:

1 -	**been able to concentrate on whatever you're doing?**	Better than usual	Same as usual	Less than usual	Much less than usual
2 -	**lost much sleep over worry?**	Not at all	No more than usual	Rather more than usual	Much more than usual
3 -	**felt that you are playing a useful part in things?**	More so than usual	Same as usual	Less useful than usual	Much less useful
4 -	**felt capable of making decisions about things?**	More so than usual	Same as usual	Less so than usual	Much less capable
5 -	**felt constantly under strain?**	Not at all	No more than usual	Rather more than usual	Much more than usual
6 -	**felt you couldn't overcome your difficulties?**	Not at all	No more than usual	Rather more than usual	Much more than usual
7 -	**been able to enjoy your normal day-to-day activities?**	More so than usual	Same as usual	Less so than usual	Much less than usual
8 -	**been able to face up to your problems?**	More so than usual	Same as usual	Less able than usual	Much less able
9 -	**been feeling unhappy and depressed?**	Not at all	No more than usual	Rather more than usual	Much more than usual
10 -	**been losing confidence in yourself?**	Not at all	No more than usual	Rather more than usual	Much more than usual
11 -	**been thinking of yourself as a worthless person?**	Not at all	No more than usual	Rather more than usual	Much more than usual
12 -	**been feeling reasonably happy, all things considered?**	More so than usual	About same as usual	Less so than usual	Much less than usual

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Appendix 24

SIR CHARLES GAIRDNER HOSPITAL

ROYAL PERTH HOSPITAL

The development of the Breast Lymphoedema Severity Symptom Questionnaire (BLYSS).

Investigator: Christine Smith, Department of Physiotherapy

Trial summary

Breast lymphoedema can develop after your treatment for breast cancer. To date, there are no reliable or repeatable ways of detecting and monitoring the symptoms of breast lymphoedema. The aim of this study is to develop a questionnaire, specifically designed for this purpose.

This study has received ethical approval from the Royal Perth Hospital Ethics Committee and the Curtin University Human Research Ethics Committee, Curtin Health Innovation Research Institute.

Your role in the trial

If you agree to be involved in this study you will be contacted, at a day and time suitable for you. You will be asked to attend the Breast Clinic at Royal Perth Hospital for an interview on one occasion with the research investigator, Breast Clinic Nurse and Breast Clinic Physiotherapist of the Royal Perth Hospital Breast Clinic.
During this interview your breasts will be viewed by the nurse and then the physiotherapist to grade the severity of breast lymphoedema. You will also be asked to complete the new questionnaire (the BLYSS) and a general health questionnaire (the GHQ-12).

Twenty four hours later you will fill in the BLYSS questionnaire again, at home. The researcher can ring you to remind you to do this. You will then mail the completed questionnaire in the supplied reply paid envelope to the researcher.

How your personal information will be handled

Special arrangements are in place to ensure that your data is handled in strict confidence and in compliance with all privacy laws (in Australia this is the Privacy Act 1988). Your name will not appear on study documents and only duly authorised persons will have access to your data. Your name will also not appear on any publications arising from the study.

Cost of participation in the trial

Participation in the study will be at no cost to you.
If you chose not to participate in the study, this will have no consequences on future treatments.

Further information
There are several sources of additional information:

1. Feel free to ask your physiotherapist questions about the study.
2. For questions relating to ethical approval, contact the Chairman of the Ethics Committee, A/Professor FM van Brockxmeer, on 9224 2244 at Royal Perth Hospital or Sir Charles Gairdner Hospital Human Research Ethics Committee, on 9346 2999.

During the study you can telephone Christine Smith (Senior Physiotherapist) during weekdays, 8am-430pm, on 9224 2076 if other questions occur to you.
If after reading this sheet you are interested in enrolling in the study you should now sign the CONSENT FORM. Please put this in the replied envelope provided and post.

Thank you for considering participating in this study.

Appendix 25

CONSENT TO AGREE TO BE CONTACTED AND PARTICIPATE IN THE DEVELOPMENT OF A BREAST LYMPHOEDEMA QUESTIONNAIRE

I,…… agree/disagree to be contacted and participate in the study described above. I have read and understood the attached Information Sheet and I have retained a copy of the signed document. I have been given the opportunity to ask questions about the study by the investigator. I understand that I may withdraw from the study at any time without affecting any future physiotherapy treatment, or the treatment of the condition which is the subject of the study.

Signed…….. Date…….

Time, day and number to contact you to make an appointment…….

……

Signature of Investigator……. Date…….

Appendix 26

Breast Lymphoedema Definition

Location

The adult female breast lies between the second and sixth ribs in the vertical axis and between the sternal edge and the midaxillary line in the horizontal axis (187)(p929-930). The average breast measures 10 to 12cm in diameter, and its average thickness centrally is 5 to 7cm. Breast tissue also projects into the axilla as the axillary tail of Spence. The contour of the breast varies but is usually dome-like, with a conical configuration in the nulliparous woman and a pendulous contour in the parous woman.

The shape of the breast may be altered due to aging, surgical removal of the tumour and surrounding tissue, radiotherapy, and oedema and/or breast lymphoedema.

Main part of the breast is superficial to the deep fascia covering Pectoralis Major, several digitations of Serratus Anterior and External Oblique and upon the upper part of the latters' aponeurosis forming the rectus sheath (187)(p929-930).

The breast can be divided into quadrants to consistently identify location of breast lymphoedema. This is illustrated in Table One and Diagram One.

Table One: Breast quadrants

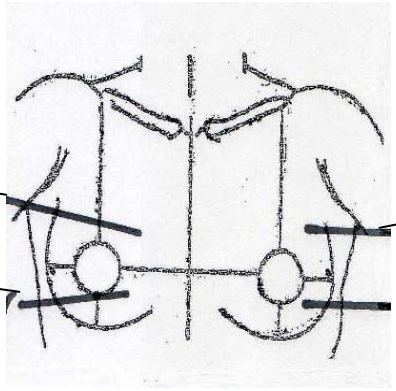
1. Lateral superior
2. Lateral inferior
3. Medial inferior
4. Medial superior

Nature

Secondary lymphoedema post breast cancer breast is "characterised by an abnormal accumulation of lymph fluid in the interstitial spaces, leading to persistent swelling in the breast" (for breast definition see location section above)(35)(48).

Table two, based on the ISL grading for peripheral lymphoedema, grades the stage of breast lymphoedema.

Diagram One: Breast quadrants



Timing

Breast lymphoedema consists of swelling in the breast that persists equal or greater to three months post surgery and/or radiotherapy.

Differential diagnosis

Diagnoses other than breast lymphoedema must be taken into account and excluded before a diagnosis of breast lymphoedema should/can be considered.

Other conditions include-

- Primary or secondary breast cancer
- Inflammatory breast carcinoma
- Breast lymphoma
- Thymic carcinoma
- Angiosarcoma
- Congestive Cardiac Failure (CCF)
- Infection including cellulitis
- Mastitis
- Subclavian or innominate vein occlusion (such as from arteriovenous haemodialysis complications)
- Trauma
- Post irradiation
- Fat necrosis
- Granulomatous diseases
- Pemphigus and other skin conditions
- Aseptic inflammatory process

Table Two: ISL Grading

ISL Grading
I. Latent or at risk
II. Intermittent with pitting
III. Persistent with pitting/or fibrotic
IV. Fibrotic and skin changes

Appendix 27

Definitions for Differential Diagnoses

Primary breast cancer- "a malignant neoplastic disease of the mammary gland" (188)(p.242-43).

Secondary breast cancer- "most patients with a locoregional recurrence of breast cancer following breast conservation therapy (BCT) present with symptoms. Ipsilateral breast tumour recurrence following BCT is experienced by five years in approximately seven percent of patients with whole breast irradiation and 26% of patients without whole breast irradiation. Most recurrences occur in the prior tumour bed, and positive pathologic margins, younger age, higher grade tumour, negative oestrogen receptor status and involvement of axillary nodes have all been reported to increase the risk of ipsilateral tumour recurrence. Detection of ipsilateral breast tumour recurrence is often difficult because of post surgical and postradiotherapy changes to the breast" (189)(p 824).

Inflammatory breast carcinoma- "is a type of locally advanced breast cancer which arises rapidly, typically over weeks, less than six months, not years. Clinical features include discolouration ranging from red to purple, and affecting at least one third of the breast, thickening or fine dimpling (peau d'orange), oedema or warmth and a palpable ridge present at the margin of induration" (190)(p762).

Breast lymphoma- "has been defined used the following criteria: (a) no prior diagnosis of extramammary lymphoma and the breast is the primary site of disease; (b) mammary tissue and lymphomatous infiltrate are in close association with no evidence of concurrent widespread disease; and (c) pathology is confirmed by technically adequate specimens" (191)(p803-804).

"Radiographic imaging features of breast lymphoma are non-specific, with the exception that calcifications are rare. Diagnosis is typically made by core biopsy of a palpable breast mass. High-grade lymphoma needs to be separated from melanoma and poorly

differentiated carcinoma because curative treatment differs radically among these tumour types" (191)(p803-804).

Thymic carcinoma- "a rare, aggressive neoplasm that has a poor prognosis. It is an epithelial tumour but cytologically it demonstrates malignant features. This cancer is most often located in the anterior mediastinum, although other sites have been reported" (192)(p872).

Angiosarcoma- "an aggressive, usually deadly neoplasm of vascular cells. Four variants of cutaneous angiosarcoma have been identified, including angiosarcoma associated with lymphoedema (Stewart-Treves syndrome), and radiation induced angiosarcoma" (193)(p1624-1625).

"Lymphoedema angiosarcoma presents as a violet coloured plaque or nodule superimposed on brawny, nonpitting oedema. Ulceration may develop soon after. The pathogenesis of lymphoedema angiosarcoma is not completely understood but could be related to imbalances in local immune regulation or angiogenesis, leading to proliferation of neoplastic cells" (193)(p1624-1625)..

"Radiation-induced angiosarcoma has been reported to occur after radiation therapy. Lesions appear at sites treated with radiation as a violaceous to red ill-defined plaque, often appearing like a bruise. As the cancer progresses, lesions increase in size, become indurated, and may eventually ulcerate. Satellite lesions are common" (193)(p1624-1625).

Congestive Cardiac Failure (CCF) – "heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs that ability of the heart to function as a pump to support physiological circulation. CCF is similar to the above but with features of dyspnoea, increased fatigue and circulatory congestion (fluid retention) such as jugular venous distension, rales, peripheral oedema and ascites" (194)(p691-692).

Infection including cellulitis and mastitis- "this can affect the skin overlying the breast (cellulitis, with or without abscess formation), and occurs either as a primary event or secondary to a lesion in the skin, such as a sebaceous cyst, or a more generalised condition, such as hidradenitis suppurativa. The most appropriate antibiotics associated with the organisms responsible for the infection should be prescribed. If the infection or inflammation fails to resolve after one course of antibiotics, then abscess formation or an underlying cancer should be suspected" (195)(p47-50).

Subclavian or innominate vein occlusion (such as from arteriovenous haemodialysis complications)- "obstruction of the subclavian veins can occur due to thrombotic obstruction, spontaneously or develop as a result of trauma, extrinsic compression or most frequently in association with catheters used for venous access" (196)(p47- 48).

Trauma- "most breast trauma is self-limited and is manifested by pain, ecchymosis and oedema of the breast. The sequelae of breast trauma are haematoma and fat necrosis. The mammographic appearance of a haematoma can include poorly defined margins suggesting the possibility of carcinoma. Also the opacity of the haematoma may obscure other abnormalities in the breast, so mammography is not usually helpful in the evaluation of acute posttraumatic breast problems" (197)(p43-44).

Post irradiation- "skin reactions associated with radiation that can include post treatment oedema that may persist many months" (198)(p518).

Granulomatous diseases- "are focal chronic inflammatory responses to tissue injury manifested by a histological picture of an accumulation and proliferation of leukocytes, principally of the mononuclear type and its family of derivatives, the mononuclear phagocyte system" (199)(p168-171).

Fat necrosis- “is a benign condition significantly correlated with trauma or surgical intervention, resulting from lipase-induced aseptic saponification of adipose tissue that can create mass like lesions that are difficult to distinguish from carcinoma” (200)(p39).

Pemphigus and other skin conditions- “in this group of immunobullous diseases pemphigus and other skin conditions are characterised by blisters that form within the epidermis with distinct subgroups with many autoantigens identified” (201)(p40.3).

Appendix 28

Granada Learning

INVOICE

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