Enhancing the prospective surveillance and early intervention model of care for women at high risk of developing breast cancer-related lymphoedema

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Abstract

Breast cancer is a major cause of illness burden in Australia, and breast cancer related lymphoedema is known as a significant survivorship issue for an individual following treatment for breast cancer which may impact them physically, psychologically, and financially. Detection of sub-clinical lymphoedema through surveillance and early intervention has been found to reduce progression to clinical lymphoedema. The primary aim of the work presented in this thesis was to explore the prospective surveillance model of care in the early detection and management of breast cancer related lymphoedema and explore ways to enhance this model of care. This primary aim was achieved through the conduct of four clinical research studies with different methodologies over a six-year period.

A retrospective analysis of breast cancer clinical data collected in a private lymphoedema clinic was conducted comparing the traditional model of care to those involved in a prospective surveillance model of care (Study I). This study found that women undergoing early surveillance received lymphoedema care almost two years earlier than women in the traditional referral group. The early surveillance group had significantly lower incidence of clinical lymphoedema than the traditional referral group and those that were diagnosed had significantly less severe lymphoedema.

A qualitative focus group approach (Study II) was carried out to gain an in-depth understanding of attitudes towards lymphoedema home monitoring using bioimpedance spectroscopy (BIS) technology among those at-risk of, or living with, lymphoedema following breast cancer. Five overarching themes were identified regarding perspectives towards home monitoring to improve self-management. These included: Lymphoedema knowledge; Facilitators of self-care; Barriers to self-care; Perceived control; and Overall perceptions of home monitoring. This study supported

the concept of home monitoring using BIS as an adjunct to clinic monitoring and self-management in lymphoedema.

Since women were supportive and encouraged by the concept of home monitoring using BIS technology, a cross-sectional study (Study III) was performed, aimed to assess whether there was a validated device that could reliably take BIS measurements in the home setting. The findings of this study supported impedance measurements being made reliably using a new stand-on device which has the potential to be used within a home setting as an adjunct to in-clinic monitoring for those at high risk for developing lymphoedema.

A feasibility study, (Study IV) was then conducted to determine whether the validated stand-on device could be successfully used as a home monitoring device for women at high risk of developing lymphoedema. This study suggests that a prospective surveillance model of care delivered in the home consisting of BIS monitoring, education and support to promote self-management and physical activity for women at high risk of developing lymphoedema is feasible and has the potential to be beneficial.

The work presented in this thesis has demonstrated that home monitoring in addition to in-clinic monitoring is feasible and may assist in detecting sub-clinical lymphoedema earlier. The findings have highlighted the benefits of adopting a prospective surveillance and early intervention model of care in breast cancer in reducing the incidence of clinical lymphoedema and how the concept of home monitoring using BIS technology may further educate, support and empower individuals in their own self-management following breast cancer.

Statement of Candidate

I, Louise Anne Koelmeyer, hereby declare that the work contained within this Thesis, *Enhancing the prospective surveillance and early intervention model of care for women at high risk of developing breast cancer-related lymphoedema* is my own and has not been submitted to any other educational institution, in part or in whole, as a requirement of a degree.

I, Louise Anne Koelmeyer, hereby declare that I was the principal researcher of all work included in this Thesis, including the work published with multiple authors. A statement from co-authors confirming the authorship contribution of the PhD candidate is provided in each of the relevant chapters.

I, Louise Anne Koelmeyer, also hereby declare that this Thesis is an original piece of work and it is written by me. Any assistance that I have received in the preparation of this Thesis has been appropriately acknowledged. In addition, I also certify that all information sources and literature used are indicated in this Thesis.

Name: Louise Anne Koelmeyer

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Supervisor's Statement

As the supervisors of Louise Anne Koelmeyer's Doctor of Philosophy (PhD) work, we certify that we consider her thesis "Enhancing the prospective surveillance and early intervention model of care for women at high risk of developing breast cancer-related lymphoedema" to be suitable for examination.

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Acknowledgement of Country

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Publications Resulting from this Thesis

This thesis is based on the following original publications which are referred to in the text by Roman numerals. Original publications are reproduced with permission from their copyright holders.

1. **Koelmeyer, L.A**., Moloney, E., Sherman, K.A., Boyages, J. & Dean, C. (2021). Prospective surveillance model in the home for breast cancer related lymphoedema: A feasibility study. *Breast Cancer Research and Treatment. 185,* 401–412. https://doi.org/10.1007/s10549-020-05953-3 [IF 3.940]

2. **Koelmeyer, L.A**., Dean, C., & Boyages, J., & Sherman, K.A. (2020). Understanding home monitoring and self-management in breast cancer related lymphedema – a qualitative study. *Journal of Lymphoedema.* (Accepted 29 October 2020), [IF 0.16]

3. **Koelmeyer, L.A**., Ward, L.C., Dean, C., & Boyages, J. (2020). Body positional effects on bioimpedance spectroscopy measurements for lymphedema assessment of the arm. *Lymphatic Research and Biology.* 18(5), 464-473. https://doi.org/10.1089/lrb.2019.0067, [6 GS citations, IF 1.493]

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Presentations Resulting from this Thesis

1. **Koelmeyer, L.A**., Ward, L.C., Dean, C., & Boyages, J. (2020, 27-30 May). Body positional effects on bioimpedance spectroscopy measurements for lymphoedema assessment of the arm. *13th ALA Virtual Conference, Modern Lymphatics: 2020 Vision.*

2. **Koelmeyer, L.A.,** Borotkanics, R.J., Alcorso, J., Prah, P., Winch, C.J., Nakhel, K., Dean, C., & Boyages, J. (2018, 17-19 May). Prospective surveillance of breast cancer-related lymphoedema results in earlier treatment and decreased disease severity over time. *12th Australasian Lymphology Association Conference*, Brisbane, QLD.

3. **Koelmeyer, L.A.,** Sherman, K.A., & Boyages, J. (2018, 17-19 May). Understanding self-management and home monitoring in breast cancer-related lymphoedema: A qualitative study. *12th Australasian Lymphology Association Conference*, Brisbane, QLD.

4. **Koelmeyer, L.,** Borotkanics, R., Alcorso, J., Winch, C.J., Prah, P., Nakhel, K., & Boyages, J. (2017, 12-14 November). Prospective surveillance of breast cancer-related lymphoedema results in earlier treatment and decreased disease severity over time. *New Zealand Breast Cancer Symposium*, Auckland, NZ.

Professional Awards received during PhD Candidature

Koelmeyer, L., Gaitatzis, K., Nelms, J., Stolldorf, D., Hughes, T.M., Elder, E., French, J., Ngui, N., & Ridner, S.H. (2020, May). "Best Oral Presentation – Clinical/Case Discussion/Quality Improvement", *13th ALA Virtual Conference, Modern Lymphatics: 2020 Vision.*

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1. **Koelmeyer, L.A.,** Thompson, B.M., Mackie, H. Blackwell, R., Heydon-White, A., Moloney, E., Gaitatzis, K., Boyages, J., & Suami, H. (2021). Personalizing conservative lymphedema management using ICG-guided manual lymphatic drainage. *Lymphatic Research and Biology. 19(1), 56-65.* [IF 1.493]

2. Boyages, J., Vicini, F.A., Shah, C., **Koelmeyer, L.A**., Nelms, J.A., & Ridner, S.H. (2021). The risk of subclinical breast cancer-related lymphedema by the extent of axillary surgery and regional node irradiation—a randomized controlled trial. *International Journal of Radiation Oncology Biology Physics. 109*(4), 987-997. [IF 5.859]

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4. Ridner, S.H., Shah, C., Boyages, J., **Koelmeyer, L.,** Ajkay, N., DeSynder, S.M., McLaughlin, S., & Dietrich, M. (2020). L-Dex, arm volume, and symptom trajectories 24 months after breast cancer surgery. *Cancer Medicine*. *9*, 5164-5173. [1 GS citations, IF3.362]

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21. Winch, C.J., Sherman, K.A., Smith, K.M., **Koelmeyer, L.A**., Mackie, H., & Boyages, J. (2016). "You're naked, you're vulnerable": Sexual well-being and body image of women with lower limb lymphedema. *Body Image*. *18*, 123-134. [9 GS citations, IF 3.124]

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24. Alcorso, J., Sherman, K., **Koelmeyer, L**., Mackie, H., & Boyages, J. (2015). Psychosocial factors associated with adherence for self-management behaviors in women with breast cancer-related lymphedema. *Supportive Care Cancer*. *24*(1), 139-146. [29 GS citations, IF 2.698]

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Additional related Presentations during PhD Candidature

1. **Koelmeyer, L.A**., Thompson, B.M., Mackie, H. Blackwell, R., Heydon-White, A., Moloney, E., Gaitatzis, K., Boyages, J., & Suami, H. (2020, 4 October) Personalizing conservative lymphedema management using ICG-guided manual lymphatic drainage. *Lymphatic Education & Research Network, 2020 Centers of Excellence Virtual Summit: State-of-the-Art Lymphatic Medicine.*

2. **Koelmeyer, L.,** Gaitatzis, K., Ridner, S.H., Boyages, J., Nelms, J., Hughes, T.M., Elder, E., French, J., Ngui, N., Hsu, J., & Stolldorf, D. (2020, 27-30 May). Implementing a prospective surveillance and early intervention model into clinical practice: Application of the RE-AIM framework. *13th ALA Virtual Conference, Modern Lymphatics: 2020 Vision.*

3. **Koelmeyer, L.** (2019, 10 November). Lymphoedema: Innovative strategies for assessment and management. *The First Iraqi Medical and Health Professional Conference*, Warwick Farm, NSW.

4. **Koelmeyer, L.A**., & Ward, L.C. (2019, 17-19 May). Survivorship starts with SOZO. Workshop presentation. *Australasian Lymphology Association Symposium*, Sydney, NSW.

5. **Koelmeyer, L.** (2019, 16 May). Understanding lymphoedema following breast cancer. *BCNA Webinar.*

6. **Koelmeyer, L.** (2019, 2 May). An innovative early-intervention model of care for breast cancer survivors. Pre-conference workshop**.** *Klose Conference*, Denver, Colorado, USA.

7. **Koelmeyer, L.** (2019, 28 March). Understanding lymphoedema following breast cancer. *BCNA Webinar.*

8. **Koelmeyer, L.** (2016, 15-17 November). Importance of early diagnosis and regular assessment (conservative management). *COSA 43rd Annual Scientific Meeting*, Gold Coast, QLD.

9. **Koelmeyer, L.** (2016, 25-29 October). Lymphoedema: Innovative strategies for assessment and management. *Leura International Breast Cancer Conference*, Leura, NSW.

10. **Koelmeyer, L.** (2016, 25 July). Seminar presentation: Monitoring for the early detection of cancer related lymphoedema: A proactive approach to early detection, assessment and management, Copenhagen, Denmark.

11. **Koelmeyer, L.** (2016, 21 July). Seminar presentation: Monitoring for the early detection of cancer related lymphoedema: A proactive approach to early detection, assessment and management, London, UK.

12. **Koelmeyer, L.** (2016, 18 July). Seminar presentation: Monitoring for the early detection of cancer related lymphoedema: A proactive approach to early detection, assessment and management, Manchester, UK.

13. **Koelmeyer, L.** (2016, 30 April). Breakfast Symposium: Monitoring for the early detection of cancer related lymphoedema: A proactive approach to early detection, assessment, and management. *Oncology Nursing Society Conference*. San Antonio, USA.

14. **Koelmeyer, L.** (2016, 16 April). Breakfast Symposium: Monitoring for the early detection of cancer related lymphoedema: A proactive approach to early detection, assessment, and management. T*he American Society of Breast Surgeons*, Dallas, USA.

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App	Application
$AUD	Australian Dollars
ALA	Australasian Lymphology Association
ALERT	Australian Lymphoedema Education, Research and Treatment
ALND	Axillary lymph node dissection
BIS	Bioimpedance Spectroscopy
BMI	Body mass index
BC	Breast cancer
BCRL	Breast cancer-related lymphoedema
CT	Chemotherapy
CV	Coefficient of variation
CI	Confidence interval
ECF	Extracellular fluid
GLM	Generalised linear model
HREC	Human Research Ethics Committee
IPEQ	Incidental and Planned Exercise Questionnaire
ICG	Indocyanine green lymphography

ISL	International Society of Lymphology
IQR	Interquartile range
kg	Kilogram
L-Dex U400	Lead device, ImpediMed Limited, Brisbane, Australia
LE	Lymphedema (USA)
LE	Lymphoedema (AUS)
LSIDS-A	Lymphoedema Symptom Intensity and Distress Survey-Arm version 2.0
MDT	Multidisciplinary teams
MRI	Magnetic resonance imaging
NACT	Neoadjuvant chemotherapy
n	Number
PSM	Prospective surveillance and early intervention model of care
RAVI	Relative arm volume increase
RT	Radiotherapy
RCT	Randomised controlled trial
RE-AIM	Reach, Effectiveness, Adoption, Implementation and Maintenance evaluation framework
R0	Resistance a 0 kHz
SLNB	Sentinel lymph node biopsy

SD	Standard deviation
SE	Standard error
SOZO	Stand-on device, ImpediMed Limited, Brisbane, Australia
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TM	Tape measure
TOST	Two one-sided t-tests

CHAPTER 1

Introduction

1.1 Preface

Breast cancer is a major cause of illness burden in Australia (Australian Institute of Health and Welfare [AIHW], 2019) and breast cancer-related lymphoedema is known as a significant survivorship issue for an individual following treatment for breast cancer which may impact them physically, psychologically, and financially (Armer et al., 2013; Hayes et al., 2012). Anecdotally, women living with lymphoedema following breast cancer treatment have reported that "you can hide the fact that you've had breast cancer, however you cannot hide lymphoedema – it is a daily reminder of having had breast cancer".

Despite developments in the management of breast cancer, it does not appear that the incidence and impact of lymphoedema is diminishing. Detection of sub-clinical lymphoedema through surveillance and early intervention has been found to reduce progression to clinical lymphoedema (Armer et al., 2013; Soran et al., 2014; Stout Gergich et al., 2011; Stout Gergich et al., 2008; Stout et al., 2012b). Anecdotally, some medical and healthcare professionals have been dismissive of lymphoedema, reporting that incidence rates have been reducing due to less invasive lymph node surgery. On the breast cancer consumer side, however, lymphoedema remains the "top information need" for those surviving breast cancer which was tabled in the Australian Parliament by Breast Cancer Network Australia in their "State of the Nation Report" published in 2018, p.40, (Breast Cancer Network Australia [BCNA], 2018). Thirty five percent of 15,000 breast cancer survivors reported that "more

needs to be done to educate women around lymphoedema to address fears and concerns and to also help those who do go on to develop lymphoedema", p.40, (BCNA, 2018). Some individuals anecdotally have reported that it is "unfair and not right" that some women have had access to a prospective surveillance and early intervention model of care, and others have not, depending on where a person lives or where they may access their breast cancer treatment. Public health options in Australia for assessment and management of lymphoedema are limited and vary between states which can dramatically increase waiting times for treatment (BCNA, 2018). The cost of treatment by private specialist lymphoedema practitioners, exacerbated by inadequate or no government funded rebates, has created a significant barrier to ongoing lymphoedema treatment in the private sector (BCNA, 2018). A strategically planned approach to determining how this model of care could be implemented routinely across the public and private healthcare settings is needed.

As an occupational therapist and lymphoedema therapist with 30 years of clinical experience working in breast cancer rehabilitation and lymphoedema management, as part of my professional development in 2008, I was introduced to the prospective surveillance and early intervention model of care. At the time I was working as part of a breast cancer multidisciplinary team in two roles - a large publicly funded teaching hospital in Sydney, Australia and as a part-time sole-practitioner in private practice. During this time, I was receiving growing numbers of referrals resulting in long waiting times for individuals requiring intensive management for advanced clinical lymphoedema following breast cancer. In my professional development I also became aware of the Bioimpedance Spectroscopy (BIS) technology that had recently been shown to detect sub-clinical lymphoedema. This sparked my interest as I began thinking that perhaps this prospective surveillance and early intervention model of care could improve quality of life for individuals, reduce the development of clinical lymphoedema and decrease my ever-growing waiting list.

As time has gone by my clinical practice has changed significantly. Individuals are now seen at the time of their breast cancer diagnosis and followed up for holistic breast cancer rehabilitation including education, psychosocial support, lymphoedema monitoring at regular intervals and management of musculo-skeletal issues. I now complete less intensive lymphoedema treatment sessions using multi-layer bandages, and my anecdotal impression is that I am seeing fewer individuals with clinical lymphoedema. Notably many individuals seem to be motivated to be proactive in their own self-management after surgery and report feeling "empowered" and interested in doing whatever they can to reduce the onset of developing lymphoedema.

As a committed and passionate clinician with an interest in making a difference for these individuals, it was time to explore some of the questions I had been thinking about over recent years more formally through PhD studies. I had often wondered myself and had been asked by others whether the prospective surveillance and early intervention model of care for which I had been an "early adopter" was making a difference? I had been practising the traditional model of care for many years and now I was seeing individuals at the time of their diagnosis for breast cancer and ongoingly through their intensive breast cancer treatment which I had not previously. This led me to my first study question:

1. Was there a difference in care use, incidence, and severity of lymphoedema between two models of care (traditional referral compared with the prospective surveillance and early intervention)?

To enhance models of care it is recommended to have a consumer voice and feedback from individuals about their opinions and recommendations. In person-centred care it is beneficial to co-design programs with consumer input and feedback. I was wanting to educate and empower women to

enhance their own self-management and gain their opinions about the concept of self-monitoring or home monitoring for lymphoedema and whether it was possible to do this using BIS technology. Thus, my second study question:

2. Do women at risk of or living with lymphoedema following breast cancer feel that home monitoring using BIS technology could complement and enhance a prospective surveillance and early intervention model of care?

If feedback from women was positive in relation to the concept of home monitoring using BIS technology, then we needed to explore whether there was a reliable and validated device that could be used by individuals easily in their home to monitor themselves which led to my third study question:

3. Is there a BIS device that is reliable and could be used in the home setting as part of a home monitoring program to complement a prospective surveillance model of care?

So finally, if we could find a reliable BIS device that could be easy to operate by an individual in the home, it would be interesting to see whether it would be practical and possible to do so which led to my fourth study question:

4. Is it feasible to use BIS as part of a home monitoring program?

The studies described in this thesis address these questions. In this introductory chapter more detail about the background of breast cancer and breast cancer-related lymphoedema is presented. In addition, the assessment and management of lymphoedema models of care and how other chronic

health conditions use self-management and home monitoring to empower individuals and achieve positive outcomes are discussed. This introductory chapter includes a critical review of the literature related to the prospective surveillance model of care material published prior to 2015, when this work commenced, the more current research is discussed within each chapter and summarised in Chapter 6.

The primary aim of the work presented in this thesis was to explore the prospective surveillance model of care in the early detection and management of breast cancer-related lymphoedema and explore ways to enhance this model of care.

1.2 Cancer overview

1.2.1 Breast cancer incidence

Cancer is a major cause of illness burden in Australia with an estimated 145,500 Australians being diagnosed with cancer, and just under 50,000 dying from cancer in 2020, which has a major impact on individuals, families, and the health-care system (AIHW, 2019). Individuals living in Australia diagnosed with cancer generally have better survival prospects than those living in other countries (AIHW, 2019).

Breast cancer refers to cancers originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk (Boyages, 2010; Khuwaja, 2004). There are several types of tumours that may develop within different areas of the breast. Most tumours are the result of benign (non-cancerous) changes within the breast whilst most breast cancers begin in the cells that line the ducts (ductal cancers) (Boyages, 2010). Some begin in the cells that line the lobules (lobular cancers), while a small number start in the other tissues (Sharma, 2010). Types of breast cancer are determined by their site of origin and whether cells have invaded surrounded tissues, lymph nodes or organs (Boyages, 2010). Stages of breast cancer are based on the cancer's characteristics, such as how large it is, whether or not it has hormone receptors, whether the cancer has spread into the lymph nodes or other parts of the body beyond the breast (Boyages, 2010). Breast cancer stage is usually expressed as a number on a scale of Stage 0 through to Stage IV which assists clinicians in determining appropriate treatment and prognostic information (Cancer Australia, 2020). Stage 0 refers to 'pre-invasive' breast cancer such as ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS). Stage I, Stage IIA and Stage IIB (early) refer to early breast cancer. Stage IIB (advanced), Stage IIIA, Stage IIIB, Stage IIIC and Stage IV refer to advanced breast cancer (locally advanced breast cancer or metastatic breast cancer) (Cancer Australia, 2020).

Breast cancer is a major cause of illness in Australia and the estimated incidence of individuals being diagnosed with breast cancer in 2020 was 19,974 (AIHW, 2019). At the end of 2014, there were more than 212,299 women alive who had been diagnosed with breast cancer in the previous 33 years (BCNA, 2018). Understanding and avoiding the risk factors associated with breast cancer can help to reduce the chance of developing cancer, while cancer screening programs increase the likelihood of detecting cancer early and enabling better outcomes (BCNA, 2018). Improvements in treatments and care are also important contributors to improvements in survival. Despite breast cancer survival rates increasing and cancer mortality rates decreasing, breast cancer accounts for around 14% of all cancer deaths in Australian women and is currently the second leading cause of cancer death in Australian women after lung cancer (BCNA, 2018). The widespread adoption of mammography screening internationally for early detection of breast cancer and treatment guidelines has resulted in 98.8% 5-year mortality rates (Hwang, 2020).

Alcohol consumption, diet, obesity and physical inactivity, family history, body mass and reproductive and hormonal factors are considered important risk factors for developing breast cancer (AIHW, 2019). For females, the risk of being diagnosed with breast cancer is estimated to be 1 in 11 before the age of 75 and 1 in 7 before the age of 85 (AIHW, 2019). The chance of surviving at least five years (five-year relative survival) has increased from 74.0 per cent in 1986-1990 to 90.8 per cent in 2011-2015 (AIHW, 2019).

1.2.2 Breast cancer management

There are many approaches for the treatment of breast cancer depending on the type and stage of breast cancer and individual circumstances. A multidisciplinary team consisting of medical specialists, nursing and allied health professionals is recommended to determine the best combination

of evidenced based treatments for the individual and may include surgery, radiation therapy, chemotherapy, and hormonal therapy (Cancer Australia, 2020). Surgery for breast cancer consists of two main options. In breast-conserving surgery, known as lumpectomy or wide local excision, only the tumour and an area of normal tissue surrounding it are removed. In a mastectomy, all breast tissue is removed (Boyages, 2010). The surgeon aims to remove the cancerous tissue in the operation and have margins clear of cancer, indicating that the cancer has been completely excised. If the removed tissue does not have clear margins, further surgery to remove more tissue may be necessary (Boyages, 2010). In most cases, breast cancer surgery also involves the removal of one or more lymph nodes from the armpit (axilla). The technique of sentinel lymph node biopsy involves injecting a dye into the breast to determine which lymph node/s may have positive cancer cells, resulting in fewer side effects. Axillary lymph node dissection involves removing several, or all, lymph nodes from the armpit (Cancer Australia, 2020).

Radiation therapy involves using high-energy X-rays or gamma rays that target a tumour or post-surgery tumour site (Boyages, 2010). These radiations are very effective in killing cancer cells that may remain after surgery or recur where the tumour was removed (Sharma, 2010). Radiation therapy for breast cancer is usually performed after surgery and is an integral component of breast-conserving therapy (Boyages, 2010). The dose of radiation is determined by the radiation oncologist and must be personalised to ensure the elimination of cancer cells (Sharma, 2010). Treatments are typically given over a period of three to six weeks, performed five days a week (Boyages, 2010; Sharma, 2010).

Chemotherapy is the use of anti-cancer drugs to treat cancerous cells (Boyages, 2010). Specific treatment for the breast cancer will be based on; overall health, medical history, age (whether pre- or post-menopausal), type and stage of the cancer, tolerance for specific medications and procedures (Boyages, 2010). Chemotherapy treatments are often given in cycles; a treatment for a period,

followed by a recovery period, then another treatment. Chemotherapy can be given before surgery to shrink the tumour (known as neoadjuvant chemotherapy) which sometimes make breast conservation surgery possible rather than a more invasive mastectomy (Cancer Australia, 2020).

Hormone therapies are drugs used to treat breast cancers that are receptive to female hormones such as oestrogen and/or progesterone (Boyages, 2010). Around two-thirds of breast cancers are hormone receptor positive, which means that they need female hormones to grow and reproduce (Boyages, 2010). Hormone therapy is given as an oral medication. It is usually taken daily for five to ten years after the completion of intensive breast cancer treatments (Cancer Australia, 2020).

1.2.3 Breast cancer and survivorship

In Australia breast cancer long-term survival rates have been steadily improving due to screening, early detection, and advances in the surgical and medical management of the condition by a multidisciplinary team (Cornish et al., 2000). As breast cancer survivorship continues to grow, an increasing recognition of the complications and side effects associated with treatment have emerged and a growing number of women with long term side effects exist (Oeffinger & McCabe, 2006; Rowland et al., 2006; Schmitz, 2011). It is recommended to consider the psychosocial impact as well as evaluate the long-term side effects and treat the late medical and physiological consequences of breast cancer such as bone health, sexuality, fatigue, body image, cardiac function and weight gain (Schmitz, 2011). Another such side effect is swelling in the affected arm or chest / breast region which is known as lymphoedema (Cornish et al., 2000; Kilbreath, et al., 2013a; Taylor et al., 2006).

1.3 Breast cancer-related lymphoedema

Lymphoedema is a chronic inflammatory condition which is the result of a functional overload of the lymphatic system whereby capillary filtration exceeds lymphatic transport capacity. An abnormal accumulation of protein-rich fluid in the interstitial space of the affected area causes swelling of limbs and other parts of the body (Armer & Stewart, 2005; Bernas, 2013; Taylor et al., 2006). Breast cancer survivors are at risk for lymphoedema because of: 1) surgical removal of tissue and tied off lymph vessels obstructing drainage and reducing lymphatic carrying capacity; 2) scarring and fibrosis secondary to radiation which impairs muscle movement; and 3) related infections and seromas which may result in fibrosis of lymph structures and surrounding tissue (Lymphoedema Framework, 2006; Ridner, 2002).

Lymphoedema may be associated with the development of physical symptoms (e.g., swelling, pain, altered sensations, heaviness, aching and reduced function) and psychosocial issues (e.g., psychological distress, body image disturbance, social isolation and economic burden) (Ancukiewicz et al., 2011; Armer et al., 2013; Cormier et al., 2010; Hayes et al., 2008b; Hormes et al., 2010; Perdomo et al., 2014). Lymphoedema is different from post-operative swelling which may occur immediately after surgery (Armer & Stewart, 2010). However, persistent post-operative limb volume changes at one month were a risk factor for development of lymphoedema (Bundred et al, 2020). It has also been recognized as a significant survivorship issue for those completing medical and surgical treatment for breast and other cancers and often a daily reminder that they have had cancer treatment (Armer & Fu, 2005). Lymphoedema is a poorly understood and under-researched complication of breast cancer treatment which can significantly reduce quality of life (DiSipio et al., 2013; Hayes et al., 2011; Hormes et al., 2010).

1.3.1 Incidence of breast cancer-related lymphoedema

The incidence of breast cancer-related lymphoedema is variable and often under-reported due to lack of standardised methods for measuring and determining criteria for diagnosing lymphoedema (Armer et al.; 2013; Bernas, 2013; Bundred et al., 2020; Dylke, 2016; McLaughlin et al., 2020; Sander et al., 2002). Some studies have demonstrated that the rates of breast cancer-related lymphoedema range from 5% with conservative treatment (lumpectomy or wide local excision and sentinel node biopsy alone without radiation therapy or chemotherapy) to greater than 20-60% in cases with axillary lymph node dissections, regional irradiation, and chemotherapy (taxane-based in particular) receipt (DiSipio et al., 2013; Hayes, 2008; Hayes et al., 2005; Hwang, 2020; Kilbreath et al., 2016; Lucci et al., 2007; McDuff et al., 2019; Mittendorf, 2020; Morrow, 2020; Torres, 2020).

Factors such as number of lymph nodes removed, chemotherapy type, radiotherapy location, obesity (increased body mass index), comorbidities, age, development of seroma or infection have consistently been shown to be risk factors for lymphoedema (Armer & Stewart, 2010; McLaughlin et al., 2020b; Perdomo et al., 2014). The large discrepancies among reported incidence rates also occur due to difficulties in measurement, diagnosis, and follow-up (Cornish et al., 2001; Dylke, 2016; Moseley & Piller, 2008) as well as lack of pre-operative baseline comparison or adjustment for changes in body mass index (Armer & Stewart, 2010). Lymphoedema can occur during cancer treatment or many years later. Thus, there is no safe period when an individual is no longer at risk. It should be noted however, that approximately 88% of lymphoedema occurs within 2 years of surgery (DiSipio et al, 2013). Once lymphoedema develops, if it is untreated, poorly managed, or treatment resistant, it may progress through four stages of severity (International Society of Lymphology [ISL], 2016).

1.3.2 Lymphoedema staging

The International Society of Lymphology (ISL) describes a four-stage system for classifying lymphoedema from Stage 0-3 (ISL, 2016). Stage 0 refers to a sub-clinical or latent phase where swelling is not yet evident despite impaired lymph transport, there may be subtle changes in tissue fluid/composition, and changes in subjective symptoms. It may exist months or years before visible oedema occurs in Stages 1-3. Stage 1 represents an early accumulation of fluid relatively high in protein content which subsides with limb elevation. Pitting may occur. Stage 2 signifies that limb elevation alone rarely reduces tissue swelling and pitting is manifest. Late in Stage 2, the limb may or may not pit as excess fat and fibrosis supervenes. Stage 3 includes lymphostatic elephantiasis where pitting can be absent and trophic skin changes may occur and further fat deposition and fibrosis have developed (ISL, 2016).

1.3.3 Lymphoedema assessment

A comprehensive and accurate assessment ideally within a multidisciplinary team approach is essential for the diagnosis and evidence-based best practice management for those at risk of or living with lymphoedema following breast cancer treatment (Armer et al., 2013; Bernas, 2013; Boyages et al., 2020). It is important in the oncology setting that the comprehensive assessment incorporates a medical assessment, physical examination, listening to the individual, and being aware of other causes of acute swelling to provide goal driven optimal person-centred management (Armer et al., 2013; Kaslow et al., 2007).

Issues that are relevant to measurement of breast cancer-related lymphoedema are the need for: reliable and valid instruments which are appropriate and cost effective in the clinical setting; timing

of measurements for most informative data-gathering and follow-up; underlying assumptions about limb volume symmetry; and assessment of self-reported symptoms in combination with anthropometric limb measurements (Armer, 2005).

Ideally anthropometric measurements for lymphoedema would be described as easy to use, non-invasive, hygienic, inexpensive, reliable, and quantifiable (Gerber, 1998). The following assessment tools may be used in the assessment of breast cancer-related lymphoedema.

Self-assessment surveys

One of the easiest and more common ways for assessing lymphoedema is to use patient self-assessment of symptoms, function, quality of life and psychological evaluation through validated questionnaires / surveys. There are several lymphoedema specific validated assessment tools (Beaulac et al., 2002; Coster et al., 2001; Keeley, 2010; Ridner & Dietrich, 2015; Viehoff et al., 2008; Weiss, 2015; Wilson et al., 2005). Psychosocial assessment may highlight areas that require referral for specialist intervention and factors that may have an impact on management and adherence to treatment (Lymphoedema Framework, 2006). Self-assessment evaluation should include asking the patient how their swelling makes them feel about themselves; anxiety levels; cognitive impairment; lack of motivation; ability to cope; symptoms and understanding of disease and treatment (Lymphoedema Framework, 2006).

Limb volume measurement

Limb volume measurement is one of the methods used to determine the severity of lymphoedema, helps to guide appropriate management, and assesses the effectiveness of treatment over time (Armer

et al., 2013). Typically, limb volume is measured at diagnosis or initial assessment and at follow-up reviews / assessments. In unilateral limb swelling, it is important to measure both the affected and unaffected limbs. The difference in limb volume is expressed in millilitres or as a percentage. Oedema is considered present if the volume of the affected limb is more than 10% greater than that of the contralateral unaffected limb. The dominant limb should be noted and may have a circumference up to 2cm greater (Lymphoedema Framework, 2006).

Water displacement

Water displacement using a volumeter (also known as water plethysmography) has been previously regarded as the "gold standard" for measuring limb volume as the water volume displaced is equal to the volume of the limb immersed in the water (Bundred et al., 2015; Perdomo et al., 2014). Water displacement has consistently demonstrated excellent inter / intra-rater reliability with good construct and concurrent validity (Chen et al., 2008; Deltombe et al., 2007; Gjorup et al., 2010; Karges et al., 2003; Sander et al., 2002; Taylor et al., 2006). Water displacement using a volumeter does not provide information about swelling localisation or the shape of the limb and is usually limited to measuring a certain part of the limb such as a hand or whole arm. Other variables such as patient positioning and the extent to how far the limb is immersed needs to be standardised (Taylor et al., 2006). Water displacement has limited clinical use due to it being cumbersome, messy and challenging from an infection control domain (Armer et al., 2013; Bundred et al., 2015; Perdomo et al., 2014).

Circumferential limb measurements

Circumferential limb measurement, the most frequently used method, involves using a consistent set of landmarks on the limb (Armer et al., 2013). The circumference is measured with a tape measure at

each point and then at fixed intervals. Circumferential measurements are inexpensive, but time-consuming and human resource intensive, and require training to achieve reliable and accurate measures (Armer et al., 2013). These measurements can be used in two ways to compare girth between at risk or lymphoedema affected limbs, or to determine whole limb volume. Circumferential measurements can be placed into a specialist computer program or calculator for determination of individual limb volume and comparison of limb volume between limbs. This technique has been used as the standard of care in randomised prospective trials and single institution studies (Shaitelman et al., 2014). While this is a method with some standardised measurement techniques, no consistent measurement protocol has been utilised across studies, and limitations include inter-observer variability and a lack of sensitivity (Deltombe et al., 2007; Hayes et al., 2008a; Hayes et al., 2008b; Nesvold et al., 2011; Stanton et al., 2000). However, a 10% change in volume of an at-risk limb, without a similar change in a non-at-risk limb, in breast cancer survivors is the most used criterion for clinical lymphoedema (Lymphoedema Framework, 2006).

Perometry measurements

Perometry (Juzo, Cuyahoga Falls, Ohio, USA) uses infrared light beams and opto-electronic sensors to calculate limb volume from the three-dimensional silhouette of the limb (Armer et al., 2013; Bundred et al., 2015). From these measurements, limb volume (not including hand volume) can be calculated quickly, accurately, and reproducibly. Perometry is efficient in time and hygienic, however is costly so has limited use in clinical settings (Armer et al., 2013; Bundred et al., 2015; Stanton et al., 1997).

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has been used with contrast agents for imaging the lymphatic system (Armer et al., 2013; Bernas, 2013; Lymphoedema Framework, 2006). This imaging technique has demonstrated detailed imaging of the anatomy and function of the lymphatic system and exploring the distribution of fluid, fat and muscle ratios partcularly in advanced Stage 3 lymphoedema for surgical planning (Boyages et al., 2015). MRI is not routinely used in the clinical setting for assessment of lymphoedema due to associated costs and needing to be completed in a medical imaging department.

Lymphoscintigraphy

This method uses a tracer molecule (serum albumin or sulfur colloid) linked to 99m-technetium that is injected intradermally or subcutaneously once in the hand or foot (Armer et al., 2013). The tracer enters the collecting lymphatic channels and is transported to the central lymphatic circulatory system (Armer et al., 2013). This dynamic examination can display the speed of tracer movement, lymph nodes, locations of blockage or slow flow, and sites of dermal diffusion of the tracer because of obstruction and/or valve incompetence (Bernas, 2013; Lymphoedema Framework, 2006).

Indocyanine green lymphography

Indocyanine green (ICG) lymphography offers a potential method for visualising lymphatics and identifying abnormal morphologies which could facilitate earlier diagnosis and intervention. In this technique, a lymphatic specific tracer (ICG dye) is injected intradermally where it binds to albumin and is absorbed into lymphatic vessels. When excited with diode light, ICG emits near-infrared fluorescence which is filtered and recorded with a charge-coupled video camera, thereby allowing

real-time imaging of lymph flow and lymphatic vasculature (Heydon-White et al., 2020). ICG lymphography has been used to identify the sentinel nodes for breast cancer surgical intervention (Kitai, 2005). It was later applied to lymphoedema assessment to locate lymphatic vessels and nodes in the microsurgical lymphatic surgeries of lympho-venous anastomosis and lymph node transfer (Suami & Chang, 2010). ICG lymphography has gained momentum as a valid and reliable tool in assessing and monitoring breast cancer related lymphoedema (Akita, 2013; Yamamoto et al., 2011). With ICG lymphography, the superficial lymphatic vessels are observed as a dynamic map within a depth of 1 to 2cm from the skin surface (Akita, 2013; Unno et al., 2010; Yamamoto et al., 2011). ICG lymphography does not expose the patient to radiation and has the advantage of using a faster-moving dye (Unno et al., 2010). It has more recently been used in determining compensatory drainage regions and pathways for lymphatic flow used in personalising manual lymphatic drainage in conservative lymphoedema management (Suami et al., 2019).

Bioimpedance spectroscopy

Increases in extracellular fluid accumulation, indicative of sub-clinical disease in at-risk limbs, occurs before there is a significant percentage change in whole arm volume and before changes are visible to the at-risk patient (Cornish et al., 2000). Technology that has been developed to identify sub-clinical extracellular fluid accumulation includes bioimpedance spectroscopy (BIS). This technology has been used successfully in both laboratory and clinical settings (Ridner et al., 2009). BIS is a technique used for the measurement of biological impedance at many frequencies including the ideal frequency of measurement, 0 kHz (Thomas, 1992). Resistance, opposition to current from body fluids, and reactance, opposition to current from cell membranes and tissue interfaces, are two components of impedance (York et al., 2009). The degree of impedance is inversely proportional to the amount of fluid volume in the tissues being measured (Ward et al., 2009). Frequency of the current being

delivered determines what is being measured (e.g., zero frequency current does not penetrate cell membranes, higher frequencies penetrate various types of tissue) (Cornish, 2006).

Conventionally, BIS measurements are performed using an impedance analyser which makes its measurements via leads attached to the skin by Ag-AgCl EKG-style electrodes (Cornish, 2006). Measurements are typically performed with the individual in supine and electrodes placed on the hands and feet, although measurements may also be performed with the individual sitting. BIS devices, such as a lead device known as the L-Dex® U400 (ImpediMed Limited, Brisbane, Australia), (Figure 1.1), measure the resistance to electrical current flow. At very low frequencies, the current travels predominantly through the extracellular fluid compartment of limbs. The L-Dex® U400 device uses an "impedance ratio" methodology to assess unilateral lymphoedema of the arm. The resistance at 0 kHz (theoretical) in the affected/at-risk arm is compared to the resistance at 0 kHz (theoretical) in the unaffected arm as represented by the following ratio (unaffected: affected/at-risk) (Ward, 2015). By this method, the unaffected arm acts as an internal and subject specific control. Alternatively, this ratio may be linearized and expressed as an L-Dex score (Ward, 2015). Abnormal L-Dex values include those outside the normal range (-10 to +10 L-Dex units) and a change of greater than 10 from baseline which is three standard deviations from the normative value (Czerniec et al., 2010). More recent research has suggested that a change of >6.5 - 7 L-Dex units from baseline, being two standard deviations from the normative value, was more indicative of diagnosing sub-clinical lymphoedema (Fu, et al., 2013). The passing of the current when taking a BIS measurement is equivalent to a person holding a AA battery.

More recently a newer BIS device has been developed known as the stand-on device (SOZO®, ImpediMed Limited, Brisbane, Australia), (Figure 1.2) (ImpediMed, 2018-2019). The stand-on device

utilises the same “impedance ratio” methodology as the lead device. L-Dex scores generated by either type of BIS device can be displayed in an L-Dex history graph that displays change over time (Figure 1.3). The stand-on device has stainless steel contact electrodes which are inbuilt within the hand and foot plates of the device (ImpediMed, 2018-2019). The current drive and sense plates are located under the sole of the feet and palm and fingers of the hands. Prior to measurement the electrode plates should be swabbed with alcohol wipes for infection control and to assist in achieving good skin contact with electrodes (ImpediMed, 2018-2019). The device is controlled with an Android tablet pre-installed with the SOZOapp (ImpediMed Limited, Brisbane, Australia). All user accounts, measurement data, and other calculated measures and trends are stored in the secure MySOZO cloud (ImpediMed Limited, Brisbane, Australia) and BIS measurements can be monitored remotely by the healthcare team through this secure connection.

BIS because it is expressed as a ratio of unaffected to affected, unlike many traditional assessment tools, provides a true measure of extracellular fluid volume and is not impacted by weight changes or changes in the muscle/fat ratio (Stout Gergich et al., 2008). BIS can be utilised easily in the clinic compared with bulkier modalities such as perometry, and it has been shown to be feasible with minimal change in clinical workflow (Ridner et al., 2009; Ridner et al., 2014b; Stout Gergich et al., 2008). BIS has been reported to be an effective non-invasive technique for the measurement of extracellular fluid and sub-clinical changes in extracellular fluid to predict the onset of lymphoedema in the arms (Cornish, 2006; Cornish et al., 2001; Soran et al., 2014; Ward et al., 2011; Ward, 2006; Ward et al., 1992). BIS has high sensitivity allowing for sub-clinical detection, has standardised cut-off measurements, and has been shown to have excellent inter-observer variability (Dylke,2016; Kilbreath, et al., 2013b). This approach can measure intra and extracellular fluid and total body water, thus allowing for determination of overall body composition (Tattersall, 2009).

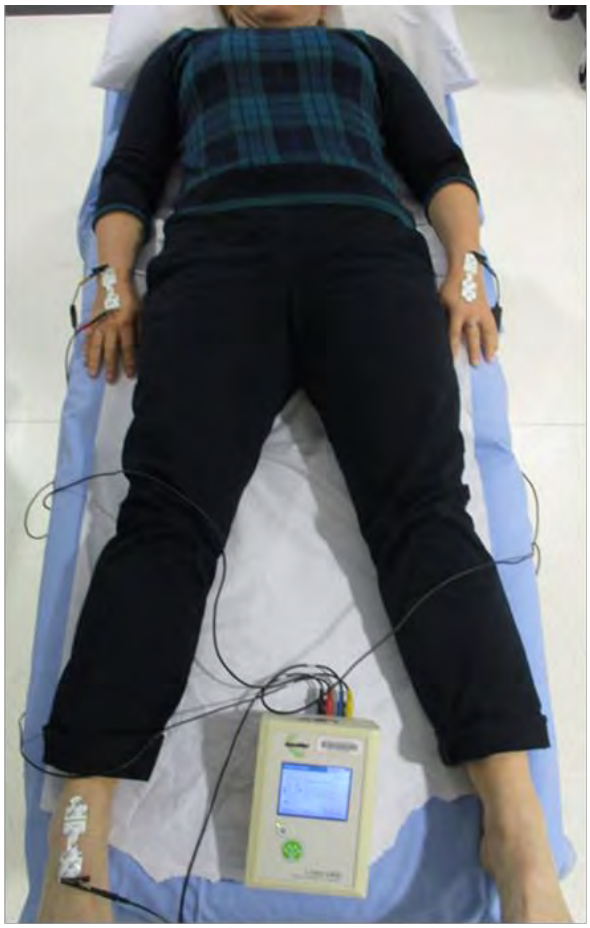

Figure 1:1 L-Dex® U400 (ImpediMed Ltd)

Figure 1.2: SOZO® (ImpediMed Ltd)

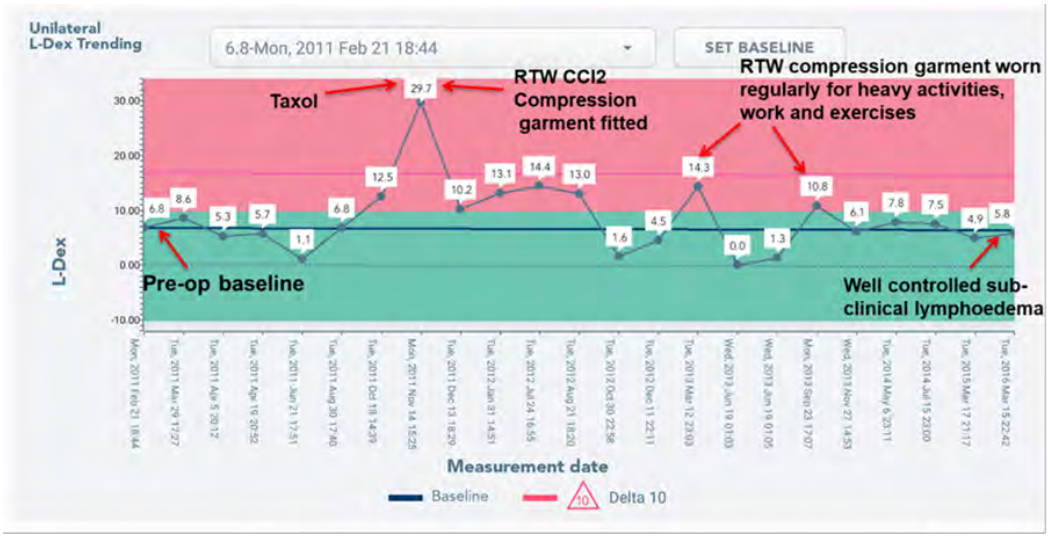

Figure 1.3: L-Dex history graph

Limitations of Lymphoedema Assessment

Various measurement techniques for determining lymphoedema have limitations including a lack of standardized cut-off, intra- and inter-observer variability, and low sensitivity eliminating the detection of early onset, sub-clinical disease (Hayes et al., 2008a). Several researchers recommend that early diagnosis must occur to decrease the number of individuals suffering from long-term complications of chronic lymphoedema (Armer et al., 2013; Sherman & Koelmeyer, 2011).

Timely recognition of worsening swelling in clinical lymphoedema is believed to result in improved patient outcomes (Ramos et al., 1999). Earlier detection and intervention require less intensive complex therapy (Armer et al., 2013; Stout Gergich et al., 2008). Currently, no objective measurement mechanism exists that can easily be used by individuals to self-monitor arm volume. Individuals generally rely on their own subjective recognition of increasing arm symptoms and volume to know when to seek treatment, thereby missing an early window of opportunity (Ridner et al., 2014b). Often large increases in limb volume occur before breast cancer survivors with lymphoedema seek medical care and often only after they have developed cellulitis in the affected limb (Sherman, 2018). This delay may result in individuals suffering unnecessary symptoms and requiring more extensive therapy, which increase health care burden and associated costs (Stout et al., 2013).

1.4 Management of lymphoedema

Traditionally best practice management for lymphoedema treatment internationally has included a two-phase intensive program which is known as complex lymphoedema therapy (CLT) or complex decongestive therapy (CDT) (Földi, 2011). Phase one or reduction phase includes an intensive daily treatment regime for four to six weeks involving manual lymphatic drainage (MLD) massage,

compression therapy (bandages, sequential intermittent pneumatic compression), exercise, skin care, education and psychosocial support provided by a qualified and skilled lymphoedema therapist (Lymphoedema Framework, 2006; Stout et al., 2012c; Stout et al., 2012b). Phase two or self-maintenance phase involves a modified home program of phase one with wearing of compression garments, self-MLD, exercise and skin care along with ongoing life-long self management and monitoring of the arm to keep it under control and reduce risks of progression of swelling, symptoms and infection (Armer et al., 2013; Lymphoedema Framework, 2006). There are also surgical options for managing both early and later stages of lymphoedema including lymphovenous anastomosis and lymph node transfer for early stage lymphoedema and liposuction for advanced lymphoedema (Boyages et al., 2015; Boyages et al., 2020; Ngo et al., 2020). It must be recognised that surgical options are not considered a cure for lymphoedema but rather assist in controlling the condition or preventing further progression. Research has shown that only sub-clinical or stage 1 lymphoedema can be reversible, while stage 2 or 3 is a chronic condition which can only be managed (ISL, 2016; Norman et al., 2009; Soran et al., 2014).

1.5 Models of care in managing lymphoedema

1.5.1 Traditional model of care

The traditional model of care relies on the management of a chronic lifelong condition that has clinically apparent visible limb swelling and associated symptoms where the individual would seek care. The model is reliant on the medical / health professionals' knowledge of lymphoedema and their ability to diagnose and refer individuals to a lymphoedema trained therapist quickly and accurately to complete a comprehensive assessment and provide intensive CLT (Stout et al., 2012b). Historically however, there has been a poor awareness of lymphoedema which has resulted in a delayed treatment referral in the advanced non-reversible stages of lymphoedema.

1.5.2 Prospective surveillance & early intervention model of care

There is a need to reduce the burden of chronic disease including lymphoedema and improve healthcare system sustainability by improving cancer and chronic disease prevention and screening services (Manca et al., 2018; Springer et al., 2010). A more recent model which includes the opportunity for prevention of breast cancer-related lymphoedema is the prospective surveillance and early intervention model of care (Gerber et al., 2012; Stout Gergich et al., 2008; Stout et al., 2012c). This model can be defined as a proactive means of providing care whereby the health professional aims to educate, support, empower, monitor and manage the physical and psychological side effects of breast cancer treatment and lymphoedema (Stout et al., 2012b). The prospective surveillance model of care allows for early intervention strategies and lymphoedema treatments to be implemented whilst clinical symptoms are minimal and ideally commencing at the time of breast cancer diagnosis (Stout Gergich et al., 2008).

As up to 80% of individuals completing intensive cancer treatments will attain full life expectancy, they should do so with full function and limited side effects of the treatments (Stout et al., 2012c)**.** Stout and colleagues (2012) proposed a prospective surveillance model of care for physical rehabilitation in breast cancer that can be integrated to create a comprehensive approach to cancer survivorship care including lymphoedema surveillance and early intervention (Stout et al., 2012b Stout et al., 2012c, Stout et al., 2012a).

The goals of this model of care are to:

i) promote surveillance for common physical impairments and functional limitations associated with breast cancer treatment

ii) to provide education to facilitate early identification of impairments

iii) to introduce rehabilitation and exercise intervention when physical impairments are identified

iv) to promote and support physical activity and exercise behaviours (Stout et al., 2012b)

Detection of sub-clinical lymphoedema through surveillance and early intervention has been found to reduce progression to clinical lymphoedema (Soran et al., 2012; Soran et al., 2014). Stout and colleagues (2008) supported these findings demonstrating early detection and intervention of sub-clinical lymphoedema reduced arm volume, ultimately decreasing the need for ongoing intensive lymphoedema treatment (Stout Gergich et al., 2011; Stout Gergich et al., 2008). Several researchers have supported the need for a prospective model targeting high risk individuals through routine screening to reduce lymphoedema progression (Box et al., 2002; Bundred et al, 2015; Erdogan et al., 2014; Johansson & Branje, 2010; Ramos et al., 1999).

The burden of breast cancer-related lymphoedema has been directly related to lymphoedema severity demonstrating a need for a prospective surveillance model of care involving regular monitoring and early intervention for those at risk of developing sub-clinical lymphoedema (Basta, 2016). In terms of lymphoedema assessment tools already discussed, BIS provides the greatest opportunity for prevention of chronic lymphoedema as it can detect ISL stage 0 sub-clinical lymphoedema (Stout et al., 2012c).

1.6 Financial costs of managing lymphoedema

There has been limited health economics research exploring the financial impact of living with lymphoedema in addition to breast cancer as well as costs associated with the implementation of a prospective surveillance model of care for individuals at high risk of developing lymphoedema.

Stout and colleagues (2012) compared a prospective surveillance model with a traditional model of impairment-based care and examined the direct treatment costs associated with each program (Stout et al., 2012c). The cost to manage early-stage breast cancer-related lymphoedema per patient per year using a prospective surveillance model was USD$636.19 compared to USD$3,124.92 being the cost to manage late-stage breast cancer-related lymphoedema using a traditional model (Stout et al., 2012c).

Other researchers have proposed breast cancer-related lymphoedema is costly in terms of treatment including therapy and compression garments, symptom burden and quality of life (National Lymphedema Network, 2011; Shih et al., 2009) and that early intervention and prevention of breast cancer-related lymphoedema could reduce the overall cost of lymphoedema after breast cancer treatment to individuals and society (Ridner et al., 2014b). For any model of care to be successful, it must be sustainable and cost-effective within a complex healthcare system.

1.7 Self-management in chronic health conditions

The term chronic health condition includes disability and disease conditions that people may 'live with' over extended periods of time (i.e. more than 6 months) (Lawn et al., 2009). The burden of chronic health conditions such as asthma, heart disease, renal disease and diabetes on individuals' and healthcare systems is substantial (Busetto 2016; Eguchi et al., 2012; Kamradt et al., 2019; Markle-Reid et al., 2018; Nelson et al., 2018; Peytremann-Bridevaux et al., 2015; Radini et al., 2017; Woe Sook & Sakano, 1996). As the population ages the burden of chronic health conditions increases and places increasing strain on healthcare budgets (Celler et al., 2014).

Prevention and management of chronic health conditions is becoming increasingly important (Lawn et al., 2009). Health professionals can enhance health outcomes for individuals with chronic health conditions including lymphoedema (Lawn et al., 2009). Finkelstein and colleague (2000) identified three healthcare delivery objectives used in the management of chronic health conditions. They include primary prevention or early detection of chronic health conditions; chronic disease control and symptom management; and personal and social support (Finkelstein & Friedman, 2000). These objectives can be translated to the prospective surveillance model of care in breast cancer in providing education, monitoring and psychosocial support to reduce the risk of lymphoedema developing as part of a package of care (Finkelstein & Friedman, 2000).

The hospital-centric public health system is often burdened by the management of chronic health conditions which could occur in the home and community settings (Celler et al., 2014). Interventions have been developed to support chronic health conditions which may include patient education, interventions that centre on the individuals' needs, encouraging the co-ordination and integration of

health services by multidisciplinary teams, and emphasising patient self-management (Peytremann-Bridevaux et al., 2015). Self-management interventions are often recommended for individuals because they demonstrate that lifestyle changes are effective and the benefits sustainable (Markle-Reid et al., 2018). These interventions may use motivational techniques to improve confidence (self-efficacy) and education to guide behaviour change (Markle-Reid et al., 2018). There is a growing interest in home-based self-management programs for individuals living with chronic health conditions because interventions which are clinic based are often resource intensive.

1.8 Home monitoring in chronic health conditions

The concept of home monitoring and self-management is not new and has been used in chronic health conditions such as diabetes, asthma, and heart failure (Basatneh et al., 2018; Erie et al., 2018; National Lymphedema Network, 2011). Activity monitoring has the potential to engage individuals as advocates in their own personalised care, as well as offer health care professional's real-world assessments of their patients' daily activity patterns (Chiauzzi et al., 2015). Medical devices embedded with sensors have previously been used in clinical trials and research studies, however, advances in technology have supported patient care and research outside of hospitals and into the home environment (Chiauzzi et al., 2015).

Modern telecommunication technologies have tremendous potential for improving the management of individuals with chronic health conditions including breast cancer-related lymphoedema and, possibly, reducing the costs due to these illnesses (Finkelstein & Friedman, 2000). Some potential sources for cost savings with the use of technology and telecommunication systems are: providing patient education for primary prevention and early detection of disease; improving adherence to self-

management regimens; collecting patient data remotely; replacing health professional visits; and timely intervention for early symptom management; and reducing unscheduled / unnecessary visits to the hospital or clinic (Finkelstein & Friedman, 2000). It is anticipated that future technological developments will expand the scope and diversity of telecommunication applications in chronic health conditions and enhance the concept of home monitoring (Finkelstein & Friedman, 2000).

There is evidence lymphoedema as a chronic health condition is amenable to self-management. Ridner and colleagues (2014) found providing education and self-monitoring of lymphoedema has been shown to enhance the effectiveness of self-care and enable the establishment of self-care goals (Ridner et al., 2014b). However, Brown and colleagues (2014) suggested that the prescription for breast cancer-related lymphoedema self-care modalities was variable and non-optimal. They recommended future research was necessary to prepare breast cancer survivors with the knowledge, skills, abilities, and resources necessary to care for this chronic lifelong condition (Brown, 2014).

It is likely that being able to closely monitor and obtain objective feedback on the impact of different lymphoedema self-care actions through devices such as home-based BIS monitoring may promote enhanced perceptions of behavioural control over lymphoedema (Ajzen, 2011; Hardeman et al., 2002; McEachan et al., 2011). This, in turn, could lead to improved motivation and enhanced adherence to self-care treatments (Ridner et al., 2014a; Ridner et al., 2014b).

There has only been one known pilot study published using BIS technology as a home monitoring tool to enhance self-management in breast cancer-related lymphoedema (Ridner et al., 2014b). The

purpose of Ridner and colleagues' pilot study (2014) was to examine the impact of arm self-measurement using a BIS lead type device on daily self-care activities and health outcomes in breast cancer survivors, 18 women with and 21 women without lymphoedema over a three-month period. They found that objective self-monitoring of arms using BIS was possible and that self-monitoring may positively impact self-care behaviours. Ridner and colleagues recommended that future research could explore prospective self-monitoring with BIS devices for breast cancer survivors who are at high risk for lymphoedema over a longer timeframe (Ridner et al., 2014b).

1.9 Aims of Thesis

As breast cancer-related lymphoedema remains a major survivorship issue for individuals following breast cancer, and that early detection using BIS in a prospective surveillance model of care shows promise, the primary aim of the work presented in this thesis was to explore the prospective surveillance model of care in the prevention and management of breast cancer-related lymphoedema and identify ways to enhance this model of care. This primary aim was achieved through the conduct of four studies with different methodologies. The broad research question for each of the four studies is outlined below:

1. Was there a difference in care use, incidence, and severity of lymphoedema between two models of care (traditional referral compared with the prospective surveillance and early intervention)?
2. Do women at risk of or living with lymphoedema feel that home monitoring using BIS could complement a prospective surveillance and early intervention model of care?
3. Is there a BIS device that is reliable and could be used in the home setting as part of a home monitoring program to complement a prospective surveillance model of care?
4. Is it feasible to use BIS as part of a home monitoring program?

Each study is presented in its own chapter and formatted as a publication or in the format of a manuscript submitted for publication. Studies I, III and IV have already been published in international peer-reviewed journals whilst Study II has been accepted for publication and is in press in an international peer-reviewed journal. In each chapter there is a "Statement from Co-authors" supporting the work conducted and a Preface that links between the chapters. Chapter 6 provides an overall discussion of the work and discusses the results in context of recent research as well as the implications for clinical practice and research. The references for all chapters are presented together

in a comprehensive reference list after Chapter 6, including the references for Chapters 2 - 5 which are also presented at the end of each submitted manuscript. Additional appendices are included at the end of the thesis.

CHAPTER 2

Study I - Early detection and management of breast cancer-related lymphoedema: a retrospective study

2.1 Preface

In Chapter 1 a synthesised literature review was discussed, providing background information about breast cancer related lymphoedema in context, lymphoedema assessment, models of care and management strategies. There has been a growing body of evidence supporting the implementation of a prospective surveillance and early intervention model of care in the early detection of sub-clinical lymphoedema which has reduced progression to clinical lymphoedema. Therefore, as an early adopter of this model of care, Chapter 2 describes a retrospective analysis of breast cancer clinical data collected in a private lymphoedema clinic over a decade comparing the traditional model of care to those involved in a prospective surveillance and early intervention model of care and whether there was a difference in the incidence of clinical lymphoedema from this new approach.

Ethical approval for this study was granted by the Macquarie University Human Research Ethics Committee (Medical Sciences) and is provided in Appendix 1.1.

This chapter is presented as the manuscript published in the Journal *Cancer*:

Koelmeyer, L., Borotkanics, R., Alcorso, J., Prah, P., Winch, C., Nakhel, K., & Boyages, J. (2019). Early surveillance is associated with less incidence and severity of breast cancer–related lymphedema compared with a traditional referral model of care. *Cancer*. *125*(6),854-862. [35 GS citations, IF 6.102]

The following conference abstracts also relates to the work conducted in this Chapter:

Koelmeyer, L. (2018, 17 May). Prospective surveillance of breast cancer-related lymphoedema results in earlier treatment and decreased disease severity over time. *Australasian Lymphology Association Conference*, Brisbane.

Koelmeyer, L. (2017, 12 November). Prospective surveillance of breast cancer-related lymphoedema results in earlier treatment and decreased disease severity over time. *New Zealand Breast Cancer Symposium*, Auckland, New Zealand.

2.2 Co-authors' statement

DEPARTMENT OF HEALTH PROFESSIONS
Faculty of Medicine, Health and Human Sciences

MACQUARIE University

Co-authors' Statement

As co-authors' of the paper, "*Early surveillance is associated with less incidence and severity of breast cancer-related lymphedema compared with a traditional referral model of care*", we confirm that Louise Koelmeyer has made the following contributions to this study:

- Conception and design of the research
- Collection and extraction of data
- Analysis and interpretation of the findings
- Drafting and revising of the manuscript
- Critical appraisal of the content

Dr Robert Borotkanics	Date: 12/08/2020
Dr Jessica Alcorso	Date: 12/08/2020
Philip Prah	Date: 12/08/2020
Caleb Winch	Date: 12/08/2020
Kristine Nakhel	Date: 12/08/2020
Professor Catherine Dean	Date: 12/08/2020
Professor John Boyages	Date: 12/08/2020

2.3 Early surveillance is associated with less incidence and severity of breast cancer-related lymphoedema compared with a traditional referral model of care

Original Article

Early Surveillance Is Associated With Less Incidence and Severity of Breast Cancer-Related Lymphedema Compared With a Traditional Referral Model of Care

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BACKGROUND: Bioimpedance spectroscopy (BIS) has enabled the early identification of breast cancer-related lymphedema. In this study, differences in health service metrics and in the incidence of breast cancer-related lymphedema are evaluated in an early surveillance model of care compared with a traditional referral model of care. **METHODS:** In a retrospective analysis of data from 753 women who underwent BIS measures between January 1, 2007 and December 31, 2016, 188 women were assigned to the "early surveillance" group if they began lymphedema monitoring presurgery (n = 121) or within 90 days postsurgery (n = 67), and 285 women were assigned to the "traditional referral" group if they began monitoring after 90 days postsurgery. Health service metrics were calculated as the time to the first BIS measure after 90 days postsurgery, the median follow-up, and the number of health care visits. Lymphedema was diagnosed based on BIS measures. **RESULTS:** Women in the early surveillance group received lymphedema care significantly earlier than those in the traditional referral group. However, there was no difference in the number of visits per year to the clinic between groups. Significantly more women in the traditional referral group were diagnosed with clinical lymphedema (stage I-III, 39 % vs 14%; $P < .001$) and with greater severity (stage II-III, 24%) compared with those in the early surveillance group (4%). **CONCLUSIONS:** The current findings support the adoption of an early prospective surveillance model of care using BIS for the early detection and management of breast cancer-related lymphedema. ***Cancer* 2019;125:854-862.** © 2018 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: bioimpedance spectroscopy (BIS), breast cancer-related lymphedema (BCRL), lymphedema, prospective surveillance, screening.

INTRODUCTION

It is estimated that breast cancer-related lymphedema (BCRL) affects 21% of patients who have breast cancer[1] and results in substantial physical,[2,3] functional,[2-4] psychosocial,[5-8] and financial[9,10] burden. Clinical guidelines and position statements from the United States, the United Kingdom, and Australia[11-14] advise that there is a need to develop early detection and intervention programs.[15-17]

A prospective surveillance model of care for women with breast cancer involves education, support, empowerment, monitoring, and management of the physical and psychological side effects of treatment. Because up to 80% of patients with breast cancer will attain full life expectancy, chronic treatment-related morbidity should be minimized.[18] Stout and colleagues proposed a prospective surveillance model of care for breast cancer rehabilitation that includes lymphedema surveillance and early intervention.[18]

A systematic review by Shah and colleagues[16] indicated that newer diagnostic modalities like bioimpedance spectroscopy (BIS) have increased sensitivity, which allows for the earlier detection of BCRL.[19,20] It has been reported that the detection of subclinical lymphedema through surveillance and early intervention reduces progression to clinical lymphedema.[15,17] For example, Soran and colleagues[17] monitored 180 women who were at high risk of lymphedema using regular BIS, and those who were diagnosed with subclinical BCRL underwent short-term physical therapy,

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education, and were prescribed compression sleeves. In that study, subclinical BCRL occurred in 33% of patients but progressed to clinical BCRL in only 4%.

Unlike other methods of clinical lymphedema assessment using volumetric measures, such as water displacement, perometry, or limb circumference, BIS is capable of detecting subclinical lymphedema.[21] BIS directly measures the extracellular fluid that is characteristic of early lymphedema.[17,21-26] When fluid accumulates and remains in the affected limb, inflammatory and hemodynamic changes increase in severity,[27] and early intervention may prevent or delay progression. Indeed, Whitworth and colleagues[28,29] observed that, of 93 high-risk patients who underwent axillary lymph node dissection and were managed with prospective surveillance, only 3% required additional therapies or had evidence of chronic BCRL over a median 2 years of follow-up. Similarly, Kilgore and colleagues[30] reported that only 6% of 146 patients developed chronic lymphedema after early intervention, supporting the observations of Whitworth and colleagues.

With the introduction of BIS in Australia in the early 2000s, our private lymphedema clinic adopted a prospective surveillance model of care and has collected data for over a decade. Therefore, we are well situated to retrospectively examine the difference between an "early surveillance" versus "traditional referral-based" model of care in BCRL management. All women received BIS assessment from the time of their initial consultation. This study did not test the efficacy of whether early surveillance prevents the development of lymphedema; rather, we were interested in exploring the differences between the 2 models of care over time in relation to the following metrics:

1. The difference in time to first measure of lymphedema beyond 90 days postsurgery and duration of follow-up;
2. The difference in health system use;
3. Differences in the incidence of and severity of lymphedema for those diagnosed with lymphedema; and
4. Difference in the evolution of BIS measurement over time for those diagnosed with lymphedema.

These 4 metrics were chosen because they are most relevant to health system use and severity of disease. We wanted to ascertain whether there was a difference in care use and the incidence and severity of lymphedema for the 2 models of care. We hypothesized that early surveillance would result in both less incidence and less severity of lymphedema. Differences between the models of care are important not only from a research perspective but also from a clinical and health services standpoint.

MATERIALS AND METHODS

Design

For this retrospective cohort study, we used prospectively collected data from 753 women who attended our clinic between January 1, 2007 and December 31, 2016. Baseline data were sourced from electronic medical records and self-report. The Macquarie University Human Research Ethics Committee provided ethical approval (reference no. 5201500844). This study is reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist.[31]

Participants

Patients were included if they were women, aged ≥18 years, diagnosed with unilateral breast cancer, and had undergone BIS. Exclusions included neoadjuvant chemotherapy, bilateral lymph node surgery, metastatic breast cancer or recurrent disease, and contraindications for BIS measurement (ie, pregnancy, pacemaker or electronic implantable device). Records were screened by 2 research assistants to determine eligibility.

We defined the *early surveillance group* as women who were assessed before their surgery for breast cancer or soon after (within 90 days) and were routinely referred from a multidisciplinary breast cancer team. The *traditional referral group* was defined as women who were assessed more than 90 days postsurgery, who typically were referred from external health centers. Women in both groups received lymphedema education and monitoring using BIS, clinical management of potential breast cancer complications (eg, scarring, cording, or swelling), as well as exercises and psychosocial support.

Outcome Measures

Timing of BIS measure, follow-up duration, and health system use

We recorded the time of the first BIS measure from 90 days postsurgery in days to ascertain differences between the groups in the timing of access to health care as well as the median follow-up duration, defined as the period between the first and last BIS measurements. We also calculated the total number of visits per year to ascertain health care utilization.

Incidence and severity of lymphedema

BIS measurements were taken in a supine position using the ImpediMed L-Dex® U400 device (ImpediMed, Brisbane, Australia). Lymphedema was diagnosed if BIS measures had increased by >10 L-Dex units from a woman's presurgical baseline or had exceeded the normative value of +10 L-Dex units or were maintained below these levels only by ongoing compression therapy. International Society of Lymphology stage (from 0 to III) at diagnosis was recorded.[32] Transient swelling within 90 days of surgery or within 270 days of commencing taxane-based chemotherapy was not defined as lymphedema.

Progression of BIS values over time

Repeated measures, mixed-effects models were created to evaluate progression in BIS values over time among women who were diagnosed with lymphedema for the 2 groups up to 5 years from surgery. Random intercepts were applied at the subject level, and random slopes with unstructured covariance matrices were used to consider the correlated results of repeated-measure data. Only women who had 2 or more BIS measures were included.

Data Analysis

Descriptive statistics were used to describe the baseline characteristics of the sample by treatment group, with 2-sample *t* tests and chi-square tests used to investigate significant differences. Nonparametric, Wilcoxon rank-sum tests were carried out on ordinal and continuous variables because of the non-normal distribution of the data overall and within study groups. Stata software (version 14; StataCorp LLC, College Station, TX) was used for all statistical analyses.

RESULTS

Characteristics of Participants

Eligible women (n = 473) were categorized into 2 groups. The early surveillance group (n = 188) was made up of those whose surveillance and intervention commenced presurgery (n = 121) or within 90 days postsurgery (n = 67) and continued for at least 90 days thereafter (Fig. 1). The traditional referral group included 285 participants. The cohort's baseline demographic and intervention characteristics are summarized in Table 1.

Time to First Measure of Lymphedema Beyond 90 Days Postsurgery

The first BIS measurement (from 90 days postsurgery) was taken significantly sooner for the early surveillance group compared with the traditional referral group (Wilcoxon $P < .001$). The median first BIS measurement (90 days postsurgery) in the early surveillance group was obtained approximately 3 months postsurgery (Table 2). This was 1.8 years sooner than that reported in the traditional referral group.

Follow-Up Duration

Given the difference in the time to first BIS measure, the follow-up duration was significantly longer for the early surveillance group than for the traditional referral group (8 vs 2 months). Therefore, most women who received early surveillance completed intervention before most women in the traditional referral group sought treatment. Irrespective of group, women who were diagnosed with lymphedema had a longer median follow-up than those without lymphedema (Table 2).

Health System Use

For those who attended surveillance for over 6 months (n = 216), the median number of health visits per year for both groups was 4 visits, which was not significantly different (Table 2).

Severity of Lymphedema at Diagnosis of Lymphedema

More women in the traditional referral group (39%) were diagnosed with clinical lymphedema (stage I, II or III) compared with those in the early surveillance group (14%; $P < .001$) (Table 3). In addition, more women in the early surveillance group (10%) were diagnosed with subclinical (stage 0) lymphedema compared with those in the traditional referral group (1%), and more women in the traditional referral group (24%) had moderate-to-severe lymphedema (stage II or III) compared with those in the early surveillance group (4%) (Table 3).

Progression of Lymphedema Over Time

Among women who were diagnosed with lymphedema, the repeated-measures model was used to predict a mean BIS of 16.1 L-Dex units (95% confidence interval [CI], 11.5-20.8 L-Dex units) at 90 days postsurgery for the early surveillance group versus 18.3 L-Dex units (95% CI, 13.2-23.4 L-Dex units) for the traditional referral group (Fig. 2). There was some evidence to suggest an increase in L-Dex scores over time for the traditional referral group, with an average increase of 2.3 L-Dex units per year (95% CI, –0.2 to 4.8 L-Dex units per year), which approached statistical significance ($P = .067$) (Table 4). In contrast, the early surveillance group had an average increase of only 1.6 L-Dex units per year (95% CI, –1.0 to 4.1 L-Dex

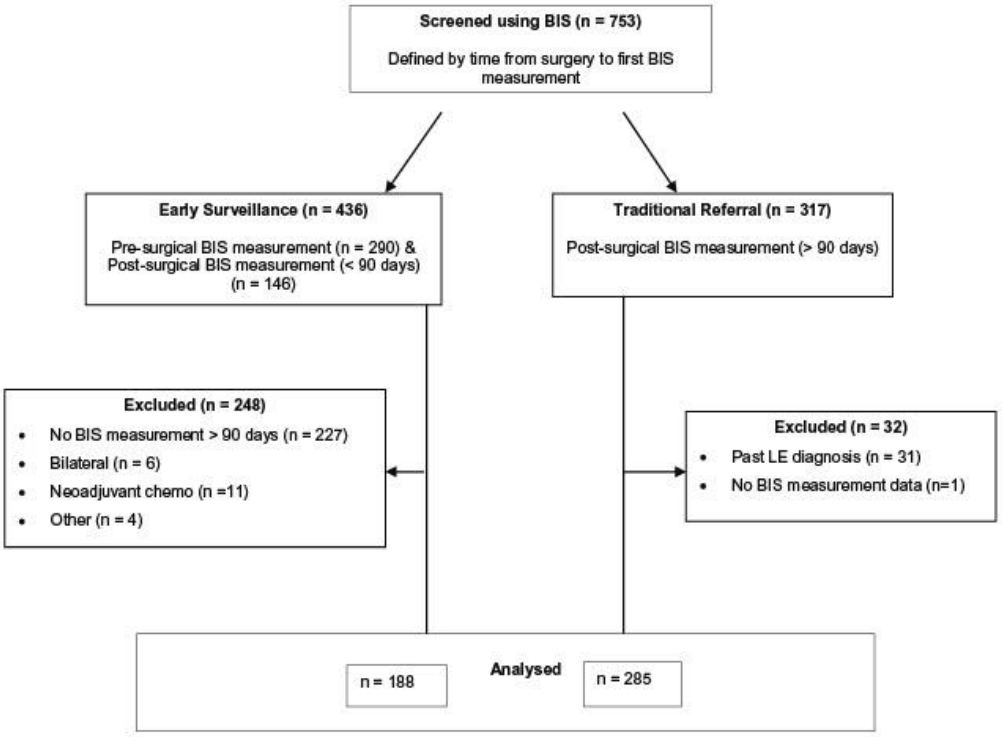

Figure 1. The study design and the flow of participants through the study are illustrated. BIS indicates bioimpedance spectroscopy; LE, lymphedema.

units per year) that was not significant (P = .232). The difference in slope between the early surveillance and traditional referral groups was not significant (P = .666).

DISCUSSION

The current results indicate that women who underwent early surveillance received lymphedema care almost 2 years earlier than women in the traditional referral group without any difference in number of visits to the lymphedema clinic. The early surveillance group had a significantly lower incidence of clinical lymphedema than the traditional referral group, and those who were diagnosed had significantly less severe lymphedema. For women who were diagnosed with lymphedema, BIS scores increased slowly over time, but the rate of increase was less for patients who underwent early surveillance.

Women undergoing early surveillance were monitored for lymphedema at a much earlier time after surgery than those in the traditional referral group. Before prospective early surveillance was practiced, the traditional referral model of care relied on a clinically apparent, visible limb swelling, for which the patient would seek care. This approach often resulted in missed or delayed diagnoses and a protracted time line for intervention.[33] Ramos and colleagues[34] reported that a greater volume in the arm required more intensive, complex decongestive treatment to achieve better outcomes. They advised early referral for lymphedema treatment in an era when BIS

TABLE 1. Baseline Characteristics of Participants

Characteristic	No. of Participants (%)			P[a]
	All, n = 473	Early Surveillance Group, n = 188	Traditional Referral Group, n = 285	
Age: Mean ± SD, y	55 ± 11	54 ± 12	56 ± 11	<.05
Arm at risk				
Right	216 (46)	84 (45)	132 (46)	.621
Left	257 (54)	103 (55)	154 (54)	
Sentinel lymph nodes dissected[b]				
No	217 (46)	55 (29)	162 (57)	<.001
Yes	256 (54)	133 (71)	123 (43)	
Axillary lymph nodes dissected[b]				
No	173 (37)	68 (36)	105 (37)	.799
Yes	301 (64)	121 (64)	180 (63)	
Medical intervention		n = 186	n = 94	
Nil adjuvant	31 (11)	19 (10)	12 (13)	<.001
RT only[c]	47 (17)	34 (18)	13 (14)	
CT only, without taxane	16 (6)	11 (6)	5 (5)	
CT only, with taxane	25 (9)	22 (12)	3 (3)	
RT + CT, without taxane[c]	161 (58)	100 (53)	61 (65)	
RT + CT, with taxane[c]	95 (34)	73 (39)	21 (22)	

Abbreviations: CT, chemotherapy; RT, radiotherapy.
[a]P values were determined with 2-sample *t* test or a chi-square test.
[b]Values for this characteristic were based on those who had a date of procedure recorded; it was assumed that all those without a date did not undergo dissection.
[c]Specific data on radiation fields were not available from therapy clinical files.

TABLE 2. Time to First Bioimpedance Spectroscopy Measure and Health System Use

Outcome	Median (IQR)		P[a]
	Early Surveillance Group, n = 188	Traditional Referral Group, n = 285	
Time to first BIS measurement, y	0.34 (0.26-0.51)	2.15 (0.97-5.41)	<.001
Follow-up duration, y	0.74 (0.12-2.17) n = 108	0.17 (0.0-1.5) n = 108	<.001
Health system use: No. of visits/y[b]	4.1 (2.9-6.0)	3.9 (2.5-5.9)	.238

Abbreviations: BIS, bioimpedance spectroscopy; IQR, interquartile range.
[a]P values were determined with a nonparametric Wilcoxon rank-sum test.
[b]Health system use was measured only among 108 women in each group who attended clinic for ≥6 months.

TABLE 3. Lymphedema Stage at Diagnosis by Patient Group

Outcome	No. of Women (%)		P[a]
	Early Surveillance Group, n = 188	Traditional Referral Group, n = 285	
Stage of lymphedema			
No lymphedema	142 (76)	173 (61)	<.001
Stage 0	19 (10)	3 (1)	
Stage I	19 (10)	43 (15)	
Stage II	8 (4)	53 (19)	
Stage III	0 (0)	13 (5)	

[a]P values were determined with a nonparametric Wilcoxon rank-sum test.

was not routinely used for the early detection of subclinical lymphedema.

The evidence supports using BIS to diagnose subclinical lymphedema to allow early intervention. For example, Soran and colleagues[17] detected subclinical lymphedema in 33% of participants who were regularly monitored using BIS. These individuals were provided with intervention, including physical therapy, compression garments, and education, and the authors observed that only 4% progressed to clinical lymphedema. Similarly, Whitworth and colleagues[28,29] also reported regular BIS monitoring and early intervention and

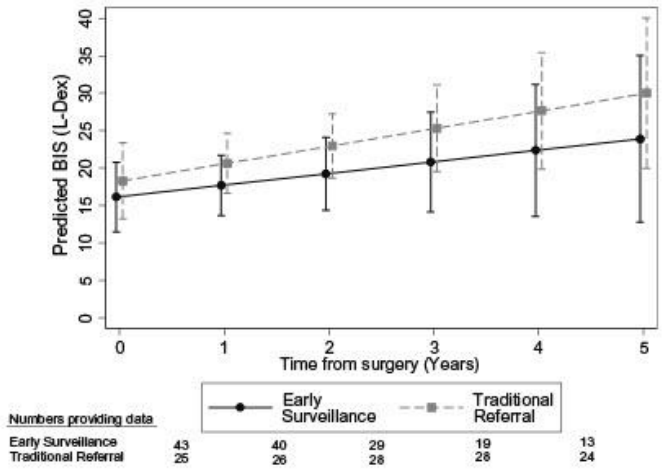

Figure 2. The predicted progression of the L-Dex score is illustrated among patients who had lymphedema along with model parameters. BIS indicates bioimpedance spectroscopy.

TABLE 4. Predicted Progression of L-Dex Score in Patients With Lymphedema along with model parameter

Model Output	L-Dex Score Estimate	SE	95% CI	P[a]
Predicted mean at 90 days postsurgery				
Early surveillance intercept	16.1	2.4	11.5-20.8	<.000
Traditional referral intercept	18.3	2.6	13.2-23.4	<.000
Progression over time				
Early surveillance slope	1.6	1.3	−1.0-4.1	.232
Traditional referral slope	2.3	1.3	−0.2-4.8	.067
Difference between slopes: Interaction	0.8	1.8	−2.8-4.4	.666

Abbreviations: CI, confidence interval; SE, standard error.
[a]P values were tested if the estimate differed statistically from zero.

observed that only 3% of 93 patients progressed from subclinical to clinical lymphedema. Iyigun and colleagues[35] reported that the detection of subclinical lymphedema in 22% of their cohort led to only 14% progressing to clinical lymphedema; and Kilgore and colleagues[30] also observed that only 6% of 146 high-risk patients developed persistent BCRL after early intervention. In our study, we noted that 10% of women who were diagnosed with lymphedema in the early surveillance group were diagnosed with subclinical lymphedema (stage 0) compared with only 1% of those in the traditional referral group, allowing for a greater proportion of women in the early surveillance group to access early intervention to prevent progression to clinical lymphedema.

We observed that the incidence of clinical lymphedema (stage I-III) differed significantly between the 2 groups (39% vs 14% in the traditional referral and early surveillance groups, respectively). Our traditional referral group incidence was similar to that reported by Soran and colleagues,[17] who observed that 36% of women in a control group were diagnosed with clinical lymphedema. Yang and colleagues also compared a surveillance group with a historical control group and reported a 5-year cumulative incidence of lymphedema at any stage of 32% in the surveillance group compared with 46% in the historical control group.[38] In the current study, fewer women in the early surveillance group were diagnosed with moderate or severe lymphedema (stage II-III, 4% vs 24%) compared with women in the traditional referral group.

In terms of health care use, there was no significant difference in the number of visits per year to the lymphedema clinic between groups. Although there were no fewer clinic visits in the early surveillance group, the actual cost of their intervention may have been lower than that for the traditional referral group.

Although no data were collected specifically on the time and cost of clinic visits for women attending the clinic for each group, generally, women without a diagnosis of lymphedema were attending for education and monitoring and were scheduled for the less expensive 30-minute (AUD$110), versus 60-minute (AUD$150), consultation sessions for the treatment of diagnosed lymphedema. Women with BCRL required more intensive lymphatic drainage massage and compression therapy, which included more costly consumable products, such as bandages, pneumatic compression pumps, custom-made garments, and possible costs of antibiotics and inpatient hospital care for those requiring intravenous antibiotics for cellulitis. We previously examined the financial cost of BCRL and observed that 80% of women in the study reported that having lymphedema affected them financially with significant out-of-pocket expenses, which increased with lymphedema severity.[10] Shih and colleagues[36] demonstrated that women with BCRL had a greater risk of infections and incurred significantly higher medical costs for their lymphedema care compared with women not diagnosed with clinical lymphedema and recommended reduction and prevention strategies, supporting an early surveillance model of care. Furthermore, Stout and colleagues[18] compared a prospective surveillance model with a traditional model of impairment-based care and examined direct treatment costs associated with each program. Those authors estimated that the cost of a prospective surveillance model of care for BCRL per patient per year was a significant 20% of the cost of managing lymphedema using the traditional referral-based model.

There are strengths and limitations of this study. The main strength is the volume of data available for analysis collected in the same clinic using the same method over a decade of practice. The data were recorded routinely as part of normal practice by 1 therapist. Women in the early surveillance group were receiving this package of lymphedema care even before adoption of the Australasian Lymphology Association's statement advocating regular monitoring for the early detection of BCRL. Second, the number of women and baseline characteristics for both groups were very similar, and these women were at greater risk for developing clinical lymphedema.

In terms of limitations, the 2 groups were not randomly assigned. Although both groups were similar, the number of women who never developed lymphedema is likely under-represented in the traditional referral group because, historically, they only sought treatment when they had developed a clinical symptom or need. Although a larger proportion of women in the early surveillance group had been prescribed taxane-based chemotherapy, this group had a lower incidence of clinical lymphedema at diagnosis compared with the traditional referral group.

It is accurate that there was no statistically significant difference in progression between the 2 groups; however, the slopes of disease progression differed over time. Herein, we reiterate an important section from our results in relation to the progression of BIS measurement. There was some evidence to suggest that, among women in the traditional referral group, there was an increase in L-Dex scores over time of up to 2.3 L-Dex units per year, on average, that approached statistical significance ($P = .067$) (Table 4). In contrast, in the early surveillance group, the average increase was only 1.6 L-Dex units per year ($P = .232$). Although there was not a statistically significant difference in the slopes between the 2 groups, the 5-year progression is noteworthy and reflects a clinically important effect. For instance, the traditional referral group gets more severe lymphedema sooner and increases the risk of unintended health outcomes like cellulitis. In contrast, the early surveillance group does progress, but more slowly. We note that the population estimates from our study sample are conservative and could be affected in part by sample size (Fig. 2, Table 4), resulting in larger expected confidence intervals.

Furthermore, no data are available for women who discontinued visits to the lymphedema clinic in either group. Women may have discontinued visits for a variety of reasons, including positive health outcomes, a low risk of developing lymphedema, and costs.

The prevention of progression from subclinical to clinical lymphedema remains important for breast cancer survivors. Although our study supports early surveillance and intervention using BIS, recent literature suggests that earlier detection may be even more beneficial using a lower threshold of a 6.5 rather than a 10 L-Dex–unit change for the detection of subclinical lymphedema.[28,37,39]

Current practice in Australia requires that "at-risk" women regularly attend clinics to be monitored for lymphedema. Typically, this occurs on a 3-month to 6-month cycle, depending on the individuals' risk of lymphedema. It is proposed that future research could explore the concept of "home monitoring" using BIS with education and support for the woman to be able to receive immediate and more frequent feedback and potentially earlier intervention, if required.

CONCLUSIONS

Scholars and guidelines[11-14] have advocated for the routine implementation of early lymphedema surveillance and intervention after breast cancer treatment. Regular clinic visits to monitor extracellular fluid present an opportunity for therapists to provide risk-management education, psychological support, physical rehabilitation, empowerment, and survivorship care. The findings from the current study support the use of BIS as part of an early prospective surveillance model of care that results in significantly earlier detection of lymphedema over time. Furthermore, the earlier detection of lymphedema will lead to lower health care costs if it results in the effective management of symptoms and prevents progression to severe clinical lymphedema.

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CONFLICT OF INTEREST DISCLOSURES

Louise A. Koelmeyer has acted as an Education Consultant to ImpediMed Limited outside the submitted work. Robert J. Borotkanics and Philip Prah were subcontracted by the ALERT Program at Macquarie University to assist in completing data analyses. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

Louise A. Koelmeyer: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, writing–original draft, and writing–review and editing. **Robert J. Borotkanics:** Data curation, formal analysis, writing–original draft, and writing–review and editing. **Jessica Alcorso:** Conceptualization, data curation, methodology, project administration, writing–original draft, and writing–review and editing. **Philip Prah:** Data curation, formal analysis, writing–original draft, and writing–review and editing. **Caleb J. Winch:** Conceptualization, data curation, methodology, project administration, writing–original draft, and writing–review and editing. **Kristine Nakhel:** Data curation, methodology, and writing–review and editing. **Catherine M. Dean:** Supervision, writing–original draft, and writing–review and editing. **John Boyages:** Conceptualization, data curation, methodology, supervision, writing–original draft, and writing–review and editing.

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CHAPTER 3

Study II - Effectiveness of self-management and home monitoring in breast cancer related lymphoedema

3.1 Preface

In Chapter 2 the retrospective study found that women undergoing early surveillance received lymphoedema care almost two years earlier than women in the traditional referral group. The early surveillance group had significantly lower incidence of clinical lymphoedema (14%) than the traditional referral group (39%) and those that were diagnosed had significantly less severe lymphoedema (4% compared to 24%). To enhance models of care in breast cancer, it would be valuable to seek opinions of what women at risk of or living with lymphoedema want in terms of education, monitoring, resources, and support. Chapter 3 is a qualitative focus group study gaining an in-depth understanding of attitudes towards lymphoedema home monitoring using BIS technology among those at-risk of, or living with, lymphoedema following breast cancer. In this study we used a sample of convenience. Participants were recruited via an email invitation through the Australian Lymphoedema Education, Research and Treatment (ALERT) Program's database at Macquarie University, Sydney. The final 31 participants represented around 25% of those invited.

Ethical approval for this study was granted by the Macquarie University Human Research Ethics Committee (Medical Sciences) and is provided in Appendix 2.1.

This chapter is presented in the format of the paper accepted for publication in the *Journal of Lymphoedema* on 29th October 2020.

Koelmeyer, L.A., Dean, C., & Boyages, J., Sherman, K.A. Understanding home monitoring and self-management in breast cancer related lymphedema – a qualitative study. *Journal of Lymphoedema* (Accepted October 2020)

The following conference abstract also relates to the work conducted in this Chapter:

Koelmeyer, L. (2018, 17 May). Understanding self-management and home monitoring in breast cancer-related lymphoedema: A qualitative study. *Australasian Lymphology Association Conference*, Brisbane.

3.2 Co-authors' statement

DEPARTMENT OF HEALTH PROFESSIONS
Faculty of Medicine, Health and Human Sciences

MACQUARIE University

Co-authors' Statement

As co-authors' of the paper, "*Understanding home monitoring and self-management in breast cancer related lymphedema – a qualitative study*", we confirm that Louise Koelmeyer has made the following contributions to this study:

- Conception and design of the research
- Collection and extraction of data
- Analysis and interpretation of the findings
- Drafting and revising of the manuscript
- Critical appraisal of the content

Professor Kerry Sherman	Date: 12/08/2020
Professor Catherine Dean	Date: 12/08/2020
Professor John Boyages	Date: 12/08/2020

3.3 Understanding home monitoring and self-management in breast cancer related lymphoedema – a qualitative study

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Running head: Lymphoedema home monitoring

Ethics Committees approval: Macquarie University Human Research Ethics Committee Reference No: 5201500929

Summary

The purpose of this qualitative focus group study was to gain an in-depth understanding of the attitudes of those at-risk of or living with lymphoedema following breast cancer towards the concept of lymphoedema home monitoring and whether it may be possible to do this using Bioimpedance Spectroscopy (BIS) technology. Thirty-one women with self-ascribed lymphoedema stage participated in one of five focus groups. Thematic analysis was used to identify five overarching themes regarding participant perspectives towards lymphoedema home monitoring to improve self-management: Lymphoedema knowledge; Facilitators of self-care; Barriers to self-care; Perceived control; and Overall perceptions of home monitoring. The findings provided support for the concept of lymphoedema home monitoring, and that BIS technology may potentially be used as an adjunct to support clinical consultations and self-management in lymphoedema.

Keywords: breast cancer, lymphoedema, home monitoring, self-management, Bioimpedance Spectroscopy, qualitative

Background

As with many chronic conditions, such as diabetes and hypertension, the need to objectively monitor the signs and symptoms of lymphoedema, a side effect of breast cancer treatment, is paramount for its long-term management (Koelmeyer et al., 2019, Kilgore et al., 2018). Lymphoedema may impact an individual physically, functionally, psychologically and financially (Hayes et al., 2008, Perdomo et al., 2014, Cormier et al., 2010, Armer et al., 2013, Ancukiewicz et al., 2011, Hormes et al., 2010, Boyages et al., 2016). The key to managing this condition is comprehensive education coupled with prospective surveillance for the early detection and management of sub-clinical lymphoedema (Whitworth, 2018, Whitworth et al., 2018, Ridner, 2019, Soran et al., 2014). At-risk individuals are recommended to undergo routine measurements at cancer or therapy clinics on a 3-6 monthly cycle

for at least two years (Stout Gergich et al., 2008, Dylke, 2019). Lymphoedema diagnosis typically occurs following clinically apparent fluid accumulation measured with standard techniques such as circumference-based measurements using a tape measure and self-assessment of visible swelling (Taylor et al., 2006). Yet, sub-clinical increases in extracellular fluid accumulation in at-risk limbs are not reliably detectable using these traditional measurement approaches (Koelmeyer et al., 2019).

Bioimpedance spectroscopy (BIS) addresses these measurement limitations by reliably identifying sub-clinical extracellular fluid accumulation using an ‘‘impedance ratio’’ methodology to assess unilateral lymphoedema of the arm (Ward et al., 2008, Ward, 2006). The device measures the electrical resistance of the limbs expressed as the unaffected: affected/at risk ratio (Ward, 2006). Alternatively, this ratio may be linearized and expressed as an L-Dex score which can be generated by the device (Ward, 2015). Abnormal L-Dex values include those outside the normal range (-10 to +10 L-Dex units) and a change of greater than 10 from baseline which is three standard deviations from the normative value (Czerniec et al., 2010). More recent research has suggested that a change of >6.5 - 7 L-Dex units from baseline being two standard deviations from the normative value be more indicative of diagnosing sub-clinical lymphoedema (Fu et al., 2013). The passing of the current when taking a BIS measurement is imperceptible to patients and would be equivalent to that received by holding a AA battery.

BIS technology has been used successfully in laboratory and clinical settings, including for patient self-measurement (Koelmeyer et al., 2020, Ridner et al., 2014a, Ridner et al., 2014b). Given that BIS monitoring is available as a portable device with stainless steel contact electrodes inbuilt within the hand and foot plates and measurements being able to be taken by an individual themselves in sitting or standing and data being able to be remotely monitored via the internet and stored in a secure cloud, this makes possible home-based objective monitoring for at-risk individuals (Koelmeyer et al., 2020).

Yet, it is unknown the extent to which women at-risk of lymphoedema will be willing to adopt and engage with this type of home-based monitoring as it requires them to interact with new technology and undertake ongoing and regular measurements at home, and for some, this may heighten anxiety. Such ongoing self-monitoring will require women to make lifestyle changes, so it is important that willingness to engage with BIS monitoring is determined as a first step in implementing such modifications to lymphoedema care. The objective of this study was to gain an in-depth understanding of attitudes towards lymphoedema home monitoring using BIS and to explore potential factors associated with acceptance of this approach to self-management for those at-risk of or living with lymphoedema following breast cancer.

Methods

Participants and procedure

Women (*N*=31) were recruited through the Australian Lymphoedema Education, Research and Treatment (ALERT) Program's database at Macquarie University, Sydney, who met the eligibility criteria: aged at least 18 years; previously diagnosed with breast cancer; and either at-risk of, or living with, lymphoedema. Participants were required to attend a single 90-minute focus group session. Women who could not speak, or understand English were excluded from the study due to language barriers and continuity of group dynamics. The Macquarie University Human Research Ethics Committee provided ethical approval for the study (Reference no. 5201500929).

Women self-reported their perceived lymphoedema stage according to International Society of Lymphology (ISL) guidelines (Lymphology, 2016). Where possible, the five focus groups (*n*=5-8) were scheduled according to similarity in the self-reported individuals' stages of lymphoedema. Women had not previously had access to or experience with any objective or formal technology such as BIS to monitor their condition in the home. Demographic, medical and lymphoedema data were

collected prior to commencement of the session using a paper-based survey. Focus groups were facilitated by an experienced occupational/lymphoedema therapist (LAK) and a research officer who took notes and supported the facilitator. Following written informed consent from participants the focus group sessions were audiotaped, transcribed verbatim and checked for accuracy against the original recording. Each participant was offered to speak and provide feedback to each question asked, ensuring that all women had the opportunity to share their own experiences and reduce the possibility of some women dominating the conversations.

To gain a general understanding of the lymphoedema status of all focus group participants, the facilitator initially welcomed participants and elicited discussion of the women's lymphoedema history and their perceived impact of lymphoedema on their daily life. Then, participants were asked a series of semi-structured questions to stimulate and guide discussion within the group addressing domains related to lymphoedema and its management: 1) lymphoedema symptoms; 2) lymphoedema management strategies (i.e., clinic / therapist-based and home / self-management); 3) monitoring lymphoedema, including objective (BIS technology) and subjective tools used by therapist and self; and, 4) use of and access to technology, such as computers and internet availability in the home.

Data Analysis

Transcribed focus group data were independently coded by three researchers (LAK, KAS, VM) using thematic analysis (Braun and Clarke, 2006). Within-case codes were initially developed for each participant to capture information that was either salient for that participant, or relevant to the research question. These codes were then categorized into sub-themes, and subsequently grouped into themes. The three coders discussed similarities and differences in coding, reaching 100% overall agreement.

Results

Participants

Thirty-one women of average age 61 (SD 10) years and mostly married participated in the study. Over a third of the women had been diagnosed with breast cancer within the previous three years whilst nearly half of the women had been diagnosed for over five years. Over half of the women reported they were at high risk of developing lymphoedema having had an axillary lymph node dissection. A quarter of the women reported they were at-risk of or living with stage 0 or sub-clinical lymphoedema whilst three quarters of the women self-reported they had clinical lymphoedema across stages 1, 2 and 3. The sample baseline demographic characteristics are summarized in Table 1 and Table 2 shows the number of women attending each focus group according to their self-ascribed ISL stage of lymphoedema. Participants in focus groups number 1, 3 and 5 tended to have more participants with moderate clinical lymphoedema and groups 2 and 4 had those with more at-risk and earlier staged lymphoedema.

Table 1. Characteristics of participants

Characteristic	*n* = 31
Age (years), mean ±SD, (range)	60.77 ± 9.75 (42-75)
Marital status, *n* (%)	
Married or partnered	19 (61.3)
Single	1 (3.2)
Divorced / separated	7 (22.6)
Widowed	1 (3.2)
Education, *n* (%)	
Less than Year 10	2 (6.5)
Higher school certificate or equivalent	4 (12.9)
Vocational qualification	10 (32.3)
Undergraduate degree	7 (22.6)
Postgraduate degree	8 (25.8)
Time since diagnosed with breast cancer, *n* (%)	
1-2 years	8 (25.8)
2-3 years	3 (9.7)
3-4 years	4 (12.9)
4-5 years	2 (6.5)
5-10 years	10 (32.3)
10-15 years	4 (12.9)
Type of lymph node surgery, *n* (%)	
Sentinel lymph node biopsy	15 (48.3)
Axillary lymph node dissection	16 (51.6)
Time since diagnosed with lymphoedema, *n* (%)	
No lymphoedema (at-risk)	7 (22.6)
1-2 years	5 (16.1)
2-3 years	4 (12.9)
3-4 years	4 (12.9)
4-5 years	1 (3.2)
5-10 years	6 (19.4)
10-15 years	4 (12.9)
Lymphoedema stage, *n* (%)	
No lymphoedema (at-risk)	5 (16.1)
0	2 (6.5)
1	7 (22.6)
2	15 (48.4)
3	2 (6.5)

n number, SD standard deviation

Table 2. Participants in each focus group self-ascribed lymphoedema stage

	Focus group number - n (%)				
	1	2	3	4	5
Lymphoedema stage					
At-risk	1 (20)	2 (29)	0 (0)	2 (33)	0 (0)
0	0 (0)	1 (14)	0 (0)	1 (17)	0 (0)
1	2 (40)	3 (43)	0 (0)	1 (17)	1 (20)
2	2 (40)	1 (14)	7 (88)	2 (33)	3 (60)
3	0 (0)	0 (0)	1 (12)	0 (0)	1 (20)

Following coding, five overarching themes were identified reflecting participants' views on lymphoedema and its monitoring, and attitudes towards technology: Lymphoedema knowledge; Facilitators of self-care; Barriers to self-care; Perceived control; Overall perceptions of home monitoring. Several sub-themes were further identified within the overarching themes. Table 3 identifies illustrative examples of quotes from participants in each of the themed domains. Pseudonyms were used to protect the identity of all participants.

Table 3. Illustrative quotations from participants describing the identified themes

Theme	Subtheme	Illustrative Quotation	ISL lymphoedema stage	Participant number (P) & Focus group number (1-5)
Lymphoedema knowledge	Education to individuals at-risk	It should be given at the start, like it did for me, and then at all your appointments, because you're only taking in so much because it's a trauma you're going through.	At-risk	P7 Group 2
	Understanding concept of monitoring for lymphoedema	You need to have a comparison. Are you getting worse are you getting better and that allows you to give yourself some indicators?	3	P5 Group 3
	Understanding of L-Dex reading	I guess you just need to know, obviously the number of what you are, and if there's a range where you should be seeking more advice or doing more things, that would be helpful.	1	P2 Group 1

	Readiness for home monitoring	I think the therapist should be the person to make that suggestion to the person. Now I think you're at a stage where you should be able to monitor it and let that be a guide, someone to guide you through and then you can take over	2	P7 Group 3
	Timing of using home monitoring device	So that's where everyone's so different. And different coping and absorbing information.	2	P1 Group 4
Facilitators of self-care	Motivation for management	I was thinking that would be a real motivator to know (the L-Dex score), just to use it as a motivation tool to get out there and keep doing what you have to do. So for me it's the benchmark, and it's where the goal sits and it's the motivator to get it back down again.	0	P5 Group 4
	Compliance and adherence to treatment	I just do normal massage, wear my sleeve when I have to, so I've got it under control so hopefully I'll keep it at that.	2	P3 Group 3

	Therapeutic relationship	And then I met my therapist and she was very encouraging, and we just worked well together.	1	P6 Group 2
	Feedback and reassurance	I think for me, because I haven't any lymphoedema, just getting that L-Dex reading, it's just a lovely reassurance that everything's okay at the moment. So, for me it's just that reassurance, and it's a preventative thing.	At-risk	P3 Group 1
Barriers to self-care	Coping	So that's where everyone's so different. And different coping and absorbing information.	2	P1 Group 4
Perceived control	Empowerment	I think it gives us more power as well. If we're in power of our own health, then we don't have to bother people like my therapist so much. And we can make our own decisions, and they're informed decisions and they're about our life. Knowing that this gardening will cause this; therefore, I know how much gardening I did, so, therefore I know how much management I need to do on that today.	1	P5 Group 5

	Confidence	It (the L-Dex score) wouldn't stop me from doing anything. It doesn't stop me from doing anything now. But it would allow me to make an informed decision about things that I do. If my arm was a high L-Dex reading, well, I mightn't choose to do something that I worked out that increases it at that time.	2	P3 Group 5
	Perceptions of lymphoedema status	What I mostly look for every day as soon as I get up, I'm checking, is this arm much fatter than this arm?	1	P4 Group 1
	Immediate objective feedback	I would use it (L-Dex device) quite a lot at the beginning until I got the feel for that and then I would know what to do. Because I know if I don't wear the sleeve for a couple of hours it's okay. But if I don’t for half a day it is not okay. So then maybe I'll change my pattern of behaviour. Then I would like to use it (L-Dex device) again to check whether it's working.	1	P5 Group 5

	Confidence and reassurance	I think it'd be great just to have a machine, so I know if it's (L-Dex score) suddenly going up or down, because I don't notice any different… but having a machine would probably give me a bit more confidence to know, yes it is fine what I'm doing, or no you need to change it.	1	P2 Group 1
	Accessibility and usability of technology	There are a lot of other women who don't have technology and who wouldn't have a clue how to use it. I've got friends my age, they've never worked, they've never really been exposed.	2	P6 Group 3
	Perceived limitations of home monitoring	My idea is to deal with what you've got. Enjoy your life as much as you can. Do everything you possibly can. Just talking to some people, I think people would get worried and not do things. That would be my negative side of that whole thing. That's just me.	3	P2 Group 5
	Affordability	I think one of the factors for me was having to give up work, my particular work and I didn't have any income coming in, even now, still trying to get back on my feet, it would be an issue, definitely.	At-risk	P2 Group 4

	Technology	I think you've got to get the people who are into technology to get into it first and then it filters down. I don't think you can go to the non-technology people and get them to start it up.	2	P7 Group 3
	Anxiety	I don't think I'd want to try and do it (L-Dex measurement) each day, I would want to do it perhaps once a week and see how I go. But if I did it every day it then becomes a moment when you're anxious about things all the time. So I would prefer to perhaps weekly or maybe even longer, just to see.	1	P1 Group 2

ISL – International Society of Lymphology

Lymphoedema knowledge

Education to women at-risk - Most participants felt it was important to be informed about lymphoedema, its risk factors, risk reduction practices, early warning signs, symptoms to be aware of, strategies for monitoring and how to manage the condition. Many shared mixed reports about the education provided to them from oncologists and surgeons. Some participants reported lymphoedema information being "not sufficient or considered a priority" and others feeling "totally informed" by their surgeon and oncologist. This seemed to relate to the timing of a participant's diagnosis– those more recently diagnosed appeared to be given more accurate information about lymphoedema. Participants discussed how lymphoedema education needed to be "evidenced-based and current" as there are "many myths and misinformation in the community" and given soon after the breast cancer diagnosis; however, the "information needed to be given slowly over time and repeated" as sometimes it was too "emotionally overwhelming for them to absorb".

Understanding the concept of monitoring for lymphoedema – Participants who had been offered lymphoedema monitoring as part of their multidisciplinary care from the time of breast cancer diagnosis felt reassured that health professionals were "keeping an eye" on things for them. Others who were not offered monitoring and subsequently developed lymphoedema indicated feeling regret for this lost opportunity of early detection and management.

Timing of using a device for monitoring – Participants unanimously agreed that lymphoedema monitoring should commence ideally at the time of breast cancer diagnosis. "Lymphoedema monitoring should be like another routine baseline test" that gives you information that can be used later to monitor change. A few participants reported that lymphoedema monitoring was quick and easy using the "L-Dex device" so could almost "be taken each time you went to the clinic for any treatment".

Understanding of BIS reading – Participants commented that their understanding in "layman's terms" of lymphoedema monitoring, including interpreting the L-Dex device and the normal L-Dex range, has helped them to be more aware of signs and symptoms of lymphoedema and what to do if they noticed any changes. Participants reported that getting immediate objective feedback was "lovely reassurance" that "everything's ok at the moment" and seeing whether the readings were stable was worthwhile and "gives you a sense of security."

Readiness for home monitoring – Participants reported that there is "a certain point in time which they would be ready or prepared to take on the responsibility" of home monitoring using a monitoring device to receive objective measurements, rather than just from their therapist. This "point of time" may be different for individuals depending on their risk of developing lymphoedema, the intensity and physical effects of their medical treatment and "everything else" they are doing during this stressful time. Others said that "everyone's so different" and have "different coping and absorbing information" abilities. It was recommended that a variety of options are needed for all women to access and benefit.

Facilitators of self-care

Motivation for management – Several participants reported the importance of motivating themselves to self-manage their lymphoedema condition to keep it under control. Internal factors included positive thinking about the benefits of self-management and potential new treatments in the future, developing focused and realistic goals, and utilizing coping mechanisms developed in previous life experiences. External motivating factors reported included having a good partnership with a qualified therapist, a supportive partner and family, and having access to the latest evidence-based treatment.

Adherence to treatment/self-management – Adherence to self-management tended to be linked to knowledge and awareness of symptoms. If participants reported adhering to recommended evidence-based treatment and felt better, they tended to continue their own self-

management. Comments like “I wear my sleeve 24/7, I hate it in summer, but I know it's not worth going without it” were common amongst participants.

Therapeutic relationship – Partnering with a lymphoedema therapist was perceived as enhancing feelings of control, “seeing my therapist helped me to feel more confident to do my own self-management”. Participants described their therapists as “the experts in knowing the latest advances in treatment and it’s important to have an overall management plan working in conjunction with the therapist”. Those reporting that their condition was well-controlled all agreed they had a positive relationship with their therapist who guided, supported, and monitored them.

Feedback and reassurance – Several participants reported that seeing their therapist on a regular basis was able to provide them with feedback, reassurance and support regarding their own self-management, a “motivation tool to get out there and keep doing what you have to do”.

Barriers to self-care

Stress & Coping - Several participants described how having lymphoedema and the ongoing management of the condition impacts their quality of life and psychological wellbeing. Comments like “I think lymphoedema is often harder to cope with than the actual breast cancer because it's something that you've got for the rest of your life. This is one of the hardest things to grapple with and to manage” was often described by those living with more advanced stages of lymphoedema. Some participants reported lack of support from their partner or family members negatively impacted their coping and self-management. Others reported that general stress in the family impacted their ability to self-manage.

Perceived control

Empowerment – Most participants reported feeling empowered by having their lymphoedema or arm at-risk being monitored regularly, with feedback given about what the

objective measurements mean in relation to their own self-management such as “I'm a numbers person. And if I can get my numbers regularly, track it like that, then I'm comfortable and then I don't stress”.

Confidence – Several participants reported feeling confident knowing what to do when the objective measurements changed. They may have to change their self-management to “be more diligent with wearing their sleeve” or perhaps they “overused their arm in the garden” so needed to rest a little or spend less time gardening in one session.

Overall perceptions of home monitoring

Perceived advantages of home monitoring with a device – Participants shared how it would be useful to have a device that can take objective measurements to monitor their lymphoedema at home in between regular therapist reviews. Discussions surrounded the usefulness and practicality/feasibility of using a BIS home monitoring device. Participants discussed how useful it would be to have a device at home that you can use to “see whether there's a positive or a negative response to what you're doing so you can change what you're doing if required”. Having a device may also give an individual “more confidence in their own self-management”.

Perceptions of lymphoedema status – Many participants felt that having a home monitoring device would allow an individual to have an accurate objective perception of their lymphoedema status, indicating fluid levels and a gauge of the effectiveness of their own self-management. Getting such feedback “would influence how I manage it”. Another participant agreed that having a device at home “would be a motivator to keep you on track without the inconvenience of always having to make an appointment to see your therapist”.

Immediate objective feedback – Having objective feedback at home would allow an individual to change their self-management based on the results and put their mind at ease or assist in reducing complacency. One participant shared how she "would not want to get too obsessive about only responding to the readings in isolation, rather than how the arm was feeling overall".

Confidence and reassurance – Several participants reported that having a home monitoring device would "probably give me more confidence to know, 'yes it is fine what I'm doing, or no you need to change'" and others reported that it gives you "more power" so that you don't have to go and see your therapist if it's not really necessary.

Technology – Participants were all generally positive about using technology to operate a BIS home monitoring device. A few of the older participants said that they had access to internet and computers or smart devices; however, they would require some training in accessing and using the device to take a measurement and they may have to get "their family to assist".

Timing options for when to commence using a BIS home monitoring device were discussed, with many indicating it would be best for the therapist and individual to determine the right timing. Most thought it should not be commenced at the time of breast cancer diagnosis, as they would be too overwhelmed, and that education and clinic monitoring was needed before introducing home monitoring. The timing of how often BIS measures should be taken at home also varied between participants. Generally, participants indicated that monitoring measurements should occur more frequently initially to get an understanding of using the technology and any normal variation in readings, but that moving forward this frequency could be tailored to the individual. Some participants indicated that "daily to weekly (measurements) initially, then moving to monthly" would be appropriate, and that measurements should be taken more regularly for those who were deemed higher risk and in the first two years since breast cancer diagnosis to monitor for early detection of sub-clinical lymphoedema. Those with long term clinical lymphoedema reported that

they may only use the device "if they noticed symptoms or if they wanted to experiment with their self-management and gain feedback". A few participants reported that they wouldn't want to take measurements too frequently as they wouldn't want to be alarmed or worried by fluctuating readings or allow it to "dominate my life".

Participants were keen to receive their monitoring data in the form of an application (app) that they could share with members of their multidisciplinary team. If they were monitoring themselves from home, participants indicated that guidelines were needed regarding what to do if the reading went outside the normal threshold limits, and how they would seek early intervention in a timely manner.

Perceived limitations of home monitoring with a device

Affordability - All participants reported that whilst they understood the value and practicality of the device, cost was an important factor when considering the feasibility of owning a device, "it would have to be affordable. I certainly understand that, because having lost all my income (during my treatment) ……yes you want to be able to do it, but you have to be able to afford to do it with everything else". Another perspective was that "I'd like to rent it first, see whether I use it… if we rented it and I used it, you then might consider buying it. Then that gives people an affordable option to try it before they commit". Another participant suggested having a "two-year rental plan like a mobile phone could be an option so that you could monitor at home for the two-year time when lymphoedema is commonly diagnosed".

Technology – Supporting people to build confidence in using the technology was regarded as important by participants, including accessing the internet and operating the device. Simple resources and training opportunities were noted as being critical to optimize usefulness of the monitoring program.

Anxiety – Some participants discussed how they would need to have a good understanding of what the readings meant and how to access help if the readings started rising, to avoid increasing

anxiety levels. The concept of home monitoring is to "reduce anxiety and I certainly don't want to be made paranoid about it (lymphoedema) developing".

Discussion

This qualitative study reported on participants' experiences of being at-risk of, or living with, lymphoedema following breast cancer treatment, focusing on identifying attitudes towards home monitoring using BIS technology, and factors that assisted or limited their current self-management approaches. Tailored evidenced-based lymphoedema education at the time of breast cancer diagnosis and at regular intervals throughout the first two years was favoured by all participants, reflecting best practice guidelines (Dylke, 2019, Stout Gergich et al., 2008, Kilgore et al., 2018, Koelmeyer et al., 2019, Whitworth et al., 2018). Participants supported lymphoedema education and monitoring commencing in the clinic setting before introducing home monitoring to complement face to face consultations. Timing for introducing home monitoring may be dependent on the individual's lymphoedema risk factors, treatment side effects and their levels of motivation.

Many participants reported on the importance of a positive and supportive relationship with their multidisciplinary breast cancer team, including a qualified lymphoedema therapist, to understand and adhere to their recommended self-management. This support enables the women to feel confident and motivated to carry out self-management, consistent with research highlighting the importance of patient knowledge for optimal adherence to a self-management regimen (Sherman and Koelmeyer, 2011, Sherman et al., 2015, Alcorso et al., 2016a, Alcorso et al., 2016b). Participants reported that receiving objective measurements via BIS home monitoring may positively affect adherence to self-management, but that it was important to have clear guidelines for how to action any elevations or fluctuations in readings. It was agreed by participants that the frequency of home measurements should differ, with those at-risk and/or in early stages of sub-clinical lymphoedema enacting more frequent measurements than those with more stable and

advanced clinical lymphoedema. These views are consistent with evidence that BIS is one of the most effective measuring tools for determining sub-clinical changes before visible signs of swelling occur and guidelines for monitoring recommending three monthly intervals for the first two years after breast cancer diagnosis (Dylke, 2019, McLaughlin, 2020a).

Providing education and self-monitoring of chronic health conditions has been shown to enhance the effectiveness of self-care, to enable the establishment of self-care goals and reinforce continuation of self-care (Ridner et al., 2014b). It is likely that being able to closely monitor and obtain objective feedback on the impact of different lymphoedema self-care actions through devices such as home-based BIS will promote enhanced perceptions of behavioural control over lymphoedema (Ajzen, 2011, McEachan et al., 2011, Hardeman et al., 2002). This, in turn, should lead to improved motivation and enhanced adherence to self-care treatments (Ridner et al., 2014a, Ridner et al., 2014b).

Study Limitations

Notwithstanding these findings, certain limitations should be considered. Small numbers of relatively well-educated Australian women self-selected to participate in these focus groups. Consequently, their views may not be representative of the general population of breast cancer survivors with lymphoedema or generalizable to non-Australian women. Personal interviews and physical examinations were not conducted as part of this qualitative study. Therefore, there are no objective data to validate participants' self-reports of arm condition, symptoms, or self-management regimes.

Conclusions

These findings provide support for the concept of BIS home monitoring as part of lymphoedema self-management and as an adjunct to clinical consultations. Future research is needed to ascertain the feasibility and acceptability of BIS home monitoring, as well as the specific benefits that can

be derived from this approach both in terms of the women affected/at-risk, as well as lymphoedema therapists and health professionals.

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Author contributions:

Louise A. Koelmeyer: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, writing - original draft, and writing - review and editing.

Kerry A. Sherman: conceptualization, data curation, formal analysis, investigation, methodology, writing - original draft, and writing - review and editing.

Catherine Dean: writing - original draft, and writing - review and editing.

John Boyages: conceptualization, methodology, writing - original draft, and writing - review and editing.

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CHAPTER 4

Study III - A comparison of the L-Dex® U400 with the ImpediMed SOZO device: A reliability and validation study

4.1 Preface

In Chapter 3, women reported that having objective measurements using BIS for home monitoring may positively affect their adherence to self-management, however, it would be important to have clear guidelines for how to action any elevations or fluctuations in readings. It was agreed by participants that the frequency of home measurements should differ, with those at-risk and/or in early stages of sub-clinical lymphoedema enacting more frequent measurements than those with more stable and advanced clinical lymphoedema. In reflecting on the qualitative feedback from the women in the focus groups, if home monitoring is going to be effective and support the prospective surveillance model of care then the BIS technology would need to be easy to use and accurate in the home. In Chapter 4 we completed a cross-sectional study design aimed to assess and compare BIS measurements made in three different body positions using two different impedance devices in women with and without arm lymphoedema.

Ethical approval for this study was granted by the Macquarie University Human Research Ethics Committee (Medical Sciences) and is provided in Appendix 3.1.

This chapter is presented in the format of the paper published in *Lymphatic Research and Biology Journal*.

Koelmeyer, L.A., Ward, L.C., Dean, C., & Boyages, J. (2020). Body positional effects on bioimpedance spectroscopy measurements for lymphedema assessment of the arm. *Lymphatic Research and Biology.* 18(5), 464-473. https://doi.org/10.1089/lrb.2019.0067, [6 GS citations, IF 1.493]

The following conference abstract also relates to the work conducted in this Chapter:

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4.2 Co-authors' statement

DEPARTMENT OF HEALTH PROFESSIONS
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Co-authors' Statement

As co-authors' of the paper, "*Body positional effects on bioimpedance spectroscopy measurements for lymphedema assessment of the arm*", we confirm that Louise Koelmeyer has made the following contributions to this study:

- Conception and design of the research
- Collection and extraction of data
- Analysis and interpretation of the findings
- Drafting and revising of the manuscript
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4.3 Body positional effects on bioimpedance spectroscopy measurements for lymphoedema assessment of the arm

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Body Positional Effects on Bioimpedance Spectroscopy Measurements for Lymphedema Assessment of the Arm

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Abstract

Background: Bioimpedance spectroscopy (BIS) measurements have conventionally been performed using a device that uses gel-backed electrodes with the patient in a supine position. More recently, impedance devices that use stainless steel electrodes with the patient in a standing position have become available. The aim of this study was to assess and compare BIS measurements made in three different body positions using two different impedance devices (lead device and stand-on device) in women with and without arm lymphedema.
Methods: A cross-sectional study design was used to recruit two cohorts of women, healthy controls ($n=47$) and those who had been diagnosed with breast cancer ($n=53$) and were either at risk of ($n=14$) or with unilateral arm lymphedema ($n=39$). BIS measurements were taken three times in each position for each device.
Results: Impedance measurements were reliably made using either a lead or stand-on device with a coefficient of variation being 0.6% or lower. Absolute impedance measurements for the stand-on device were larger than the comparable lead device values due to the difference in electrode position, but were highly correlated ($r=0.92$, $p<0.0001$). Interarm impedance ratios and L-Dex scores were slightly (3.1% equivalence), but significantly different.
Conclusion: The findings support impedance measurements being made reliably using either the lead or stand-on device, representing supine and upright measurement positions, respectively. Data between devices were, however, not directly interchangeable.

Keywords: lymphedema, bioimpedance spectroscopy (BIS), impedance, L-Dex

Introduction

Lymphedema is a chronic inflammatory condition, which is the result of a functional overload of the lymphatic system, whereby the lymph volume exceeds lymphatic transport capacity. As a consequence, abnormal accumulation of protein-rich fluid in the interstitial space of the affected area occurs, causing swelling of limbs and other parts of the body.[1–3] Lymphedema is a poorly understood and underresearched complication of cancer treatment, which can significantly reduce quality of life.[4–6]

When lymphedema is present, lymph and other fluids build up in the interstitial spaces of the tissues. This results in an overall increase in the total amount of extracellular fluid (ECF) in the limb, causing swelling. This can be quantified by measuring the impedance (opposition) to a low-frequency current that has been passed through the limb. Low-frequency current (<10 kHz) travels predominantly through the ECF, where the lymphedema manifests. As lymph accumulates, that is, ECF increases, the impedance to the current proportionally decreases. This decrease in impedance is a quantitative measure of lymphedema.[7]

Bioimpedance spectroscopy (BIS) is a technique used for the measurement of biological impedance at many frequencies, including the ideal frequency of measurement, 0 kHz.[8] BIS has been reported to be effective for the measurement of ECF and subclinical changes in ECF to predict the onset of lymphedema in the arms.[7,9,10] It is a noninvasive technique that directly measures the accumulating ECF, which is characteristic of early subclinical lymphedema.[7,11–13]

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Detection of subclinical lymphedema through surveillance and early intervention has been found to reduce progression to clinical lymphedema.[11,14]

Conventionally, BIS measurements are performed using an impedance analyzer, which makes its measurements by leads attached to the skin by Ag-AgCl electrocardiography-style electrodes.[12] Measurements are typically performed with the patient supine and electrodes placed on the hands and feet, although measurements may also be performed with the patient sitting. More recently, impedance devices have become available for which the patient remains upright, while standing on stainless steel electrode plates with hands in contact with electrodes located on a bar or handle.[15,16] These devices are more convenient to use and are able to make measurements of all body segments simultaneously and save time by avoiding the need for the operator to move skin surface electrodes around the body and making repeat measurements. While these stand-on devices have been used extensively for body composition assessment[17–20] and to a limited extent for lymphedema assessment,[21] they have not been systematically assessed for comparability with conventional lead-type measurements.[22] van Zanten and Ward.[15] undertook a small-scale study comparing the two types of devices and found that, while stand-on devices are acceptable, the methods were not directly interchangeable. Thurlow et al. and Esco et al. reported that stand-on devices had several reported practical advantages, including permanently incorporated electrodes standardizing anatomical positioning and reduced total measurement time, all potential critical factors in obtaining accurate and precise measurements.[17,23]

The aim of this study was to assess and compare BIS measurements made in three different body positions using two different impedance devices (lead device and stand-on device) in healthy women and those at risk of or living with arm lymphedema consequent to breast cancer treatment. Specifically, we plan to evaluate the following:

1. Intrareliability measurement (technical) error across positions and between devices.
2. Repeatability of BIS measurements over time using stand-on device.
3. Differences in impedance measurements for control and lymphedema groups across three body positions and two devices.
4. Impedance ratio differences between devices.
5. Ratio and L-Dex scores comparing current clinical protocol (lying, lead device) with proposed new protocol (standing, stand-on device).

Method

Design

A cross-sectional study design was used to recruit two cohorts of women, healthy controls and those with breast cancer and were either at risk of or living with unilateral arm lymphedema, who were invited to participate in the study from the Australian Lymphoedema Education, Research and Treatment (ALERT) Program's database held at Macquarie University as well as by invitation flyers displayed around the university campus and lymphedema clinics. Ethical approval was obtained from the Macquarie University Human Research Ethics Committee (reference no. 5201700439) and all participants provided written informed consent.

Participants

Eligibility criteria for both groups included women who were between 18 and 90 years of age with self-described health as satisfactory. Participants included both women with clinically ascribed lymphedema as a result of treatment for breast cancer and also those at risk of lymphedema (lymphedema group) and healthy women with no prior incidence of breast cancer (controls). No attempt was made to age match participants between groups as we were exploring the operational equivalence of two impedance devices and different body positions. Participants attended the Macquarie University Lymphedema Clinic on a single occasion for a 45- to 60-minute appointment with all measurements being taken by two trained research assistants. Participants were allocated a case identification number so that all data would be de-identified for analysis.

Participants were excluded from the study if they had implantable devices such as pacemaker or other inbuilt stimulator, or if they were pregnant as these are contraindications for impedance measurement. Participants were also excluded if they reported having a health condition that might affect body fluid status such as renal disease or were taking diuretic medication.

Anthropometric measurements

Demographic information for each participant was obtained along with information regarding cancer, adjuvant treatments, and lymphedema history. Height was measured to the nearest 0.1 cm in a standing position without shoes using a stadiometer (SECA 213, Hamburg, Deutschland). Weight was measured by standing on electronic scales (SECA 813, Hamburg, Deutschland) without shoes and in light clothing to the nearest 0.1 kg. Body mass index (BMI) was calculated from weight in kilograms divided by height in meters squared. Age was calculated from date of birth. Self-ascribed limb dominance was recorded. For those at risk of or living with lymphedema, the at-risk arm was the side of their breast cancer treatment. Stage of lymphedema was determined using the International Society of Lymphology (ISL) classification guidelines.[24] For the healthy control group, the dominant limb was considered the ''at-risk'' limb.[9]

Impedance measurements

Devices. Participants completed BIS measurements of arms using two commercially available impedance devices in a lying (supine), sitting, and standing position for the lead device and in a standing and sitting position for the stand-on device. BIS measurements were taken three times in each position on each device and all data collected were recorded on a Case Report Form and saved in the software for each device securely.

The lead device (L-Dex® U400; ImpediMed Limited, Brisbane, Australia) is a BIS device, which uses an ''impedance ratio'' methodology to assess unilateral lymphedema of the arm and leg.[25] The device measures the resistance at 0 kHz (R0) of the unaffected limb and compares this to the resistance at 0 kHz of the affected/at-risk limb expressed as

the following ratio (unaffected: affected/at risk). Alternatively, this ratio may be linearized and expressed as an L-Dex score.[25] The lead device is battery powered and portable. It has a tetra-polar set of leads, which were attached to self-adhesive dual-tab pre-gelled Ag-AgCl electrodes (ImpediMed Limited) by means of alligator clips. The electrodes were placed on the hands and feet and the sense electrode aligned with the ulnar styloid and malleolus as per the manufacturer's protocol. The dual-tab electrode automatically locates the current drive electrode 9.5 cm distally. Electrode sites were cleaned with alcohol swabs before electrode attachment.

The newer stand-on device (SOZO®; ImpediMed Limited) is also a BIS device utilizing the same ''impedance ratio'' methodology as the lead device; however, instead of skin gel electrodes, stainless steel contact electrodes are used. The stainless steel electrodes are inbuilt within the hand and foot plates of the device. The current drive and sense plates are located under the sole of the feet and palm and fingers of the hands. Before measurement, electrode plates were swabbed with alcohol wipes for infection control and to assist in achieving good skin contact with electrodes.

Measurement protocol. Participants were measured in sitting and standing positions for both devices and in supine position only for the lead device. In seated and standing positions, arms were abducted with hands resting on table or hand plate, palms facing down. For the lead device, the table height was adjusted to be the same as the hand unit of the stand-on device. For supine measurements, arms were slightly abducted and palms facing down with the participant lying on a nonconductive examination bed. All jewellery on the wrists and ankles were removed.

The order of measurements was using the lead device in supine, sitting and then standing, followed by standing and sitting measurements with the stand-on device. All measurements were performed on both arms and in triplicate. The stand-on device automatically makes simultaneous measurements on both arms. For the lead device, the operator was required to transfer the leads between electrodes on each arm. All measurements were made according to the principle of equipotentials.[12,26]

Data analysis

Electrical resistance values at zero current frequency (R0, measured in ohm) for each arm in each measuring condition (device and position) were obtained from the recorded impedances according to Cole theory as described by Ward[25] using manufacturer's software (Impsoft V2.2.0.1) for the lead device and in-built software for the stand-on device. ECF, including lymph, is optimally quantified from R0. Unfortunately, a number of technological and safety issues preclude being able to measure R0 directly. Instead, R0 is estimated by modeling the impedance data (measured in ohms) obtained from measurements made within the practical measurement region of 5–1000 kHz.[25] R0 data and L-Dex scores for this study were extracted from the software and imported into a spreadsheet for further analysis. Data were expressed as mean ± standard deviation (SD). Data that were manually entered from the case report form into an electronic spreadsheet were checked for accuracy.

Descriptive statistics (mean, SD, and coefficient of variation [CV]) were used to describe the baseline characteristics of the sample by group with group *t*-tests used to investigate significant differences.

Impedance ratios were calculated as R0 unaffected: R0 affected according to dominance as described above. Comparability of the two devices was assessed using generalized linear model (GLM) with paired *t*-tests for *post hoc* multipole comparisons for normally distributed data, concordance correlation,[27] limits of agreement analysis,[28] and equivalence testing using two one-sided *t*-tests (TOST).[29]

Statistical analyses were carried out using either NCSS version 10.0.12 (NCSS LLC, East Kaysville) for GLM or MedCalc version 19.0.5 (MedCalc Software bvba, Ostend, Belgium) for other analyses.

Results

Characteristics of participants

One hundred participants were enrolled into the study and were divided into one of two groups. The healthy control group included 47 women who had no history of breast cancer or lymphedema, and the lymphedema group included 53 women who were at risk of ($n = 14$) or had been diagnosed with unilateral arm lymphedema ($n = 39$) following breast cancer treatment. Those with no known history of lymphedema (but at risk) were defined within the lymphedema group as they may have had undiagnosed subclinical lymphedema.[30] The demographic characteristics of participants are summarized in Table 1. The lymphedema group was significantly older and heavier, but significantly shorter than the healthy controls. For those participants with lymphedema, the mean time since their breast cancer surgery was 7.2 and 5.7 years since lymphedema diagnosis. The majority (60%) diagnosed with lymphedema were classified as ISL stage 1 or 2 and 26% were classified at risk.

Intrareliability measurement (technical) error across positions and between devices

Both devices were found to have excellent reliability with the CVs being 0.6% or lower (Table 2). Irrespective of body position and whether in the lymphedema group or control group, both devices measured impedance with the similar precision as indicated by the similar low (<1%) CVs. In the lymphedema group, the absolute R0 values were significantly lower (10.5%, $p < 0.0001$) in the affected arm compared to the unaffected arm. These differences were observed irrespective of body position of measurement or impedance device. A similar significant, but smaller difference (1.5%, $p < 0.009$ to $p < 0.012$) in impedance values was also seen in the control group, indicative of the larger ECF volume in the dominant arm (Table 2). Absolute impedance values were significantly greater ($p < 0.001$) when measured by the stand-on device compared to the lead device irrespective of whether the participant was measured in sitting or standing. This reflects the longer interelectrode distance between the palm and the sole of the foot in the stand-on device compared to the wrist to ankle distance for the lead device.

Table 1. Characteristics of Participants

Characteristic	Groups: Control n = 47	Groups: Lymphedema n = 53	p
Age (year), mean ± SD (range)	37.9 ± 15.6 (19–74)	60.6 ± 9.9 (39–80)	<0.0001
Dominance (R:L)	43:4	49:4	
Arm at risk (R:L)		22:31	
Weight (kg), mean ± SD (range)	66.9 ± 14.2 (45.8–104.7)	77.0 ± 15.3 (48.6–132.5)	0.001
Height (cm), mean ± SD (range)	166.7 ± 6.4 (152.5–177.8)	163.2 ± 6.1 (148.5–176.0)	0.006
Body Mass Index (kg/m^2), mean ± SD (range)	24 ± 4.7 (15.5–37.0)	28.8 ± 5.0 (21.4–44.1)	<0.0001
Time since cancer surgery (years), mean ± SD (range)		7.2 ± 5.2 (1–28)	
Time since lymphedema diagnosis (years), mean ± SD (range)		5.7 ± 4.2 (0.75–16)	
ISL lymphedema stage, *n* (%)			
At risk		14 (26)	
0		4 (8)	
1		17 (32)	
2		15 (28)	
3		3 (6)	
Adjuvant treatments, *n* (%)			
Axillary node dissection		44 (83)	
Sentinel node biopsy		9 (17)	
Radiotherapy treatment		43 (81)	
Chemotherapy treatment		42 (79)	
Hormonal treatment		32 (60)	

ISL, International Society of Lymphology ; *n*, number; SD, standard deviation.

Repeatability of BIS measurements over time using stand-on device

The measurement protocol using the stand-on device provided an opportunity to obtain repeat measurements after a 15-minute interval. Irrespective of sitting or standing positions for both controls and lymphedema participants, there was no significant difference in R0 measurements obtained with the stand-on device over the 15-minute time interval. Data at time zero and 15 minutes were highly correlated [$r_c = 0.993$, $p < 0.0001$; $r_p = 0.994$, $p < 0.0001$; SEE = 5.33 ohm (1.4%)] (Fig. 1).

Differences in impedance measurements for control and lymphedema groups across three body positions and two devices

The effects of dominance/nondominance for the control group and affected/unaffected for the lymphedema group were assessed when comparing devices and across different measurement positions (Fig. 2). R0 of the dominant limbs were lower than the nondominant values in the control group (6.2%, $p < 0.0001$), while in the lymphedema group, R0 of the affected limb was less compared with the unaffected limb (10.6%, $p < 0.0001$) (Fig. 2A, C). Irrespective of device or measurement position, impedance values were lower (9.8%, $p < 0.0001$) (Fig. 2C, D) for the lymphedema-affected arms compared to the contralateral unaffected arm reflecting the greater volume of ECF in these limbs. As expected, impedance measurements for the stand-on device were higher than the comparable lead device values due to the difference in position of electrodes, providing a longer interelectrode length (wrist to palm). These differences were consistently observed for measurements obtained in lying, sitting, or standing positions (Fig. 2).

Impedance ratios: interdevice comparison

Overall, there were no significant differences in impedance ratios between the two devices, irrespective of position of measurement (sitting or standing) or clinical condition (control or lymphedema) (Fig. 3A–D). However, there was, as expected, a significant effect of clinical condition with mean values for the lymphedema group being significantly larger (9.2%, $p < 0.001$) irrespective of measurement position or device (Fig. 3A, B compared to Fig. 3C, D). However, small, but significant differences were seen between devices for both measurement positions when paired comparisons were tested separately for the control and lymphedema groups. Within the control group, the stand-on device values were 1.7% larger ($p < 0.001$) and 2.0% larger ($p < 0.001$) than the comparative lead device values for the sitting and standing positions, respectively. For the lymphedema group, the converse was found with the stand-on device values being 1.6% smaller ($p < 0.001$) than the comparable values for the lead device for both standing and sitting measurements.

Ratio and L-Dex scores: measurement protocol comparison

Comparisons of the lead device in lying, the current protocol, with the stand-on device in standing, the newly proposed measurement protocol, are presented in Figure 4. The two approaches were highly correlated irrespective of whether data were analyzed as impedance ratios or L-Dex scores ($r_c = 0.921$, $p < 0.0001$; $r_c = 0.925$, $p < 0.0001$; Fig. 4A and B

TABLE 2. INTRAMEASUREMENT ERROR ACROSS POSITIONS AND BETWEEN DEVICES

	Lying						*Sitting*						*Standing*					
	Unaffected[a]			*Affected*			*Unaffected*[a]			*Affected*			*Unaffected*[a]			*Affected*		
Group	*Mean*	*SD*	*CV (%)*	*Mean*	*SD*	*CV (%)*	p[b]	*Mean*	*SD*	*CV (%)*	*Mean*	*SD*	*CV (%)*	p[b]	*Mean*	*SD*	*CV (%)*	*Mean*	*SD*	*CV (%)*	p[b]
Lead device																					
Control	367.5	0.9	0.2	361.4	1.8	0.5	0.009	377.8	1.5	0.4	371.6	2.1	0.6	0.009	359.3	2.0	0.5	353.4	1.8	0.5	0.012
LE	334.1	1.4	0.4	299.2	1.1	0.4	0.0001	349.3	1.2	0.3	312.8	1.0	0.3	0.0001	331.7	1.3	0.4	295.7	1.1	0.4	0.0001
Stand-on device																					
Control								449.7	2.8	0.6	431.5	2.8	0.6	0.0001	424.8	2.3	0.6	407.0	2.6	0.6	0.0001
LE								401.8	2.0	0.5	364.4	2.0	0.6	0.0001	371.5	1.9	0.5	337.2	1.8	0.5	0.0001
Absolute difference between devices (%)																					
Control								71.9 (19.0)			59.9 (16.1)				65.5 (18.2)			53.6 (15.2)			
LE								52.5 (15.0)			51.6 (16.5)				39.8 (12.0)			41.5 (14.0)			

Data presented as R0 values (ohm).
[a]For control group, "Unaffected" was assigned as the nondominant arm.
[b]Significance of difference Unaffected versus Affected.
CV, coefficient of variation; LE, lymphedema.

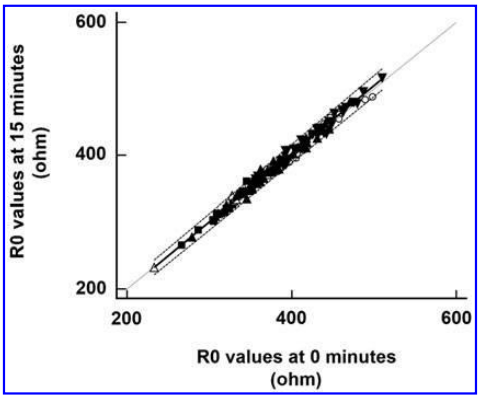

FIG. 1. Repeatability of impedance measurements when standing at 0- and 15-minute intervals for control and lymphedema groups. ○, control dominant; ▼, control nondominant; △, dominant affected; ▲, dominant unaffected; ■, nondominant affected; ▲, nondominant unaffected; ——, 95% confidence interval; · · · · ·, line of identity; ——, best fit line.

for impedance ratios and L-Dex scores, respectively). Limits of agreement analysis showed no significant ($p = 0.92$, paired *t*-test) biases in R0 ratio or L-Dex score between lying measurements using the lead device compared to standing measurements obtained using the stand-on device (Fig. 4C, D). The 2 SD limits of agreement were ±0.10 impedance ratio units (±9.8%) equivalent to a difference of approximately ±10 L-Dex units. However, it is clear from Figure 4C and D that the spread of individual data for the lymphedema group was wider compared with the control group. Results of separate limits of agreement for the control group were ±0.07 for impedance ratios compared with ±0.12 for lymphedema group; the same differences were observed when the data were transformed to L-Dex scores (Fig. 4D).

L-Dex scores for all individuals and group data (as box plots) for the two measurement protocols are presented in Figure 5. The relative positions of individuals within are not identical for two measurement protocols as exemplified by the two highlighted participants. The L-Dex score for participant A was lower (10.1 L-Dex units) when measured with the stand-on device in standing compared to the lead device in lying L-Dex score (20.9 L-Dex units), the reverse being observed for participant B, 4.2 and 16.0 L-Dex units for lying and standing, respectively. Notably, these differences are greater than 10 L-Dex units, the 3 SD threshold indicative of lymphedema, and hence potentially leading to misclassification. While overall there was no difference in mean values, equivalence testing (TOST procedure) indicated that data were equivalent, to within 3.1%, again reflecting differences within individuals. It is noteworthy that this level of equivalence is at least a twofold improvement compared to typical impedance-based prediction of body composition.[31]

Discussion

BIS is an important tool used for the early detection of subclinical lymphedema following breast cancer[32] and is recommended in practice guidelines for the detection

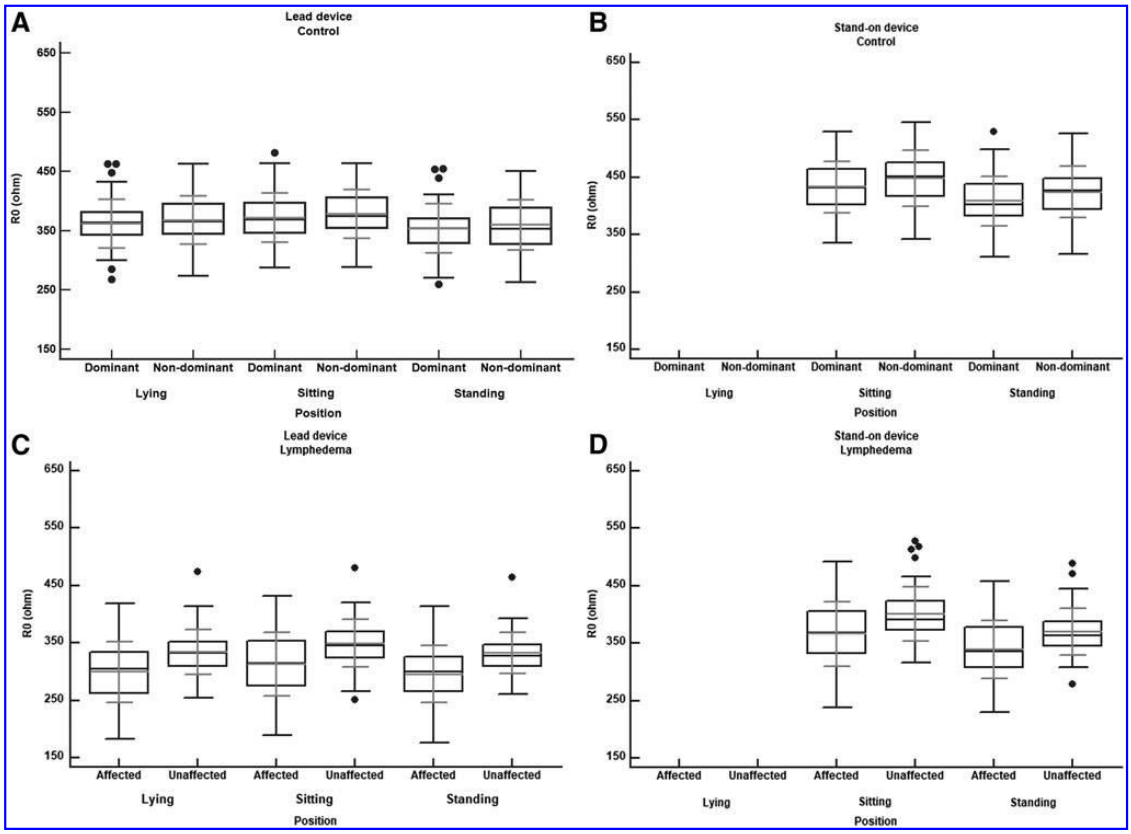

FIG. 2. Effect of limb dominance and presence of lymphedema for control and lymphedema groups across three body positions and two measurement devices. **(A)** Control group dominant versus nondominant limb using lead device in lying, sitting, and standing. **(B)** Control group dominant versus nondominant limb using stand-on device in sitting and standing. **(C)** Lymphedema group affected versus unaffected limb using lead device in lying, sitting, and standing. **(D)** Lymphedema group affected versus unaffected limb using stand-on device in sitting and standing. ●, outside values†; ⊤, 1 standard deviation bar; —, mean; ——, median; ⊤, range for all data excluding outside values†; ▭, 25th to 75th percentile. †Defined as a value that is smaller than the lower quartile minus 1.5 times the interquartile range, or larger than the upper quartile plus 1.5 times the interquartile range (MedCalc Software bvba, Ostend, Belgium).

of breast cancer related lymphedema.[33] The currently accepted BIS measurement protocol for lymphedema assessment is to have the patient in a supine position[33] using a lead device. This study found that, impedance measurements can be reliably made using either the lead device or stand-on device. Irrespective of body position (lying, sitting, or standing), device used, or whether participants had lymphedema or were non-lymphedema controls, both devices measured impedance with similar high precision. Instrumental error (technical measurement error) for each device was small (CV <0.6%), comparable to that found for other BIS devices.[34] It was also shown for the stand-on device that there was little variation in impedance measurements over a 15-minute interval, consistent with the results of Thurlow et al.,[23] suggesting that flexibility in the time of measurements during consultations in clinical practice is possible. However, significant differences between the devices in absolute measures resistance were observed, which means, in the clinic or research setting, the devices should not be used interchangeably.

The significant differences between the devices in absolute measures were not surprising for several reasons. First, there are differences in the anatomical position of the sense electrodes, located at the wrist and ankle for the lead device and on the palm of the hand and the sole of the foot for the stand-on device. This effectively increases the interelectrode length and the electrical volume being measured using the stand-on device, leading to an increase in the measured resistance. The magnitude of this effect is also likely to be increased further since the additional tissue volume of hands and feet is of relatively small cross-sectional area compared to the rest of the limb or trunk and impedance is inversely related to cross-sectional area. Second, when moving from upright to supine, fluid that tends to pool in the extremities due to gravity redistributes to the trunk.[35] Since, the trunk is of larger cross-sectional area than the limbs, this has the effect of decreasing the measured resistance,[36,37] observed to be $\sim$2.5% in this study. Thus, changing from a supine, wrist-ankle measurement to an upright, palm-sole measurement will be the sum of

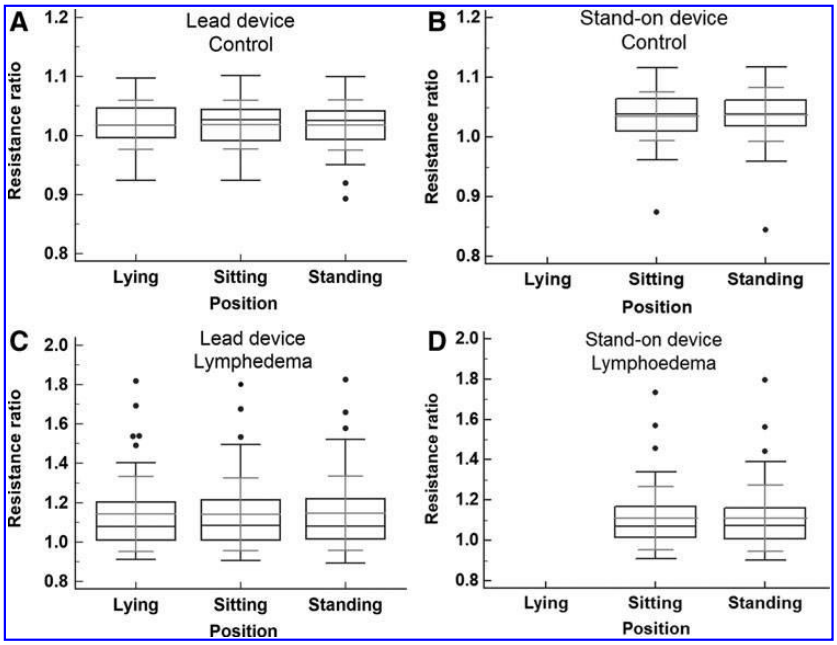

FIG. 3. Impedance ratio interinstrument comparison. **(A)** Control group using lead device in lying, sitting, and standing; **(B)** control group using stand-on device in sitting and standing; **(C)** lymphedema group using lead device in lying, sitting, and standing; **(D)** Lymphedema group using stand-on device in sitting and standing. ●, Outside values †; ⊤, 1 standard deviation bar; —, mean; ——, median; ⊤, range for all data excluding outside values†; ▭, 25th to 75th percentile. †Defined as a value that is smaller than the lower quartile minus 1.5 times the interquartile range, or larger than the upper quartile plus 1.5 times the interquartile range (MedCalc Software bvba).

these two opposing effects. These data where stand-on device measurements were, on average, 15% larger than supine lead device values, suggest that changing interelectrode distance has a much greater overall effect than fluid redistribution on measurement of impedance.

The anatomical and physiologically based differences in impedance noted above will affect both limbs similarly; consequently, this should minimize differences when expressing arm impedances as interlimb ratios. The results of this study support this view with overall no significant difference in ratios or L-Dex scores between the two devices and measurement protocols. Nevertheless, there were small (<2%) differences observed when the data were analyzed by participant group, control, and lymphedema. Furthermore, the effect was in opposite directions in each group. The reasons for this are unclear. It is possible that, when measured in standing, the inclusion of hand volume magnifies the effect of limb dominance on measured impedance. The dominant hand is ~3% larger than the nondominant hand[38] and has an increased ECF volume detectable by impedance.[39] In this study, impedance ratios were calculated as unaffected R0: affected (or at risk) R0 in the lymphedema participants and as nondominant: dominant in the controls. For those with lymphedema, superimposed upon any dominance effect on measured impedance would be a decrease in impedance due to the presence of localized hand lymphedema if present. The larger spread of impedance ratios in the lymphedema cohort compared to controls (Fig. 4) may indicate that, at least in some participants, hand lymphedema may have been present.

The potential clinical significance of these observations deserves consideration. The two measurement approaches were highly correlated with essentially no mean difference between methods (Fig. 4) and both devices may be considered equivalent, (within 3%) at the population level. However, for any individual being measured, the limits of agreement analysis show a 2 SD limit, which is potentially a clinical difference of ±0.1 ratio units or approximately ±10 L-Dex units. Since 10 L-Dex units is the conventionally accepted threshold presumptive of lymphedema,[25] this raises the possibility of misclassification of patients who are at risk for lymphedema. In this study population, the difference between the standard clinical measuring protocol of the two devices (lead device in lying and stand-on device in standing) could potentially lead to a misclassification of patients with clinically ascribed lymphedema in only 2% (two individuals in this cohort of 100).

There are practical and clinically significant implications arising from this study. Use of the lead device in lying is more time-consuming and cumbersome. A nonconductive measuring bed is required and patients are required to lie down for a period, while separate measurements of limbs are made, necessitating the clinician to move device leads between different combination of electrodes during the measurement procedure. Electrodes are disposable and cost of electrodes may be a significant disincentive to use. The advantage of the stand-on device is that it is self-contained, makes

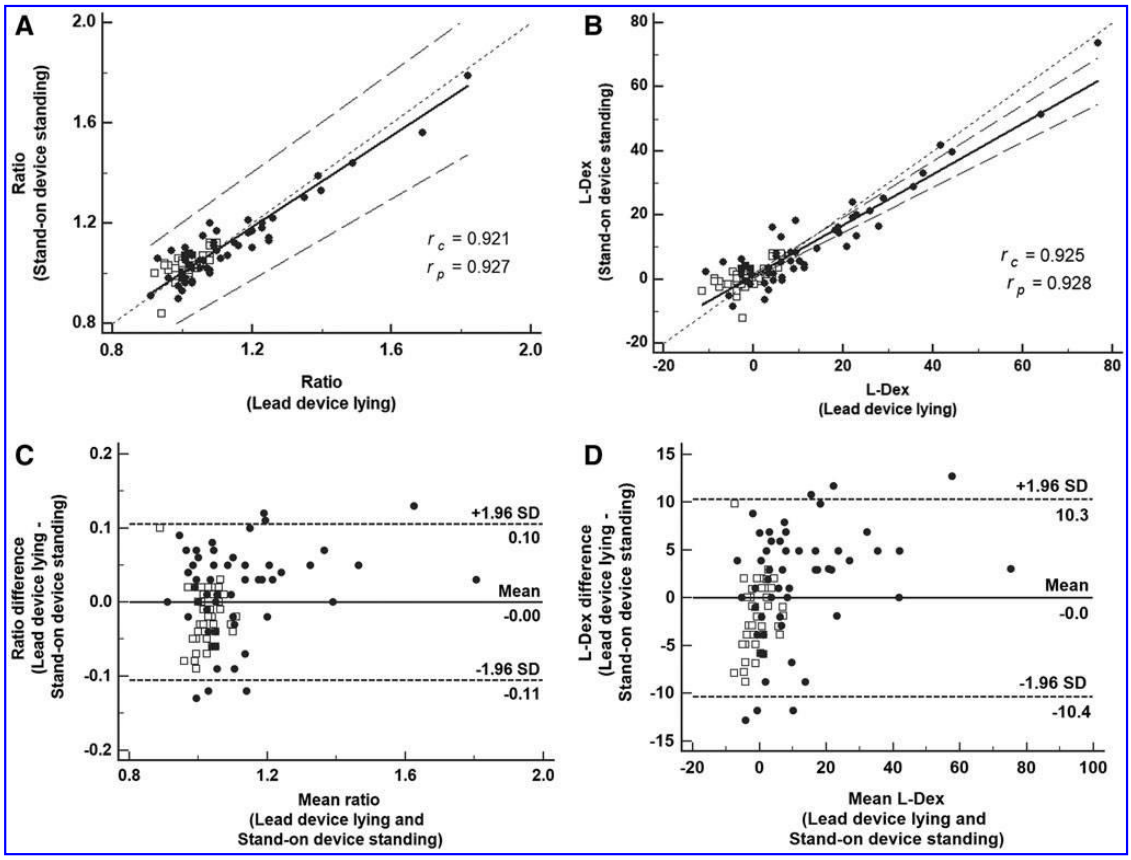

FIG. 4. Comparisons of ratios and L-Dex scores and mean ratios and mean L-Dex scores for lead device in lying with stand-on device in standing. □, Control group; ●, lymphedema group; ——, 95% confidence interval; · · · · ·, line of identity ; ——, best fit line. **(A, B)** Paired samples *t*-test; Passing and Bablok regression analysis. **(C, D)** Bland-Altman plots.

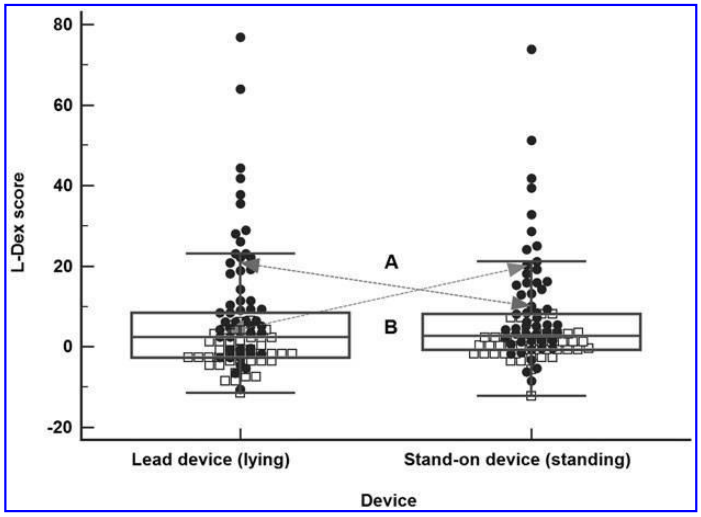

FIG. 5. Comparison of L-Dex scores for individuals using lead device in lying to stand-on device in standing. ●, Lymphedema group; □, control group; ⊤, range for all data excluding outside values†; ——, median of all data; ▭, 25th to 75th percentile of all data; ……., lines connecting paired data for two participants, A and B. †Defined as a value that is smaller than the lower quartile minus 1.5 times the interquartile range, or larger than the upper quartile plus 1.5 times the interquartile range (MedCalc Software bvba).

measurement of all body segments automatically, and there is no requirement for ongoing consumable electrodes.

There are strengths and limitations of this study. The main strength is that the two devices were compared to each other at the same time following the same protocol and all aspects of the protocol were completed by two trained research assistants. Participants were also from a broad range of ages and BMIs, although neither age nor BMI matched between groups. Limitations include that this study is limited to comparing two particular impedance devices and the results may not be generalizable to measurements obtained with impedance devices from other manufacturers. Although both devices are capable of measuring impedance of the legs, these results are applicable to arms only.

In conclusion, this study has shown that both measurement approaches reliably measure arm impedance and L-Dex scores. They are, however, not directly interchangeable. The two methods are within 3% equivalence, but nevertheless, this difference has the potential for misclassification of a small number of individuals when transferring between devices. It is recommended to avoid using the two devices interchangeably, particularly for serial monitoring of patients in prospective surveillance and early intervention model of care programs, where 6.5 L-Dex ($\approx$2 SD impedance ratio) or 10 L-Dex (3 SD) unit change may be considered clinically significant and trigger early intervention.[40,41]

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Authors' Contributions

L.A.K.: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, writing—original draft, and writing—review and editing. L.C.W.: data curation and analysis, methodology, supervision, writing—original draft, and writing—review and editing. C.D.: conceptualization, data curation and analysis, methodology, supervision, writing—original draft, and writing—review and editing. J.B.: conceptualization, data curation and analysis, methodology, supervision, writing—original draft, and writing—review and editing.

Author Disclosure Statement

L.A.K. has acted as an Education Consultant to ImpediMed Limited. L.C.W. provides consultancy services to ImpediMed Limited. ImpediMed Limited had no involvement in the conception, design, execution, and data analysis for this study or in the preparation of the article. ImpediMed Limited was sent the final draft version before submission to confirm technical information was accurate. All other authors declare that they have no individual conflicts of interest or financial ties to disclose.

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CHAPTER 5

STUDY IV: Feasibility and useability of the SOZO device for home monitoring of lymphoedema

5.1 Preface

The findings of Study III described in Chapter 4 supported impedance measurements being made reliably using the lead or stand-on devices with the new stand-on device having the potential to be used within a home setting as an adjunct to clinic monitoring for those at high risk for developing lymphoedema. Data between devices were, however, not directly interchangeable which means that if an individual was being monitored by a clinic or therapist using the lead device that it would be important to take measurements with both devices at the same appointment to ensure any small differences between them from the different electrode positioning could be recognised before transferring to home monitoring using the stand-on device. Now that we have found that there is a user-friendly, accurate and reliable impedance device that can be used in the home environment for self-monitoring, this Chapter describes a feasibility study (Study IV) exploring the feasibility of the stand-on BIS device being used as a home monitoring device for women at high risk of developing lymphoedema to aid in preventing the development of chronic clinical lymphoedema in a prospective surveillance model of care. The prospective surveillance model of care tested in this feasibility study was effectively co-designed with women at risk of or living with breast cancer related lymphoedema as it was informed by the findings from the focus groups presented in Study II (Chapter 3). Specifically, insights from the women regarding the timing of the commencement of home monitoring, the educational component and guidance on self-management strategies were all included in the protocol for Study IV.

Ethical approval for this study was granted by the Macquarie University Human Research Ethics Committee (Medical Sciences) and the Adventist HealthCare Limited Human Research Ethics Committee and is provided in Appendix 4.1 & 4.2.

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5.2 Co-authors' statement

DEPARTMENT OF HEALTH PROFESSIONS
Faculty of Medicine, Health and Human Sciences

MACQUARIE University

Co-authors' Statement

As co-authors' of the paper, "*Prospective surveillance model in the home for breast cancer related lymphoedema: A feasibility study*", we confirm that Louise Koelmeyer has made the following contributions to this study:

- Conception and design of the research
- Collection and extraction of data
- Analysis and interpretation of the findings
- Drafting and revising of the manuscript
- Critical appraisal of the content

Emma Moloney	Date: 12/08/2020
Professor John Boyages	Date: 12/08/2020
Professor Kerry Sherman	Date: 12/08/2020
Professor Catherin Dean	Date: 12/08/2020

Pages 91-102 of this thesis have been removed as they contain published material. Please refer to the following citation for details of the article contained in these pages.

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CHAPTER 6

Discussion and concluding remarks

6.1 Preface

The primary aim of the work presented in this thesis was to explore the prospective surveillance model of care in the early detection and management of breast cancer-related lymphoedema, and to explore ways to enhance this model of care. This primary aim was achieved through the conduct of four clinical research studies with different methodologies including a retrospective analysis of breast cancer clinical data collected in a private lymphoedema clinic comparing the traditional model of care to those involved in a prospective surveillance model of care; a qualitative focus group study to gain an in-depth understanding of attitudes towards lymphoedema home monitoring using BIS technology; a cross-sectional study aimed to assess the reliability of a new stand-on BIS device, which could enable independent home monitoring; and, a feasibility study to determine whether the validated stand-on BIS device could be successfully used as a home monitoring device for women at high risk of developing lymphoedema. In this chapter the main findings of the studies presented in this thesis are summarised. These findings with reference to the latest evidence as well as the limitations of the work are discussed.

6.2 Summary of findings

6.2.1 Study I

Study I consisted of a retrospective analysis of routine breast cancer clinical data prospectively collected for 473 women who attended a private lymphoedema clinic in Sydney, Australia by one lymphoedema therapist over a decade. A traditional referral-based model of care was compared to a prospective surveillance and early intervention model of care which showed that the incidence of clinical lymphoedema was reduced from this new approach. This study found that women undergoing early surveillance received lymphoedema care almost two years earlier than women in the traditional referral group without any difference in visits to the lymphoedema clinic. The early surveillance group had lower incidence of clinical lymphoedema (14%) than the traditional referral group (39%), and those that were diagnosed had less severe lymphoedema (4% compared to 24%). For those diagnosed with lymphoedema, BIS scores increased slowly over time, but the rate of increase was less for individuals undergoing early surveillance.

The findings of Study I supported the use of BIS as part of a prospective surveillance model of care that resulted in earlier detection of lymphoedema over time. Furthermore, the earlier detection of lymphoedema may lead to lower health care costs if it results in the effective management of symptoms and prevents progression to severe clinical lymphoedema.

6.2.2 Study II

Study II used a qualitative focus group approach to gain an in-depth understanding of the attitudes of those at-risk of or living with lymphoedema following breast cancer towards the concept of lymphoedema home monitoring and whether it may be possible to do this using BIS technology.

Thirty-one women (age range 42-75 years) ranging from one to 15 years post-breast cancer diagnosis and time living with lymphoedema, participated in one of five focus groups. A range of lymphoedema stages were represented in the sample from at risk to mild, moderate, and severe lymphoedema to explore the differences of women living with different severities. Five overarching themes were identified regarding participant perspectives towards home monitoring to improve self-management. These included: Lymphoedema knowledge; Facilitators of self-care; Barriers to self-care; Perceived control; and Overall perceptions of home monitoring. Tailored evidenced-based lymphoedema education at the time of breast cancer diagnosis and at regular intervals throughout the first two years was favoured by all participants. Women supported lymphoedema education and monitoring commencing in the clinic setting before introducing home monitoring to complement face to face consultations.

Many participants reported on the importance of a positive and supportive relationship with their multidisciplinary breast cancer team, including a qualified lymphoedema therapist, to understand and adhere to their recommended self-management. This support enabled the women to feel confident and motivated to carry out self-management. Women reported that receiving objective measurements via BIS home monitoring may positively affect adherence to self-management, but that it was important to have clear guidelines for how to action any elevations or fluctuations in readings. It was agreed by participants that the frequency of home measurements should differ, with those at-risk and/or in early stages of sub-clinical lymphoedema enacting more frequent measurements than those with more stable and advanced clinical lymphoedema. Study II supported the concept of home monitoring using BIS as an adjunct to clinic monitoring and self-management in lymphoedema.

6.2.3 Study III

The primary aim of Study III was to assess the validity of BIS technology used in three different body positions using two different impedance devices (traditional lead device and new stand-on device) in women with and without arm lymphoedema. Impedance measurements were reliably made using either the lead or stand-on device with a co-efficient of variation being 0.6% or lower. Absolute impedance measurements for the stand-on device were larger than the comparable lead device values due to the difference in electrode position but were highly correlated (r = 0.92, p <0.0001). Impedance measurements were made reliably using either the lead or stand-on device representing supine and upright measurement positions, respectively. Data between devices were, however, not directly interchangeable.

The findings of Study III supported impedance measurements being made reliably using both devices with the new stand-on device having the potential to be used within a home setting as an adjunct to clinic monitoring for those at high risk for developing lymphoedema.

6.2.4 Study IV

The primary aim of study IV was to explore whether it was feasible to deliver a prospective surveillance and early intervention model of care in the home for women at high risk of developing lymphoedema following breast cancer and whether this model had the potential to decrease lymphoedema incidence, symptom intensity and distress, and to increase lymphoedema self-management, and physical activity.

This Phase I feasibility study found that a prospective surveillance model of care delivered in the home consisting of BIS monitoring, education and support to promote self-management and

physical activity for women at high risk of developing breast cancer-related lymphoedema was feasible and has the potential to be beneficial. At a time when individuals often have their diaries filled with medical, allied health and treatment appointments, BIS home monitoring may support and empower individuals to reduce unnecessary appointments and trips to hospitals and clinics if they know that their lymphatic fluid levels are not fluctuating and are feeling confident in the prospective surveillance model of care at home.

Women generally adhered to the BIS monitoring protocol three times per week. However, it appeared that some participants may have felt empowered to vary the monitoring schedule. Approximately one in five of the participants who had no change or fluctuation in L-Dex scores in the initial three-month monitoring period completed BIS measurements at home less than once per week for the second three-month monitoring period. Likewise, one in four participants who had increasing or fluctuating L-Dex scores increased the number of measurements taken in the second three-month monitoring period.

Only five participants in this group of high-risk women met the criteria for sub-clinical lymphoedema during the initial six-month monitoring period, and many of these were still undergoing adjuvant chemotherapy or radiotherapy treatment. The time to meet the sub-clinical criteria of +6.5 L-Dex score from baseline for participants was quite variable (2 days to 67 days) which suggested adherence to home monitoring was important for timely intervention. This cohort of women were three months post-surgery for breast cancer on entering the study and reported low levels of symptoms causing distress. The women increased the number of self-management strategies that they implemented over the six months, with the most notable increases being in exercise and use of compression. Skin care was the most utilised strategy with >85% undertaking it at baseline. Planned physical activity increased over six months to 5.9 hours / week, a frequency

that exceed the recommended Clinical Society of Oncology guidelines in terms of the recommended 2.5 hours / week duration.

6.3 Comparison with recent evidence

The work presented in this thesis has developed over a six-year period and there have been advances and changes in the management of breast cancer and lymphoedema during this time as well as further international research published to support the prospective surveillance model of care. These are briefly discussed in this section and compared with current evidence.

6.3.1 Evidence supporting prospective surveillance model of care

Scholars and guidelines have advocated that prospective surveillance and early intervention be implemented routinely in breast cancer treatment which aligns with the work of this thesis (Armer et al., 2019; Bundred et al., 2020; Iyigun et al., 2018; Kaufman, 2017; Kilgore et al., 2018; McLaughlin et al., 2020a; Ridner et al., 2019; Shah et al., 2016; Whitworth & Cooper, 2018; Whitworth et al., 2018; Barrio et al., 2019; Shah et al., 2021). As up to 80% of individuals completing intensive breast cancer treatments will attain full life expectancy, they should do so without incapacity from the side effects of the treatments (McLaughlin et al., 2020a). The prospective surveillance model of care recommends a clinical pathway that starts with a baseline assessment of the individual at the time of breast cancer diagnosis, prior to commencing cancer treatments, and proceeds with screening for lymphoedema at regular intervals throughout the cancer treatment to identify a clinically meaningful change from baseline (McLaughlin et al., 2020a). The findings presented in Study I within this thesis, in particular those individuals in the

"early surveillance" group support this prospective surveillance model of care and recommended best practice.

Over the last six years, the prospective surveillance and early intervention model of care has been recommended to reduce the incidence of clinical lymphoedema by key cancer agencies internationally such as the National Cancer Control Network (NCCN), the American Society of Clinical Oncology (ASCO), the National Accreditation Program For Breast Centers (NAPBC), the Oncology Nursing Society (ONS) as well as the National Institute for Health and Care Excellence in United Kingdom (NICE) who have all developed guidelines and position statements recommending the implementation of this model of care or parts of it based on the growing body of research (Armer JM et al., 2020 ; National Institute for Health and Care Excellence, 2018; McLaughlin et al., 2020a; Sanft et al., 2019; American College of Surgeons, 2018).

McLaughlin and colleagues (2020) discussed how the prospective surveillance model of care is recognized as an optimal framework for the American Society of Clinical Oncology to guide clinical implementation of a screening method for the early identification and management of breast cancer treatment–related impairments including lymphoedema (McLaughlin et al., 2020a). Using the prospective surveillance model of care in clinical practice enables the early identification and treatment of sub-clinical lymphoedema, when intervention may prevent the progression to a more severe form of the condition (Kaufman, 2017; Kilgore et al., 2018; Laidley & Anglin, 2016; Shah et al., 2016; Whitworth & Cooper, 2018).

The results of Study I demonstrated that regular clinic visits to monitor extracellular fluid provided an opportunity for health professionals to provide lymphoedema risk-management education, psychological support, physical rehabilitation, empowerment, and survivorship care. In Australia,

the recommended practice is for “at-risk” women to regularly attend clinics to be educated and monitored for lymphoedema. Typically, this occurs on a 3-6 monthly cycle depending on the individuals’ risk of lymphoedema and is supported by the peak national lymphoedema association (Dylke, 2019) and national cancer and consumer agencies (BCNA, 2018; Cancer Australia, 2020; NSW Agency for Clinical Innovation, 2018).

Unlike other methods of objective clinical lymphoedema assessments, BIS can detect sub-clinical lymphoedema (Cornish et al., 2001; Coroneos et al., 2019; Dylke, 2016; Ridner et al., 2020; Shah et al., 2021). BIS directly measures extracellular fluid that is characteristic of early lymphoedema and so can be used in the prospective surveillance model of care (Kilgore et al., 2018; Laidley & Anglin, 2016). More recent literature has also confirmed the more sensitive cut-off for the diagnosis of sub-clinical lymphoedema using BIS being two standard deviations from the normative value (>6.5 L-Dex change from baseline) rather than three standard deviations (>10 L-Dex change from baseline) that was previously recommended (Dylke, 2016; Ridner et al., 2018). Consistent with the evidence for this more sensitive threshold, it should be noted that Study 1 used the original threshold whereas in Study IV the more sensitive criteria (>6.5 L-Dex change from baseline) was used to identify sub-clinical lymphoedema. Detection of sub-clinical lymphoedema through surveillance and early intervention has been found to reduce progression to clinical lymphoedema (Shah et al., 2021; Kilgore et al., 2018; Laidley & Anglin, 2016; Ridner et al., 2019; Whitworth et al., 2018).

The time-course of lymphoedema development also has implications for the prospective surveillance model of care. McDuff and colleagues (2019) discussed how the time course for lymphoedema development depends on the breast cancer treatment received and ranges from 12 to 30 months postoperatively. This group conducted a prospective study of over 2000 breast cases

using perometry with a 10% volume difference defined as a lymphoedema diagnosis. Axillary lymph node dissection without regional lymph node radiation appears to be associated with early-onset lymphoedema (6-12 months postoperatively), regional lymph node radiation is associated with late-onset lymphoedema (18-24 months postoperatively), and 36-48 months postoperatively for those receiving sentinel node biopsy and regional node radiation. These results can influence clinical practice to guide lymphoedema surveillance strategies, patient education regarding risk and potential home monitoring protocols.

Ridner and colleagues (2019) enrolled 1200 women who were diagnosed with breast cancer and randomised to tape measure or BIS monitoring at regular intervals for three years to determine the rate of progression to clinical lymphoedema (PREVENT study) (Ridner et al., 2019). An interim analysis of 508 women who had completed at least twelve months of follow-up with either tape measure or BIS monitoring was completed. Women who triggered sub-clinical lymphoedema criteria underwent early intervention of wearing a compression sleeve and gauntlet (compression hand piece) for 28 days. Results demonstrated that surveillance with BIS reduced the absolute rates of progression of clinical lymphoedema requiring intensive complex lymphoedema therapy by approximately 10%, which is a clinically meaningful improvement. These results support the concept of surveillance with BIS to detect sub-clinical lymphoedema and commence early intervention. As the Australian Principal Investigator for this international multicentre study, in which we recruited and managed 450 women of the total 1200 cohort across ten sites and the only site being outside of the USA, it will be interesting to analyse the completed three-year study data at the conclusion of 2020 (Ridner et al., 2019).

Other studies such as Whitworth and colleagues (2018) found that of 93 high-risk axillary lymph node dissection patients managed with prospective surveillance, only 3% required additional

therapies or showed evidence of chronic lymphoedema over a median two-year follow-up period (Whitworth & Cooper, 2018; Whitworth et al., 2018). Similarly, Kilgore and colleagues (2018) supported Whitworth's findings with only 6% of 146 patients developing chronic lymphoedema after early intervention (Kilgore et al., 2018). Of note, in our Study I, 10% of women diagnosed with lymphoedema in the early surveillance group were diagnosed with sub-clinical (Stage 0) compared with only 1% of women in the traditional referral group, allowing for a greater proportion of those in the early surveillance group being able to access early intervention to prevent progression to clinical lymphoedema.

One common component of the prospective surveillance model of care is the use of compression therapy. The "early intervention" compression therapy protocols used to support this model of care requires further research because there has not been a standardised protocol published and used in surveillance studies. For example, Stout Gergich and colleagues (2008), defined sub-clinical lymphoedema as a 3% limb volume change against preoperative baseline (assessed by perometry) and the intervention was a four-week course of compression garment use. The outcome for this study was whether subsequent clinical lymphoedema (limb volume change greater than 10%) could be prevented with the compression garment no longer required to be worn (Stout Gergich et al., 2008). Soran and colleagues (2014) reported progression from sub-clinical (assessed by BIS) to clinical lymphoedema (assessed by arm circumference difference) which appeared to depend upon the ongoing use of compression garments (Soran et al., 2014). It could be considered that the former described what might be primary prevention where shorter-term intervention prevents clinical lymphoedema developing compared to the latter representing secondary prevention where progression of lymphoedema is reduced by the ongoing use of the intervention. Issues to consider for an intervention in a screening study may include decisions made on the class, style, fabric of compression garments as well as wearing regime (number of hours worn daily and for what activities). Some studies have used intervention diaries to capture some of this information

however these are often poorly completed or adhered to by individuals and may not be reliable (Ridner et al., 2019; Kilbreath et al., 2016). In Study I, early intervention compression therapy was not worn for a 4–6-week period as in many clinical trials but rather in consultation and monitoring of the individual woman accounting for objective measurements results, related breast cancer treatments, time of year (summer or winter) and subjective assessment of symptoms. Often a weaning period from compression therapy in reducing wearing time of garment occurred rather than a complete change.

Despite growing support for the prospective surveillance model of care, some researchers are less convinced of the utility of BIS for monitoring (Barrio et al., 2015, Barrio et al., 2019, Bundred et al., 2020). Despite supporting lymphoedema screening programs, Barrio and colleagues (2019) from the United States have challenged the interim results of the PREVENT study stating that the two methods of measurement (BIS and tape measure) are not interchangeable and are measuring different things so cannot be compared (Barrio et al., 2019).

In the United Kingdom, Bundred and colleagues (2020) explored the prospective surveillance model of care in a large (1100 enrolled) prospective study. They compared five methods including BIS for diagnosing lymphoedema and explored which patients were most at risk of developing lymphoedema and would most benefit from surveillance (Bundred et al., 2020). Although Bundred's study recommended volume measurement using perometry as the most reliable method for surveillance, the study defined lymphoedema as a relative arm volume increase (RAVI) of >10%, despite by their own admission, and which has been defined by other authors as clinical lymphoedema and not sub-clinical lymphoedema (Dylke, 2016; Fu, Cleland, et al., 2013). Early volume changes (RAVI > 5%) at 24 months were more closely correlated with L-Dex changes than RAVI >10% (Bundred et al., 2020). Screening for sub-clinical lymphoedema is only

appropriate if objective measures (RAVI > 5%) are used to allow early intervention with compression-sleeves and if this intervention reduces the risk of developing clinical lymphoedema (Ridner et al., 2019). The issue the authors had with BIS was also related to the theoretical identification of sub-clinical lymphoedema leading to unnecessary health care utilisation, so it is prudent to keep abreast of measurement and criteria used in research studies as they may impact future recommendations for research and clinical practice.

6.3.2 Self-management enhances the prospective surveillance model of care

The work presented in this thesis, in particular Studies II and IV highlighted that home monitoring together with self-management as a package of care may enhance the prospective surveillance model of care in clinical practice. Ostby and colleagues (2014) recommended that physical methods for monitoring and assessment, combined with early-intervention compression garments, and referral for complete decongestive therapy as required, are all interventions to consider in the development of a breast cancer-related lymphoedema surveillance program (Ostby et al., 2014). In addition, they recommended supportive-educative programs and interactive engagement for symptom self-management as being beneficial (Ostby et al., 2014).

Temur and Kapucu conducted a randomised controlled study to explore the effect of lymphoedema self-management in the prevention of breast cancer-related lymphoedema and quality of life (Temur & Kapucu, 2019). They randomised patients to a self-management lymphoedema prevention program which included education on lymphoedema symptoms, how to protect the affected arm from infection and trauma, the importance of maintaining a proper weight, exercise, skin care, and simple lymphatic drainage massage, as well as the importance of follow-up care. They found that the self-management lymphoedema prevention program was effective at

preventing lymphoedema development and improving quality of life as compared with the control group (Temur & Kapucu, 2019). It is likely that being able to closely monitor and obtain objective feedback on the impact of different lymphoedema self-care actions through devices such as home-based BIS may promote enhanced perceptions of behavioural control over lymphoedema. This, in turn, may lead to improved motivation and enhanced adherence to self-care treatments (Alcorso et al., 2016a; Sherman et al., 2015).

The importance of interdisciplinary collaboration was also recommended by Ostby and colleagues (2014) as being integral to the success of an effective personalised medicine program in breast cancer-related lymphoedema surveillance (Ostby et al., 2014). Many participants enrolled in Study II reported the importance of a positive and supportive relationship with their multidisciplinary breast cancer team, including a qualified lymphoedema therapist, to understand and adhere to their recommended self-management. This support was perceived by the participants as enabling them to feel confident and motivated to carry out self-management, consistent with research highlighting the importance of patient knowledge for optimal adherence to a self-management regimen (Alcorso et al., 2016a; Sherman et al., 2015; Alcorso et al., 2016b; Ostby & Almer, 2015). Participants reported in Studies II and IV that receiving objective measurements via BIS home monitoring may positively affect adherence to their own self-management; however, it was important to have clear guidelines for how to action any elevations or fluctuations in readings.

Prior to conducting Study IV there had only been one known pilot study published using BIS technology as a home monitoring tool to enhance self-management in breast cancer-related lymphoedema (Ridner et al., 2014a). Ridner and colleagues (2014) recommended that future research could explore prospective self-monitoring with BIS devices for breast cancer survivors who are at high risk for lymphoedema. An important outcome of Study IV and of this thesis is that our research supports the growing body of literature that early intervention can potentially reduce

sub-clinical lymphoedema from progressing to chronic lymphoedema, and that early identified clinical lymphoedema treated with earlier intervention produces clinically significant results (Kilgore et al., 2018; Ridner et al., 2019). Such prospective longer-term studies could lead to earlier detection of sub-clinical lymphoedema and trigger immediate interventions that could enhance better patient outcomes and less intensive treatment for those developing chronic lymphoedema.

6.3.3 Implementation of the prospective surveillance model of care

Although evidence-based research demonstrates that early identification and intervention is key, bridging the gap between research and clinical practice in health care systems internationally has been difficult (Koelmeyer et al., 2021). In Australia, a limited number of hospitals and multidisciplinary teams use evidence-based practices to support the prospective surveillance model of care. Implementation and dissemination of monitoring breast cancer patients pre- and post-operatively is currently not standard practice as in the early surveillance group of Study I. There are several perceived barriers to implementing a prospective surveillance model of care in breast cancer. Lymphoedema is often not regarded as important within the context of breast cancer care and lack of multidisciplinary team awareness of the benefits of early detection of sub-clinical lymphoedema (Koelmeyer et al., 2021).

Frequently, implementation is limited by resource availability and infrastructure needs, access to equipment, staff training and time constraints, clinical protocols, and referral pathways for ongoing clinical care (Koelmeyer et al., 2021). Understanding the process of translating effective interventions into standard care practice is important for improving uptake and sustainability. Implementation science aims to facilitate the translation of clinically efficacious interventions into practice. The RE-AIM framework is a common tool used to promote implementation (Glasgow et al., 2013; Phillips et al., 2014; Wozniak et al., 2012). This framework was used retrospectively to

evaluate the implementation of the prospective surveillance model of care in the large international randomised control trial known as PREVENT study (Koelmeyer et al., 2021). The main finding was that research can drive changes in practice. Koelmeyer and colleagues (2020) using the framework demonstrated an extensive reach to individuals who participated in the study from both public and private hospital settings, low progression rates (1.8%) to clinical lymphoedema and all hospital sites initially approached adopted the prospective surveillance model of care. Key implementation strategies necessary for effectiveness of this model of care included education to health professionals and individuals, staff acceptability, and development of a referral and care pathway. Maintenance dimensions were evaluated both at the individual level and organisational level. For all non-optional study assessments over the two-year period, 92–100% adherence rates were achieved. At the organisational level, the prospective surveillance model of care was sustained after recruitment ceased for the research study and has been maintained three years later. The implementation of the prospective surveillance model of care used in the randomised control trial has assisted in changing clinical practice and improving the quality and effectiveness of the health care system (Koelmeyer et al., 2021).

Research which is co-designed with stakeholders may also facilitate implementation into practice (Churruca, 2019). Having researchers working within the multidisciplinary team may enhance the translation from research to clinical practice more easily as having local knowledge of people, systems and practices can allow evidenced based changes to occur.

When considering the use of home monitoring using BIS, in addition to or part of a prospective surveillance model of care, implementation issues would need to be considered (Koelmeyer et al., 2021). Lessons from implementation science research along with recommendations from the studies within this thesis may be used to enhance the implementation of the prospective

surveillance model of care and potentially also introduce BIS home monitoring as an adjunct to routine clinic monitoring to improve outcomes for those at risk of or living with lymphoedema.

6.4 Limitations of the thesis

The work undertaken for this thesis has provided significant contributions to the prospective surveillance model of care in the early detection and management of breast cancer-related lymphoedema yet, there are some limitations of this work to be considered. In terms of Study I, the two groups (early surveillance and traditional referral) were not randomly assigned. The participants were women who attended a private lymphoedema clinic and who were assessed and managed by a specialist lymphoedema therapist over a ten-year period. These women were referred by their breast surgeon or member of their healthcare team who were aware of the importance and benefits of having a prospective surveillance model of care as part of their multidisciplinary team management. The assessment and treatment given to both groups was standard clinical management by an experienced lymphoedema therapist. It was not initially planned for the ten-year routine clinical data to be analysed as part of a retrospective research study. Being real-time prospective clinical practice has meant that the "trigger for" and "early intervention" protocols were not set in stone like in a prospective clinical research study. This potential limitation may build on supporting, caring and providing evidenced based management for women at risk of or living with lymphoedema according to their individual physical and psychological needs and goals and thus personalizing their treatment. Over two thirds of the women in the early surveillance group for Study I had baseline pre-surgical L-Dex measurements whilst the other third of this group who were assessed within 90 days post-surgery did not have a pre-treatment baseline. There has been increasing support of pre-surgical measurements as part of a prospective surveillance model to gain a true baseline and it could be recommended that further sub-analysis of these groups be considered to explore any differences and whether this

retrospective clinical data supports more recent evidence (Kilbreath et al., 2016; Ridner et al., 2018; McLaughlin et al., 2020a). Despite the data for the study being collected prospectively, it was analysed retrospectively which meant there was some missing data because we were reliant on the clinical information being recorded by the therapist during routine clinical care rather than following completed research records. Stage of lymphoedema for those who developed the condition was determined following a comprehensive assessment by the single experienced practitioner who provided clinical care and documented the lymphoedema stage in the medical record. The information was extracted from the medical records by a research assistant prior to data analysis. Lymphoedema risk factors for women in both study groups were determined by lymph node surgery and adjuvant medical treatments as other potential risk factors had not been documented routinely in the medical record. More recent studies report on the benefit of a multi-modal risk assessment for lymphoedema including medical and surgical treatment, individual patient factors, as well as potentially modifiable risk factors such as body mass index (McLaughlin et al., 2020b; Kilbreath et al., 2016; Taghian et al., 2014). Although the two groups were similar, the number of women who never developed lymphoedema was likely under-represented in the traditional referral group as historically they only sought treatment when they had developed a clinical symptom or need.

Further, no data were available for women in Study I who discontinued visits to the lymphoedema clinic for either group. Women may have discontinued visits for a variety of reasons, including positive health outcomes, (i.e., not developing symptoms of lymphoedema and recovering well post-breast cancer and returning to work or normal activities); being identified as low risk for developing lymphoedema and educated to contact the therapist if they experienced a problem; or having difficulty managing the prohibitive costs associated with attending a private lymphoedema clinic with few financial rebates available, minimizing the likelihood that they attended follow-up clinic visits.

Another limitation is the relatively small and selective sample of participants studied across all the included studies I - IV. The participants across all studies were relatively well-educated Australian women who self-selected to participate and were required to have sufficient cognition and language skills to be able to read and understand written English. The majority of participants in these studies were recruited from within the private healthcare system which may mean that individuals were from a higher socio-economic background and they chose or were able to afford private health insurance and privately funded breast cancer medical treatment. Consequently, these women or their views may not be representative of the general population of breast cancer survivors at risk of or living with lymphoedema or generalisable to non-Australian women.

Finally, the time point for home monitoring using BIS in Study IV was six months of monitoring which was nine months following breast cancer surgery for each woman. It is known that women are at life-time risk for lymphoedema after treatment, however, the most common time for development of lymphoedema is in the first three years (Armer et al., 2019), so our study was not able to really explore the long-term effects of home monitoring and early intervention due to the relatively short study period. The pilot home monitoring study conducted by Ridner and colleagues (2014) monitored in the home for three months, with a recommendation that future studies assess this over a longer period; by assessing up to six months Study IV has achieved this recommendation (Ridner et al., 2014b).

6.5 Implications for clinical practice

The work conducted in this thesis has identified an innovative and promising approach to enhance the prospective surveillance model of care in breast cancer clinical practice. Over the last six years there have been advances in the medical and surgical management of breast cancer and how the prospective surveillance model of care fits into the multidisciplinary breast cancer management program.

6.5.1 Implementation of the prospective surveillance model of care

The findings of the four studies in this thesis have highlighted several issues to be considered in enhancing the prospective surveillance model of care with BIS home monitoring. Prior to implementing the concept of home monitoring there needs to be work carried out to ensure that all individuals diagnosed with breast cancer have access to the prospective surveillance model of care to allow for early detection and management of lymphoedema. There remains a great deal of work needed to educate and motivate multidisciplinary cancer teams to facilitate the implementation of this important model of care. Champions in the field need to understand and promote the evidence, identify clinical pathways, and provide support to guide implementation. Funding sources also need to be identified and allocated to ensure that all individuals have access to routine surveillance following breast cancer diagnosis. Following the implementation of the standard prospective surveillance model of care we can then consider the additional pathways of adding BIS home monitoring for a carefully selected high risk group of individuals.

In an ideal world, it is recommended to use the same type of BIS device whether in the clinic or in the home. Study III found differences in absolute impedances due to differing electrode positions between devices. Therefore, where use of the same type of device is not possible across

settings, we recommend concurrent measures using both devices at least once to ensure accurate translation of data between differing devices.

6.5.2 Home monitoring in chronic health conditions

The concept of self or home monitoring and self-management has been used in chronic health conditions such as diabetes and heart failure (Basatneh et al., 2018; Erie et al., 2018). The rise of internet medical technology has opened digital transformation of home-based care through individual data driven treatment regimens and feedback tailored to individual requirements (Basatneh et al., 2018). This enables better patient engagement, personalised care, and smarter management of chronic health conditions. Remote monitoring may be promising for individuals at risk of developing lymphoedema following breast cancer to address the challenges of anxiety and fear associated with the condition. Home monitoring may be empowering as the individual has the information to change their self-management or seek formal care as required. Moreover, the knowledge a health professional is monitoring from afar may provide additional reassurance. Women who participated in Study IV acknowledged the support from the research team remotely monitoring their L-Dex readings was beneficial and encouraging to them.

6.5.3 Remote monitoring & telehealth opportunities

The prospective surveillance model of care with BIS home monitoring is made up of a package of care where the BIS monitoring is only one aspect of the care package. Having the breast cancer team or lymphoedema therapist remotely monitoring the L-Dex readings may give confidence and support to the individual that their self-management is going well or possibly not so well which may encourage them to take action sooner. BIS home monitoring can potentially save people waiting for care within the hospital or clinic setting allowing more time for those requiring

intensive complex treatment. It can provide tailored surveillance and earlier intervention to those at high risk when they need it which may be sooner than routine three monthly clinic monitoring. In Study IV the mean time taken to trigger the >6.5 L-Dex change from baseline was 36 days ranging from 2 days to 67 days. This could mean that individuals may be able to access early intervention when they trigger the >6.5 L-Dex change rather than waiting for their next scheduled clinic appointment. Having the option of telehealth consultations could also be considered to avoid unnecessary waiting times and travel to hospital or clinic especially for those with compromised immune systems undergoing chemotherapy treatment. COVID-19 has certainly seen the successful use of telehealth consultations increase in the healthcare setting which could have ongoing opportunities for the prospective surveillance model of care with BIS home monitoring and remote monitoring in the breast cancer setting (Liu et al., 2020).

6.5.4 Technological & design advances

A future recommendation with respect to the current available BIS technology could be the development and design of a web-based application allowing an individual to access their own L-Dex readings, regardless of whether measurements were taken in a single or multiple hospital or clinic setting, or within the home. This would allow the individual to feel empowered and in control of their own data which may also provide additional educational prompting to enhance their own self-management. It could also be worthwhile exploring the current design of the stand-on device used in Study IV and whether there could be opportunities for the development of a smaller, more portable device. A smaller, less medically oriented device that can be hidden away from visiting guests may be less of an obvious reminder of breast cancer, and may be viewed more favourably than having a larger medical device positioned in the bedroom or bathroom setting as is the case for the current stand-on device.

6.5.5 Anxiety screening

Home monitoring may not necessarily be beneficial for everyone at risk of developing lymphoedema. Study IV recruited women who were at higher risk and even in that cohort there were a few women who may have felt a little anxious about the concept of home monitoring, the associated fear of developing lymphoedema, having fluctuating L-Dex readings and also having that regular reminder of needing to self-monitor for a condition relating to their breast cancer which may or may not develop. It could be worthwhile in future research or clinical applications to consider whether a validated anxiety / stress tool could be suitable for use to screen women who may not be considered appropriate for home monitoring due to higher levels of anxiety.

6.6 Implications for future research

Despite growing evidence to support this prospective surveillance and early intervention model of care in breast cancer rehabilitation, there are still concerns internationally around the definitions, methods of assessment and diagnosis of lymphoedema following breast cancer. Specifically, there is contention regarding the preferred measurement tool and diagnostic thresholds (Kilbreath et.al., 2016; Kilbreath et al., 2013a; Kilbreath et al., 2013b; Dylke et al. 2016; Bundred et al., 2020; Barrio et al., 2015; Barrio et al., 2019). International consensus around definitions of clinical and sub-clinical lymphoedema is a priority area for future research. Such consensus will enable data to be pooled across studies in comprehensive meta-analyses which should facilitate identification of effective interventions which can be translated into practice.

Further in terms of assessment and diagnostic thresholds, it has been recommended by some that the development of lymphoedema (whole limb and segmental) following breast cancer is

multifactorial, influenced by multimodality locoregional and systemic treatment strategies, individual patient factors such as the ability to form collateral lymphatic pathways after injury, as well as potentially modifiable risk factors such as body mass index (McLaughlin et al. 2020b). Therefore, some researchers recommend a multi-modal / multi-tool approach for assessment and diagnosis of lymphoedema (sub-clinical and clinical) (Kilbreath et.al., 2016; Kilbreath et al., 2013a; Kilbreath et al., 2013b; Dylke et al. 2016; Bundred et al., 2020). For example, Barrio and colleagues recommended that clinicians and researchers need to work together to provide data that support the establishment of breast cancer related lymphoedema screening programs using whatever validated and reliable tool as dictated by financial resources, space, and clinic workflow (Barrio et al., 2019). Similarly, McLaughlin and colleagues (2020) acknowledge the multifactorial nature of breast cancer-related lymphoedema and advocate that the modern-day breast cancer physicians must acknowledge the contribution and synergism of individual local, regional, and systemic therapies on lymphoedema risk (McLaughlin et al. 2020b). Screening for lymphoedema should be standard practice, including baseline bilateral objective measurements. Patient education should start at the time of breast cancer diagnosis, and longitudinal screening programs, including subjective and objective measures and clinical exam, are imperative for early diagnosis and possible effective management. McLaughlin and colleagues identify lymphoedema as a breast cancer treatment adverse effect that must be considered by the multidisciplinary team and breast cancer community at large (McLaughlin et al. 2020b). Despite the lack of international consensus, the body of work included in this thesis signposts exciting new directions for future research in enhancing the prospective surveillance and early intervention model of care in breast cancer management. Specific research opportunities are outlined below.

6.6.1 Long-term understanding of the outcomes of home monitoring using BIS in a prospective surveillance model of care

Study IV in this thesis showed that it was feasible and potentially beneficial for a prospective surveillance model of care delivered in the home consisting of BIS monitoring, education and support to promote self-management and physical activity in addition to standard clinic monitoring for women at high risk of developing lymphoedema. At a time of high stress and anxiety for individuals diagnosed with breast cancer who are at risk of lymphoedema, BIS home monitoring may support and empower individuals to reduce unnecessary appointments and trips to hospitals and clinics if they know that their fluid levels are not fluctuating and are feeling confident in the prospective surveillance model at home. A Phase II randomized trial for up to three years is warranted to support the timeframe when women are at greatest risk of developing lymphoedema and to establish the likely size of the effect (Dylke, 2019; McLaughlin et al., 2020a).

The results of Study II and IV showed that the women wanted more advice and meaning to fluctuations in L-Dex readings. Study IV captured an incredible amount of impedance data over the six-month home monitoring timeframe which has not yet been fully analysed. Reviewing the raw data of Study IV and other longitudinal BIS datasets may give some valuable information for women and clinicians about normal variation and fluctuations in L-Dex data to inform advice about should they be worried and how frequently they should monitor themselves. Data driven advice may help to alleviate some of the anxiety and stress that home monitoring may cause.

6.6.2 Financial costs associated with implementing home monitoring using BIS in a prospective surveillance model of care

There has been limited health economics research exploring the financial impact of living with lymphoedema in addition to breast cancer, as well as costs associated with the implementation of a prospective surveillance model of care for individuals at high risk of developing lymphoedema.

In an Australian online survey of 361 women conducted by Boyages and colleagues (2016b), both breast cancer and lymphoedema resulted in significant out-of-pocket financial costs borne by women. Of individuals with breast cancer and lymphoedema, 80% indicated that their breast cancer diagnosis had affected them financially compared with 67% in the breast cancer only group. For individuals with lymphoedema, over half indicated that the lymphoedema specifically affected them financially and that costs increased with lymphoedema severity (Boyages et al., 2016b). Higher treatment related costs became more evident for those with more severe clinical lymphoedema including compression garments, therapy sessions and intermittent compression pumps as well as inpatient costs associated with hospital admissions due to cellulitis. Thus, the importance and relevance of implementing the prospective surveillance and early intervention model of care to reduce progression to clinical lymphoedema is evident (Boyages et al., 2016b).

In a survey of 129 breast cancer survivors in the USA where 47% had lymphoedema, Dean and colleagues (2019) found that long-term cancer survivors with lymphoedema may face up to 112% higher out-of-pocket costs than those without lymphoedema, which influences lymphoedema management, and has lasting impact on savings and productivity. The findings reinforce the need for actions at policy, provider, and individual patient levels, to reduce lymphoedema costs (Dean et al., 2019).

An informal cost analysis was completed by Shah (2019) to evaluate the impact of BIS surveillance on the cost of breast cancer-related lymphoedema management for women participating in the international randomised controlled trial, PREVENT study (Ridner et al., 2019; Shah, 2019). He suggested that utilising BIS may increase the upfront costs for breast cancer-related lymphoedema assessment, which would potentially be offset when accounting for breast cancer-related lymphoedema treatment. Additionally, the cost savings are further magnified (more than USD $16000 cost savings per patient) when accounting for hospitalisations due to cellulitis (Shah, 2019). These findings support that BIS should be considered a value-added surveillance strategy for breast cancer-related lymphoedema and health systems should consider reimbursement for BIS prospectively to reduce costs.

Whilst the prospective surveillance model of care is emerging as the gold standard of care in breast cancer treatment, further analysis of indirect costs and utility is necessary to assess cost-effectiveness. Further formal research exploring the costs associated with implementing the prospective surveillance model of care in a breast cancer multidisciplinary setting and additionally using BIS home monitoring for high-risk individuals would be beneficial. If this innovative model of care is to be translated into clinical practice effectively, it must be affordable and cost efficient to the individual and the healthcare system. Qualitative survey and focus group research with both health care professionals and those at risk of developing breast cancer-related lymphoedema could explore options for how the model of care could be implemented. Potential rental options or monthly payment plans like mobile phone plans could be considered as options for translating this model of care into practice in a cost-effective way with further research outcomes. This could be incorporated into the proposed Phase II randomized trial to explore both clinical and health

economical outcomes from implementing the prospective surveillance model of care with and without BIS home monitoring.

6.6.3 Enhancing other components of the prospective surveillance model

The prospective surveillance model of care involves education and self-management however research into how to personalise these components also have potential to improve outcomes for individuals at risk of breast cancer-related lymphoedema. For example, manual lymphatic drainage techniques are frequently recommended as part of lymphoedema self-management (Brown et al., 2014; Temur & Kapucu, 2019; Thompson et al., 2020). The introduction of ICG fluorescent lymphography has significantly changed research. In addition, it has been translated into clinical practice, specifically used to guide personalised manual lymphatic drainage techniques and sequences in breast cancer-related lymphoedema (Suami et al., 2019; Suami et al., 2018). ICG Lymphography can be used for assessing severity of lymphoedema according to the MD Anderson Cancer Center (MDACC) lymphoedema staging system (Chang, 2013) and for therapeutic planning of personalised manual lymphatic drainage (Suami et al., 2019). Following disruption to the lymphatic system from cancer and its treatment, the body may develop compensatory drainage regions to encourage lymphatic drainage from the area of congestion (Suami et al., 2018). ICG lymphography has the potential to be used in future research within the prospective surveillance model of care comparing ICG lymphography with BIS at time of breast cancer diagnosis and then at six- or twelve-monthly intervals to compare the lymphatic vessels with extracellular fluid levels and the development of sub-clinical lymphoedema.

Similarly, exercise is an important evidence-based recommendation in cancer rehabilitation to improve function and reduce the negative impact of treatment-related symptoms like

lymphoedema (Clinical Oncology Society of Australia [COSA], 2018; Armer et al., 2020 ; Brown et al., 2014; Temur & Kapucu, 2019). Women in study IV increased exercise and activity levels which is aligned with the findings of a recently published systematic review of rehabilitation and exercise recommendations in oncology guidelines (Stout et al., 2020). Our study IV results only reported increased duration of exercise and not intensity or type of exercise. Further research to explore ways of personalising exercise prescription programs for individuals following comprehensive assessment would be useful to ensure all aspects of the exercise guidelines are met.

The stand-on BIS device may be useful in research beyond sub-clinical lymphoedema identification as the device can also measure body composition. It is common for women to gain or lose weight during their intensive breast cancer treatment and some preliminary work exploring body composition changes during cancer treatment has been undertaken showing the benefits of being able to provide body composition data to motivate lifestyle-related behaviour such as exercise and nutrition. Further research exploring body composition data over the whole breast cancer treatment and survival time would be beneficial.

6.7 Conclusions

The findings of this thesis have highlighted the benefits of adopting a prospective surveillance and early intervention model of care in breast cancer in reducing the incidence of clinical lymphoedema and how the concept of home monitoring using BIS technology may further educate, support and empower individuals in their own self-management following breast cancer. This model of care has been shown to be feasible to deliver and highly acceptable to individuals with breast cancer and at risk of lymphoedema. Although efficacy in regard to long term outcomes of home monitoring is not yet established, the work presented in this thesis has demonstrated

positive results from preliminary testing that potentially offers both clinicians and individuals with breast cancer an alternative to, or augmentation of, the traditional model of care that is feasible. The work presented in this thesis has demonstrated that the standard prospective surveillance model of care may be enhanced by incorporating home monitoring using BIS technology in detecting sub-clinical lymphoedema earlier and improving the quality of life for those at risk of lymphoedema after breast cancer.

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Appendices

Appendix 1.1: Ethical Approval – Study I

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(Research)

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90 952 801 237

MACQUARIE University
SYDNEY·AUSTRALIA

24 March 2016

Dear Ms Louise Koelmeyer

Reference No: 5201500844

Title: *Early detection and management of breast cancer related lymphoedema: a retrospective study*

Thank you for submitting the above application for ethical and scientific review. Your application was considered by the Macquarie University Human Research Ethics Committee (HREC (Medical Sciences)).

I am pleased to advise that ethical and scientific approval has been granted for this project to be conducted at:

- Macquarie University

This research meets the requirements set out in the *National Statement on Ethical Conduct in Human Research* (2007 – Updated May 2015) (the *National Statement*).

Standard Conditions of Approval:

1. Continuing compliance with the requirements of the *National Statement,* which is available at the following website:

http://www.nhmrc.gov.au/book/national-statement-ethical-conduct-human-research

2. This approval is valid for five (5) years, subject to the submission of annual reports. Please submit your reports on the anniversary of the approval for this protocol.

3. All adverse events, including events which might affect the continued ethical and scientific acceptability of the project, must be reported to the HREC within 72 hours.

4. Proposed changes to the protocol and associated documents must be submitted to the Committee for approval before implementation.

It is the responsibility of the Chief investigator to retain a copy of all documentation related to this project and to forward a copy of this approval letter to all personnel listed on the project.

Should you have any queries regarding your project, please contact the Ethics Secretariat on 9850 4194 or by email ethics.secretariat@mq.edu.au

The HREC (Medical Sciences) Terms of Reference and Standard Operating Procedures are available from the Research Office website at:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human research ethics

The HREC (Medical Sciences) wishes you every success in your research.

Yours sincerely

Professor Tony Eyers
Chair, Macquarie University Human Research Ethics Committee (Medical Sciences)

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research* (2007) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

Details of this approval are as follows:

Approval Date: 2 March 2016

The following documentation has been reviewed and approved by the HREC (Medical Sciences):

Documents reviewed	Version no.	Date
Macquarie University Ethics Application Form		Received 16/10/2015
Correspondence responding to the issues raised by the HREC (Medical Sciences)		Received 8/2/2016

Appendix 1.2: Publication License – Study I

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Appendix 1.3: Data Form A - Study I

L-DEX SURVEILLANCE STUDY DATA FORM

RA initials		**Senior review needed** Y N		**Entered electronically** Y N	
Patient name				**Date of birth**	/ /
Record Number		**Participant ID**		**Odyssey** Y N	**Profile** Y N

ELIGIBILITY CRITERIA

Inclusion Criteria:

- female ☐
- over 18 years of age ☐
- diagnosed with breast cancer ☐
- preoperative upper limb L-Dex and at least one follow-up measure ☐

Exclusion Criteria:

- breast cancer not surgically treated e.g. neoadjuvant chemotherapy ☐
- bilateral lymph node surgery ☐
- contra-indicated for L-Dex measurement (i.e. pregnancy, pacemaker) ☐
- **uncontrolled** cardiovascular disease (i.e. cardiomyopathy, heart failure) ☐
- other **uncontrolled** morbidities causing chronic peripheral swelling (i.e. diabetic nephropathy, peripheral vascular disease) ☐

PATHOLOGY

Histological type (pathology report)	Ductal Carcinoma In Situ (DCIS) ☐	Invasive with predominant DCIS ☐
Infiltrating ductal ☐	Infiltrating lobular ☐	Other ☐
Histological size of dominant tumour ☐☐☐☐ mm		**Number of lesions** ☐
Histological grade (1-3) ☐	**Oestrogen (ER)** + -	**HER2 (ISH)** + -
SNB Date / /	**Sentinel nodes** +ve ☐ of # ☐	**TNM 7th ed. Stage (pathological)** T ☐ N ☐
ALND Date / /	**Axillary nodes** +ve ☐ of # ☐	

CANCER TREATMENT

Most extensive surgery	WLE (inc. quadrantectomy) ☐	Mastectomy ☐
Mastectomy + Expander ☐	Mastectomy + Implant (NSM/SSM) ☐	Mastectomy + DBR (Flap, expander) ☐
Surgery notes		**Date of surgery** / /
RT to breast Y N	**RT to chest wall** Y N	**Axillary RT** Y N
Internal mammary chain RT Y N	**Supraclavicular fossa RT** Y N	
Name of rad onc		**Date of 1st RT** / /
Chemotherapy	None ☐	Yes, without taxane ☐
Yes, with taxane ☐	Date commenced first taxane treatment	/ /
Hormonal therapy Y N		

FOLLOW-UP & COMMENTS

Cancer recurred Y N	**Date cancer recurred**	/ /
Patient is deceased Y N	**Date of patient's death**	/ /
Censoring rule triggered	No ☐	Yes, cancer recurred ☐
Yes, new cancer on opposite side ☐	Yes, new axillary surgery on opposite side (NOT prophylactic mx alone) ☐	
Other (describe) ☐		**Date censored** / /
Comments		

Appendix 1.4: Data Form B - Study I

L-DEX TREATMENT DATA FORM

RA initials		**Record Number**		**Participant ID**	
Patient name				**Date of birth**	/ /
SNB Date	/ /	**ALND Date**	/ /	**Date of surgery**	/ /
Date of 1st RT	/ /	**Date 1st Tax cycle**	/ /	**Elevated L-Dex**	/ /
Censoring rule				**Date censored**	/ /

LYMPHOEDEMA DIAGNOSTIC & STAGING CRITERIA

Diagnostic Considerations:

- In Louise's opinion, not associated with post-surgical swelling (i.e. ≥ 90 days)
- In Louise's opinion, not associated with Taxane therapy
- Lympohoedema diagnosis may or may not follow edema diagnosis, or be made in the absence of prior edema

Staging Criteria (ISL):

Stage 0 - 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 1 - 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 2 - Limb elevation alone rarely reduces swelling and pitting is manifest. There may or may not be pitting as tissue fibrosis is more evident.

Stage 3 - The tissue is hard (fibrotic) and pitting is absent. Skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits, and warty overgrowths develop.

EDEMA DIAGNOSED ☐Y ☐N

+ve L-Dex Date	/ /	**+ve L-Dex value**		**Within 90 days of surgery**	☐Y ☐N
Within 90 days of first Taxane	☐Y ☐N	**Other exclusion for lymphoedema**			

Treatment - Specify earliest date prescribed after edema noted

MLD - Therapist	/ /	MLD - Self	/ /	Scar management	/ /
Compression sleeve	/ /	Exercise	/ /	Skin care	/ /

LYMPHOEDEMA DIAGNOSED ☐Y ☐N

+ve L-Dex Date	/ /	**+ve L-Dex value**		**Lymphoedema Stage (0 - 3)**	☐

Treatment - Specify earliest date prescribed after lymphoedema diagnosed

MLD - Therapist	/ /	MLD - Self	/ /	Scar management	/ /
Compression sleeve	/ /	Exercise	/ /	Skin care	/ /

FINAL FOLLOW-UP

Final L-Dex Date	/ /	**Final L-Dex value**	
Final Diagnosis		Transient edema only ☐	Edema then lymphoedema ☐
Lymphoedema alone ☐		**Lymphoedema Stage at final follow-up (N/A, 0 - 3)**	☐

Comments

Appendix 2.1: Ethical Approval – Study II

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(Research)

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90 952 801 237

22 December 2015

Dear A/Prof Kerry Sherman

Reference No: 5201500929

Title: Effectiveness of self-management and home monitoring in breast cancer related lymphoedema"

Thank you for submitting the above application for ethical and scientific review. Your application was considered by the Macquarie University Human Research Ethics Committee (HREC (Medical Sciences)) at its meeting on 26 November 2015 at which further information was requested to be reviewed by the Ethics Secretariat.

The requested information was received with correspondence on 11 December 2015.

I am pleased to advise that ethical and scientific approval has been granted for this project to be conducted at:

- Macquarie University

This research meets the requirements set out in the *National Statement on Ethical Conduct in Human Research* (2007 – Updated March 2014) (the *National Statement*).

This letter constitutes ethical and scientific approval only.

Standard Conditions of Approval:

1. Continuing compliance with the requirements of the *National Statement,* which is available at the following website:

http://www.nhmrc.gov.au/book/national-statement-ethical-conduct-human-research

2. This approval is valid for five (5) years, subject to the submission of annual reports. Please submit your reports on the anniversary of the approval for this protocol.

3. All adverse events, including events which might affect the continued ethical and scientific acceptability of the project, must be reported to the HREC within 72 hours.

4. Proposed changes to the protocol must be submitted to the Committee for approval before implementation.

It is the responsibility of the Chief investigator to retain a copy of all documentation related to this project and to forward a copy of this approval letter to all personnel listed on the project.

Should you have any queries regarding your project, please contact the Ethics Secretariat on 9850 4194 or by email ethics.secretariat@mq.edu.au

The HREC (Medical Sciences) Terms of Reference and Standard Operating Procedures are available from the Research Office website at:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research ethics

The HREC (Medical Sciences) wishes you every success in your research.

Yours sincerely

Professor Tony Eyers
Chair, Macquarie University Human Research Ethics Committee (Medical Sciences)

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research*

Details of this approval are as follows:

Approval Date: 22 December 2015

The following documentation has been reviewed and approved by the HREC (Medical Sciences):

Documents reviewed	Version no.	Date
Macquarie University Ethics Application Form	2.3	Received 12/11/15
Correspondence from Louise Koelmeyer responding to the issues raised by the HREC (Medical Sciences)		Received 11/12/2015
MQ Participant Information and Consent Form (PICF) entitled Effectiveness of self-management and home monitoring in breast cancer related lymphoedema	1.0	11/11/15
Focus Group Questions	1.0	8/11/15
Pre-focus group survey	1.0	11/11/15
Flyer	1.0	November 2015
Focus Group Invitation	1.0	11/11/15

Appendix 2.2: Manuscript Acceptance - Study II

From: Adam Bushby <abushby@omniamed.com>
Sent: Thursday, 29 October 2020 11:50 PM
To: Louise Koelmeyer
Subject: Re: Manuscript submission to Journal of Lymphoedema

Hi Louise,

I hope all's well and thanks for getting in touch. Cases rising here so I am essentially on lockdown.

I am happy to accept your article to be published in Journal of Lymphoedema 2021 edition. Good luck with your studies!

Regards

Adam

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W: www.omniamedcommunications.com

From: Adam Bushby <abushby@omniamed.com>
Sent: Tuesday, 20 October 2020 1:27 AM
To: Louise Koelmeyer <louise.koelmeyer@mq.edu.au>
Subject: Re: Manuscript submission to Journal of Lymphoedema

Hi Louise,

I hope all's well and you had a good weekend. Trying to get your head around the restriction changes when they are as clear as mud (as ever) is quite the challenge! Hope it's a little better where you are.

Many thanks for sending over your revised article. I'll send this over to be reviewed now and will be back in touch once I hear back.

Regards

Adam

ADAM BUSHBY
MANAGING EDITOR

Wounds Group
OmniaMed Communications
108 Cannon Street | London | EC4N 6EU

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WOUNDSGROUP

From: Louise Koelmeyer <louise.koelmeyer@mq.edu.au>
Date: Monday, 19 October 2020 at 11:17
To: Adam Bushby <abushby@omniamed.com>
Subject: RE: Manuscript submission to Journal of Lymphoedema

Hello Adam,

I hope this finds you well and coping with changing COVID situation in UK. We have been fortunate where we are with our borders closed.

Many thanks for your email and positive response to my manuscript being published in the Journal of Lymphoedema. Please find attached a letter outlining the changes made as well as highlighted and clean copy of revised manuscript incorporating most of reviewers suggestions. Many thanks for considering this revised manuscript for publication. I look forward to your response.

Kind regards,

Louise

Louise Koelmeyer BAppSc (OT)
Director & Senior Lecturer, ALERT Program
Australian Lymphoedema **E**ducation, **R**esearch & **T**reatment

Department of Clinical Medicine | Faculty of Medicine, Health & Human Sciences
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Macquarie University, NSW 2109, Australia

T: +61 2 9850 2358 | **M:** +61 404 496 554
E: louise.koelmeyer@mq.edu.au | **W:** mqhealth.org.au/alert

From: Adam Bushby <abushby@omniamed.com>
Sent: Tuesday, 22 September 2020 9:02 PM
To: Louise Koelmeyer <louise.koelmeyer@mq.edu.au>
Subject: Re: Manuscript submission to Journal of Lymphoedema

Hi Louise,

I hope all's well and you had a good weekend. How is the Covid situation where you are?

I have heard back from the reviewer and they described your article as "a great paper".

It has been accepted on the proviso that a few amends are made for clarity.

The reviewer said: "There are a few areas which need clarification and a couple of areas where clarity of the presentation could be improved. While we acknowledge it's a qualitative study, we wonder if there is a possibility of adding a graph or two of the frequency of themes across the focus groups (if they were selected on "Grade") or if not then a graph of themes across the stages irrespective of the focus group."

There are a few mark ups on the attached Word document. Would you please make the suggested amends and resend your article? As the Journal of Lymphoedema is an annual publication, the next issue won't be out until next summer so by all means, please take your time on this!

Regards

Adam

ADAM BUSHBY
MANAGING EDITOR

Wounds Group
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WOUNDSGROUP

From: Adam Bushby <abushby@omniamed.com>
Sent: Wednesday, 12 August 2020 2:43 AM
To: Louise Koelmeyer <louise.koelmeyer@mq.edu.au>
Subject: Re: Manuscript submission to Journal of Lymphoedema

Hi Louise,

I hope all's well and thank you for sending your article over.

I will send this out for review tomorrow now and will be back in touch once I have heard back. This could take a few weeks so please bear with me.

Also, just to stress, the Journal of Lymphoedema is an annual publication so this would be considered for the 2021 edition, likely to go to press during the summer.

Regards

Adam

ADAM BUSHBY
MANAGING EDITOR

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WOUNDSGROUP

From: Louise Koelmeyer <louise.koelmeyer@mq.edu.au>
Date: Tuesday, 11 August 2020 at 03:38
To: Adam Bushby <abushby@omniamed.com>, Neil Piller <neil.piller@flinders.edu.au>
Subject: Manuscript submission to Journal of Lymphoedema

Hello Neil and Adam,

I hope this finds you well and coping with this changing COVID situation.

On behalf of my co-authors we wish to submit the attached manuscript with cover letter for review to the Journal of lymphoedema. Please do not hesitate to contact me if you require any further information or if I am meant to submit this via an online portal. I look forward to receiving your feedback. Many thanks.

Kind regards,

Louise

Louise Koelmeyer BAppSc (OT)
Director & Senior Lecturer, ALERT Program
Australian Lymphoedema Education, **R**esearch & Treatment

Department of Clinical Medicine | Faculty of Medicine, Health & Human Sciences
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MACQUARIE University

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Appendix 2.3: Participant Information and Consent Form - Study II

Department of Psychology

Faculty of Human Sciences

MACQUARIE UNIVERSITY NSW 2109

Phone: +61 (0)2 9850 6874
Fax: +61 (0)2 9850 8062

Email: Kerry.sherman@mq.edu.au

Chief Investigator's Name & Title: Associate Professor Kerry Sherman

Participant Information and Consent Form

Name of Project: Effectiveness of self-management and home monitoring in breast cancer related lymphoedema.

You are invited to participate in a study of exploring ways that women who are at risk of, or living with, lymphoedema from breast cancer treatment determine their daily self-care and how they may feel about using a home monitoring device to monitor their lymphoedema or detect early changes from undetected lymphoedema.

The purpose of the study is to understand attitudes towards lymphoedema home monitoring and factors associated with acceptance of this approach to self-management.

The study is being conducted by Mrs Louise Koelmeyer to meet the requirements of the Doctor of Philosophy Post Graduate Degree Program under the supervision of Associate Professor Kerry Sherman from Department of Psychology, Faculty of Human Sciences (Telephone +612 9850 6874 or email Kerry.sherman@mq.edu.au) and Professor John Boyages from Department of Clinical Medicine, Faculty of Medicine & Health Sciences (Telephone +612 9812 3508 or email John.Boyages@mq.edu.au).

If you decide to participate, you will be asked to attend a one-off 1.5-hour session at Macquarie University to participate in a discussion focus group that will help us gather information on how you currently manage your lymphoedema, what symptoms you have, whether you may be interested in monitoring your arm with a home L-Dex device and also how you use technology in your daily life. We are wanting to determine if home monitoring for lymphoedema can be an effective tool to assist women in gaining better outcomes. The session will be audio-taped so that information can be reviewed and analysed for future research. Free parking will be available on Macquarie University Campus.

Any information or personal details gathered in the course of the study are confidential, except as required by law. No individual will be identified in any publication of the results. Only Associate Professor Kerry Sherman, Professor John Boyages and Mrs Louise Koelmeyer *will have access to the data.* A summary of the results of the data can be made available to you on request. The data identified through the focus group sessions will be used to form the basis for future studies in home monitoring using an L-Dex device.

Participation in this study is entirely voluntary: you are not obliged to participate and if you decide to participate, you are free to withdraw at any time without having to give a reason and without

consequence. Investigator Koelmeyer is also a qualified occupational therapist and lymphoedema therapist working in a clinical role for one day a week in her own private clinic. She is also employed at Macquarie University as the Lymphoedema Program Manager. This combined clinical and research role has been approved by Macquarie University and has been financially supported by ImpediMed Limited. Any withdrawal from this research will not prejudice or impact any future care or relationship with investigators in any way.

I, *(participant's name*) have read *(or, where appropriate, have had read to me)* and understand the information above and any questions I have asked have been answered to my satisfaction. I agree to participate in this research, knowing that I can withdraw from further participation in the research at any time without consequence. I have been given a copy of this form to keep.

Participant's Name:_____

(Block letters)

Participant's Signature:_____ Date:_____

Investigator's Name:_____

(Block letters)

Investigator's Signature:_____ __ Date:_____

The ethical aspects of this study have been approved by the Macquarie University Human Research Ethics Committee. If you have any complaints or reservations about any ethical aspect of your participation in this research, you may contact the Committee through the Director, Research Ethics & Integrity (telephone (02) 9850 7854; email ethics@mq.edu.au). Any complaint you make will be treated in confidence and investigated, and you will be informed of the outcome.

(INVESTIGATOR'S [OR PARTICIPANT'S] COPY)

Appendix 2.4: Focus Group Questions - Study II

Focus Group Questions

PART 1: Introductions

1. Welcome to everyone and thank you for participating in this focus group research session, Introductions, Group rules regarding confidentiality, Recording of session, Free to withdraw at anytime

2. Lymphoedema background
    a) Can you share with us about your lymphoedema - how long ago were you diagnosed? How long after your breast cancer diagnosis was lymphoedema diagnosed? Were you monitored for lymphoedema by a qualified lymphoedema therapist during your breast cancer treatment? If so how was this done?
    b) How would you rate the severity of your lymphoedema?
    c) How does lymphoedema impact on your daily life?

PART 2: Lymphoedema Symptoms

a) Can you describe the symptoms that lymphoedema gives you e.g heaviness, aching, swelling, fullness, altered sensation etc?
b) Can you share how your symptoms fluctuate and if you identify whether there are specific triggers to fluctuating symptoms?
c) What do you do to reduce your lymphoedema symptoms?

PART 3: Lymphoedema self-management strategies

a) How often do you see a qualified lymphoedema therapist to assist you in managing your lymphoedema?
b) When you see your lymphoedema therapist what happens at these sessions?
c) What have you been recommended to do to best manage your lymphoedema at home?
d) Out of all these recommendations what do you find the easiest to do for yourself? Why?
e) What do you find the most difficult to do? And why?
f) How much time each day or week do you put in to managing your lymphoedema?
g) How motivated are you to complete lymphoedema self-management?
h) Thinking about your compression garments, how often do you wear your garment? What are your reasons for wearing or not wearing your garments?
i) How does having lymphoedema make you feel?
j) What advice would you give to other women about self-managing their lymphoedema?

PART 4: Home monitoring

a) How often do you see your lymphoedema therapist to monitor your condition and progress?
b) How does your lymphoedema therapist monitor your progress? E.g. circumference measurements, L-Dex measurement, feel your arm, symptom review
c) How do you monitor changes in your lymphoedema symptoms?
d) Do you see a relationship between your self-management and lymphoedema symptoms e.g do your symptoms improve or worsen with certain strategies / activities / weather / exercises?
e) If you have been monitored by your therapist using L-Dex, have you seen variations in your L-Dex reading according to the symptoms you have?
f) Would it be useful to have an objective measurement to monitor your lymphoedema at home?
g) Would it be useful to monitor your arm using a home L-Dex monitoring device?
h) If so how often would you think you would want to measure your arm using a home L-Dex device? E.g daily, second daily, weekly, monthly, quarterly
i) What information would you want to receive from taking an L-Dex reading at home? E.g L-Dex score, change from previous time?
j) Would you want your lymphoedema therapist to have access to your L-Dex readings taken at home?
k) Would you consider going to a pharmacy or other facility to have your L-Dex taken?

PART 5: Use of and access to technology

a) What sort of technology do you have in your home?
b) Do you have access to the internet? If yes, how do you access the internet i.e 3G/4G cellular network, NBN, ADSL etc.
c) What is your perceived level of computer literacy? Very confident, somewhat confident, not confident at all.
d) How often do you use a computer or smart device (phone, Ipad, tablet)?
e) What do you use a computer or smart device for?

Appendix 2.5: Data Collection Form - Study II

Participant Survey

Effectiveness of self-management and home monitoring in breast cancer-related lymphoedema

1. **How old are you? Please enter your age in years. 42-75**

2. **Do you identify as being an Australian Aboriginal, Indigenous or Torres Strait Islander?**
   - o Yes
   - o No

3. **What is your marital status?**
   - o Single, never married
   - o Married or De Facto
   - o Divorced
   - o Widowed
   - o Separated

4. **What is the highest level of education that you have completed?**
   - o Less than Year 10
   - o High School Certificate or equivalent
   - o Vocational / TAFE
   - o Undergraduate degree
   - o Postgraduate degree

     Other

5. **What is your household income?**
   - o Less than $50,000
   - o $50,000 to $99,000
   - o $100,000 to $150,000
   - o More than $150,000
   - o I prefer not to say

6. **How long ago were you diagnosed with breast cancer?**
   - o 1 to <2 years
   - o 2 to <3 years
   - o 3 to <4 years
   - o 4 to <5 years
   - o 5 to <10 years
   - o 10 to < 15 years
   - o 15 to < 20 years
   - o 20 years or more

7. What treatment did you have for your breast cancer? (Select all that apply)

- o Conservative surgery (e.g. lumpectomy, wide local excision) without radiation
- o Conservative surgery and radiation
- o Mastectomy
- o Mastectomy and radiation
- o Breast reconstruction-flap (TRAM, DIEP, Lat Dorsi)
- o Breast Reconstruction (Implant type)
- o Sentinel lymph node biopsy
- o Axillary lymph node dissection
- o Chemotherapy (taxol or taxotere)
- o Chemotherapy (other)
- o Hormonal treatment (e.g tamoxifen or arimidex)
- o Other (Please specify: _____)

8. Have you been diagnosed with breast cancer-related lymphoedema?

- o Yes
- o No

9. How long ago were you diagnosed with lymphoedema?

- o 1 to <2 years
- o 2 to <3 years
- o 3 to <4 years
- o 4 to <5 years
- o 5 to <10 years
- o 10 to < 15 years
- o 15 to < 20 years
- o 20 years or more

10. Based on the descriptions below, what stage of lymphoedema do you currently have?

Stage 0 (sub-clinical/latent): There are no visible changes to your arm, hand, or upper body at this point, but you may notice a difference in feeling, such as mild tingling, unusual tiredness, or slight heaviness. You can have stage 0 lymphoedema for months or years before obvious symptoms develop.

Stage 1 (mild): The arm, hand, trunk, breast, or other area appears mildly swollen. When you press the skin, a temporary small dent (or pit) forms. When you elevate the affected area of your body, the swelling is reduced; however, the swelling returns when you return to a normal position.

Stage 2 (moderate): The affected area is swollen and elevating it does not help. Pressing on the skin does not leave a pit or dent. Some changes to the skin have happened, such as inflammation, hardening, or thickening.

Stage 3 (severe): The affected area is very large and misshapen. The skin has become leathery, wrinkled, discoloured and/or lost elasticity.

- o Stage 0
- o Stage 1
- o Stage 2
- o Stage 3
- o I don't know

11. Were you monitored for lymphoedema by a qualified lymphoedema therapist during your breast cancer treatment? If so how was this done?

- o L-Dex measurements
- o Circumference measurements
- o Other?

12. How does your arm at risk and / or your lymphoedema arm impact on your daily life?

13. Can you describe the symptoms that lymphoedema gives you e.g heaviness, aching, swelling, fullness, altered sensation etc?

14. Can you share how your symptoms fluctuate and if you identify whether there are specific triggers to fluctuating symptoms?

15. What do you do to reduce your lymphoedema symptoms?

16. How often do you see a qualified lymphoedema therapist to assist you in managing your lymphoedema?

17. What have you been recommended to do to best manage your lymphoedema at home?

18. Out of all of these recommendations what do you find the easiest to do for yourself? Why?

19. What do you find the most difficult to do? And why?

20. How much time each day or week do you put in to managing your lymphoedema?

Appendix 3.1: Ethical Approval – Study III

Office of the Deputy Vice-Chancellor
(Research)

Research Office

Research Hub, Building C5C East
Macquarie University

NSW 2109 Australia

T: +61 (2) 9850 4459

http://www.research.mq.edu.au/
ABN 90 952 801 237

30 May 2017

Dear Professor Dean

Reference No: 5201700439

Title: *A comparison of the L-Dex® U400 with the ImpediMed SOZO device: A reliability and validation study*

Thank you for submitting the above application for ethical and scientific review. Your application was considered by the Macquarie University Human Research Ethics Committee (HREC (Medical Sciences)).

I am pleased to advise that ethical and scientific approval has been granted for this project to be conducted at:

- Macquarie University

This research meets the requirements set out in the *National Statement on Ethical Conduct in Human Research* (2007 – Updated May 2015) (the *National Statement*).

Standard Conditions of Approval:

1. Continuing compliance with the requirements of the *National Statement,* which is available at the following website:

http://www.nhmrc.gov.au/book/national-statement-ethical-conduct-human-research

2. This approval is valid for five (5) years, subject to the submission of annual reports. Please submit your reports on the anniversary of the approval for this protocol.

3. All adverse events, including events which might affect the continued ethical and scientific acceptability of the project, must be reported to the HREC within 72 hours.

4. Proposed changes to the protocol and associated documents must be submitted to the Committee for approval before implementation.

It is the responsibility of the Chief investigator to retain a copy of all documentation related to this project and to forward a copy of this approval letter to all personnel listed on the project.

Should you have any queries regarding your project, please contact the Ethics Secretariat on 9850 4194 or by email ethics.secretariat@mq.edu.au

The HREC (Medical Sciences) Terms of Reference and Standard Operating Procedures are available from the Research Office website at:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research ethics

The HREC (Medical Sciences) wishes you every success in your research.

Yours sincerely

Professor Tony Eyers
Chair, Macquarie University Human Research Ethics Committee (Medical Sciences)

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research* (2007) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

Details of this approval are as follows:

Approval Date: 25 May 2017

The following documentation has been reviewed and approved by the HREC (Medical Sciences):

Documents reviewed	Version no.	Date
Correspondence responding to the issues raised by	N/A	Received
Perceived Conflict of Interest Management Strategy Document from Prof Rick Kefford	N/A	19 May 2017
Revised HREA Signature page of new Principal	N/A	18 May
Human Research Ethics Application Form (HREA)	1*	Received 12 April 2017
Protocol (Clean & Tracked Changes)	2	14 May 2017
Study Invitation	1	18 Mar 2017
Macquarie PICF (Clean & Tracked Changes)	2	14 May 2017
Case Report Form Version 2 (Clean & Tracked changes)	2	14 May 20

Appendix 3.2: Publication License – Study III

From: Ballen, Karen<KBallen@liebertpub.com>Tue 1/09/2020 3:15 AM

To: Stanley G Rockson <rockson@stanford.edu>;Reisz, Sophie <SReisz@liebertpub.com>; Louise Koelmeyer

Cc: Emma Moloney;Brunson, Alexandra <abrunson@liebertpub.com>

Dear Louise:

Copyright permission is granted for the inclusion of your article published in LYMPHATIC RESEARCH AND BIOLOGY in your PhD thesis.

Please give proper accreditation to the journal and to the publisher.

Kind regards,

Karen Ballen

Manager, Reprints/ePrints, Permissions, and Liebert Open Access

Mary Ann Liebert, Inc.

New Rochelle, NY

Appendix 3.3: Participant Information and Consent Form – Study III

Department of Clinical Medicine

Faculty of Medicine and Health Sciences

MACQUARIE UNIVERSITY NSW 2109

Phone: +61 2 9850 2358
Fax: +61 2 9812 3600

Email: louise.koelmeyer@mq.edu.au

Chief Investigator's / Supervisor's Name & Title: Prof Catherine Dean

Participant Information and Consent Form

Name of Project: A comparison of the L-Dex® U400 with the ImpediMed SOZO device: A reliability and validation study

You are invited to participate in a study to determine whether two medical devices used in the monitoring and early detection of lymphoedema actually detect fluid changes and whether or not they produce consistent readings. Before you agree to be a volunteer, it is important that you read the following information. Please ask as many questions as necessary to be sure you understand the study requirements.

When Lymphoedema is present, fluids build up within the tissues, resulting in the swelling of the affected limb. This can be assessed by measuring the resistance to low frequency currents that have been passed through the limb. The resistance to the current decreases as fluid builds up. The L-Dex® U400 and SOZO devices detects changes in extracellular fluid and is a tool used to detect lymphoedema using this method. The purpose of the study is to compare the new SOZO device with the L-Dex® U400 to determine its validity (whether or not it correctly detects lymphoedema) and reliability (whether or not it produces consistent readings).

The study is being conducted by Louise Koelmeyer to meet the requirements of a Doctor of Philosophy (PhD) under the supervision of Prof Catherine Dean, Department of Health Professions, Faculty of Medicine & Health Sciences, Macquarie University. If you have any questions about the purpose of the study and/or what participation will involve, please contact Prof Catherine Dean by phone (02 9850 6620 or e-mail (catherine.dean@mq.edu.au).

This study is sponsored by ImpediMed Limited (Brisbane, Australia), the manufacturers of the L-Dex® U400 and SOZO devices. PhD student Koelmeyer is an experienced lymphoedema therapist and has been involved in research, education, training and clinical work with the ALERT program (Australian

Lymphoedema Education, Research and Treatment) at Macquarie University. She has been an education consultant to ImpediMed on a casual basis for five years; however, has no further commitments whilst this study is being conducted. Measures will be put in place to avoid any perceived conflict of interest issues or coercion to study participants. The conduct, data collection, analysis and dissemination of results for this study will not involve ImpediMed and this arrangement has been formalised through a Macquarie University Collaborative research agreement. A research assistant will be trained to assist in data collection particularly for participants who have had a relationship with Koelmeyer in another role. Any problems with the ImpediMed devices will be reported to the study sponsor and the Macquarie University ethics committee.

If you decide to participate, you will be asked to attend the MQ Health Lymphoedema Clinic for a single 45-60-minute visit. During this time, you will complete a survey assessing baseline health, demographic information and medical history. Then you will undergo weight, height, circumference measurements (using a tape measure), perometry (volume measurements in a sitting or standing position) and L-Dex® measurements using the U400 device (lying, sitting and standing position) and the SOZO device (in a sitting and standing position). The L-Dex® measurements are painless and this study presents negligible risk to participants.

Any information or personal details gathered in the course of the study are confidential, except as required by law. No individual will be identified in any publication of the results. All data collected will be de-identified and stored in locked filing cabinets (physical data) or on a secure, password-protected network. Only the researchers involved in this study will have access to the data. If you would like to receive a summary of the results of the study, please inform the principal investigator (Prof Catherine Dean) or any member of the research team.

Participation in this study is entirely voluntary: you are not obliged to participate and if you decide to participate, you are free to withdraw at any time without having to give a reason and without consequence. A decision to withdraw from the study will in no way affect the treatment that you receive or your relationship with your therapist.

I, *(participant's name*) have read *(or, where appropriate, have had read to me)* and understand the information above and any questions I have asked have been answered to my satisfaction. I agree to participate in this research, knowing that I can withdraw from further participation in the research at any time without consequence. I have been given a copy of this form to keep.

Participant's Name:_____

(Block letters)

Participant's Signature: _____ Date:_____

Investigator's Name:_____

(Block letters)

Investigator's Signature: _____ __ Date:_____

The ethical aspects of this study have been approved by the Macquarie University Human Research Ethics Committee. If you have any complaints or reservations about any ethical aspect of your participation in this research, you may contact the Committee through the Director, Research Ethics & Integrity (telephone (02) 9850 7854; email ethics@mq.edu.au). Any complaint you make will be treated in confidence and investigated, and you will be informed of the outcome.

(INVESTIGATOR'S [OR PARTICIPANT'S] COPY)

Appendix 3.4: Data Collection Form - Study III

Principle Investigator: Prof Catherine Dean

Site location: MQ Health Lymphoedema Clinic, Suite 301, Building F10A, 2 Technology Place Macquarie University

Date of Visit: ____/____/_____ (dd/mm/yyyy)

1. Informed Consent

Has written informed consent been obtained from the participant? *Note: Consent must be obtained prior to any study procedures.*

❍ Yes
❍ No

2. Participant Information

Date of Birth (dd/mm/yyyy): _____
Height (cm): _____
Weight (kg): _____
Sex (m/f): _____

3. Demographic Information

Do you identify as being an Australian Aboriginal, Indigenous or Torres Strait Islander?

❍ Yes
❍ No

What is your marital status?

❍ Single, never married
❍ Married or De Facto
❍ Divorced
❍ Widowed
❍ Separated

What is the highest level of education that you have completed?

❍ Less than Year 10
❍ High School Certificate or equivalent
❍ Vocational / TAFE
❍ Undergraduate degree
❍ Postgraduate degree

What is your household income?

❍ Less than $50,000
❍ $50,000 to $99,000
❍ $100,000 to $150,000
❍ More than $150,000
❍ I prefer not to say

4. Inclusion Criteria

	Yes	**No**
Between the ages of 18-90 years		
Self-describe health as satisfactory		
Understand the proposed study and be willing and fully able to comply with the study procedures		
If Lymphoedema Group: Have been previously diagnosed, by current clinical practice, as having unilateral/bilateral lymphoedema of the arm/leg of any severity		

5. Exclusion Criteria

	Yes	**No**
Have a known heart condition or an implantable device such as a pacemaker or ICD		
Suffer from a renal disorder		
Be taking diuretic medications		
Be pregnant or currently breastfeeding		

6. Medical History

Do you have a metallic surgical implant (e.g., total hip replacement, not including small implants such as sternal wires or surgical staples)?

❍ Yes. Location: _____
❍ No

Have you been diagnosed with lymphoedema?

❍ Yes
❍ No (If no, skip to Section 7. Measurements)

Type of lymphoedema:

❍ Primary
❍ Secondary

If secondary lymphoedema, what type of cancer?

❍ Bladder Cancer
❍ Breast Cancer
❍ Colon and Rectal Cancer
❍ Endometrial Cancer
❍ Kidney (Renal Cell) Cancer
❍ Leukemia
❍ Melanoma
❍ Non-Hodgkin Lymphoma
❍ Pancreatic Cancer
❍ Prostate Cancer
❍ Thyroid Cancer
❍ Gynaecological Cancer
❍ Lung Cancer
❍ Other (Please Specify): _____

Cancer treatment (select all that apply):

Surgery
Radiation
Chemotherapy
Hormone Therapy

If surgical removal of lymph nodes, what type of surgery?

❍ Arm – Sentinel Node
❍ Arm – Axillary
❍ Groin – Sentinel Node
❍ Groin - Axillary

Year diagnosed with cancer: _____

Year diagnosed with lymphoedema: _____

What part of the body is affected by lymphoedema?

❍ Right upper limb
❍ Left upper limb
❍ Both upper limbs
❍ Right lower limb
❍ Left lower limb
❍ Both lower limbs
❍ None – Healthy Participant - Assign affected limb as right

Lymphoedema stage (ISL Criteria):

❍ At risk of lymphoedema
❍ Stage 0 (sub-clinical/latent)
❍ Stage I (mild)
❍ Stage II (moderate)
❍ Stage III (severe)

**Note: Always nominate RIGHT limb at risk for healthy controls*

Measurements

Dominant limb:

❍ Right
❍ Left

Circumference						
	0cm	10cm	20cm	30cm	40cm	50cm
Right arm						
Left arm						

	0cm	10cm	20cm	30cm	40cm	50cm	60cm	70cm	80cm	90cm
Right leg										
Left leg										

U400 – Perform measurements in order below			
	L-Dex reading 1	L-Dex reading 2	L-Dex reading 3
Arms **First name code:** **Family name code:**			
Lying			
Sitting			
Standing			
Legs **First name code:** **Family name code:**			
Lying			
Sitting			
Standing			

SOZO – Perform measurements in order below			
	L-Dex reading 1	L-Dex reading 2	L-Dex reading 3
Arms			
Standing			
Sitting			
Legs			
Sitting			
Standing			

SOZO Email Address (Arms): _____@alertvs.com.au

SOZO Email Address (Legs): _____@alertvs.com.au

Researcher Initials: _____

Appendix 4.1: Ethical Approval – Study IV MQ

Office of the Deputy Vice-Chancellor
(Research)

Research Office

Research Hub, Building C5C East
Macquarie University

NSW 2109 Australia

T: +61 (2) 9850 4459

http://www.research.mq.edu.au/
ABN 90 952 801 237

30 May 2017

Dear Professor Dean

Reference No: 5201700440

Title: *Feasibility and useability of the SOZO device for home monitoring of lymphoedema*

Thank you for submitting the above application for ethical and scientific review. Your application was considered by the Macquarie University Human Research Ethics Committee (HREC (Medical Sciences)).

I am pleased to advise that ethical and scientific approval has been granted for this project to be conducted at:

- Macquarie University

This research meets the requirements set out in the *National Statement on Ethical Conduct in Human Research* (2007 – Updated May 2015) (the *National Statement*).

Standard Conditions of Approval:

1. Continuing compliance with the requirements of the *National Statement,* which is available at the following website:

http://www.nhmrc.gov.au/book/national-statement-ethical-conduct-human-research

2. This approval is valid for five (5) years, subject to the submission of annual reports.

Please submit your reports on the anniversary of the approval for this protocol.

3. All adverse events, including events which might affect the continued ethical and scientific acceptability of the project, must be reported to the HREC within 72 hours.

4. Proposed changes to the protocol and associated documents must be submitted to the Committee for approval before implementation.

It is the responsibility of the Chief investigator to retain a copy of all documentation related to this project and to forward a copy of this approval letter to all personnel listed on the project.

Should you have any queries regarding your project, please contact the Ethics Secretariat on 9850 4194 or by email ethics.secretariat@mq.edu.au

The HREC (Medical Sciences) Terms of Reference and Standard Operating Procedures are available from the Research Office website at:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics

The HREC (Medical Sciences) wishes you every success in your research. Yours

sincerely

Professor Tony Eyers
Chair, Macquarie University Human Research Ethics Committee (Medical Sciences

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research* (2007) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

Details of this approval are as follows:

Approval Date: 25 May 2017

The following documentation has been reviewed and approved by the HREC (Medical Sciences):

Documents reviewed	Version no.	Date
Correspondence responding to the issues raised by the HREC (Medical Sciences)	N/A	Received 18 May 2017
Perceived Conflict of Interest Management Strategy Document from Prof Rick Kefford	N/A	19 May 2017
Revised HREA Signature page of new Principal Investigator Prof Catherine Dean	N/A	18 May 2017
Human Research Ethics Application Form (HREA)	1*	Received 12 April 2017
Protocol (Clean & Tracked Changes)	2	14 May 2017
Study Invitation (Clean & Tracked Changes)	2	17 May 2017
Macquarie PICF (Clean & Tracked Changes)	2	14 May 2017
Baseline Case Report Form	2	14 May 2017
Follow-Up Case Report Form (Clean & Tracked changes)	2	14 May 2017

Appendix 4.2: Ethical Approval – Study IV Adventist Care

28 May 2019

Ms Louise Koelmeyer Dept of
Clinical Medicine Level 1, 75
Talavera Rd

Macquarie University NSW 2109

Dear Ms Koelmeyer

HREC Project ID: 2018-036

Project Title: Home monitoring of Breast-Cancer-Related Lymphoedema using SOZO: A feasibility and usability study

Thank you for submitting the above project for ethical review. The project was considered by the Adventist HealthCare Limited Human Research Ethics Committee (HREC) at its meeting on 27 March 2019.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007, updated 2015), Australian Code for the Responsible Conduct of Research (2018) and the CPMP/ICH Note for Guidance on Good Clinical Practice.*

I am pleased to advise that the Adventist HealthCare Limited Human Research Ethics Committee has granted ethical approval of the research for five (5) years 28 May 2024.

The documents approved for use are:

Document Title
Research Checklist (signed)
HREA Application updated 10-Sep-2018_EM03299_EM03299 v1 - v2 Changes
Protocol v3 dated 04-Mar-2018_EM03299_SM02935_SOZO Home monitoring - Project Description Protocol V.1 - 4 3 18_v1_v1
EM03300_EM03299_SM02935_Appendix 1 SOZO Home monitoring - Study Invitation V3_19.03.2019_CLEAN
EM03299_SM02935_Appendix 2 SOZO Home monitoring - Screening eligibility form V.1 6.03.2018
EM03299_SM02935_Appendix 3 SOZO Home Monitoring_PICF v4 dated 12-Apr-2019
EM03300_EM03299_SM02935_Appendix 4 SOZO Home monitoring - Baseline CRF V3_18.02.2019_CLEAN COPY
EM03299_SM02935_Appendix 5 SOZO Home monitoring - Circumference & U400 BIS measurement protocol 6.03.18_v1
EM03299_SM02935_Appendix 6 SOZO Home monitoring - SOZO protocol 6.03.18_v1_v2

EM03299_SM02935_Appendix 7 SOZO Home Monitoring Study - Optional Focus Group Questions V1 - 6.03.2018
EM03300_EM03299_SM02935_Appendix 8 SOZO Home monitoring - Log V3_19.03.2019_CLEAN
EM03299_SM02935_Appendix 9 SOZO Home monitoring - Follow-Up CRF V.2 - 10.09.2018
EM03299_SM02935_Appendix 10 SOZO Home monitoring- Understanding_lymphoedema_fact_sheet_6.03.2018_v1_v2
EM03299_SM02935_Appendix 11 SOZO Home monitoring ImpediMedStudies_Perceived Conflict of Interest Management Strategy ALERT_17 05 17_Final_v1_v2
PICF v4_12-Apr-2019_(tracked and clean)
MQ General & Products Liability Protection
MQ Professional Liability Protection
Manufacturer's Declaration of Conformity dated 20-Jun-2017__SOZO_TGA
ARTG no 107108
ATRG no 134672
CV Louise Koelmeyer
CV Michael Hughes

Please note the following conditions of approval:

1. **Special Conditions**
   - The HREC will be notified, giving reasons, if the project is discontinued before the expected date of completion.
   - The Coordinating Investigator will provide an annual report to the HREC and a final report at completion of the study, in the specified format. Your annual review date is [insert month]. Failure to submit the report will result in ethical approval being suspended.
   - This letter constitutes ethical approval only. You must not commence this research until separate site authorisation has been received from the Research Governance Office.
   - You must comply with the Adventist HealthCare Limited Research Policy. A copy of the policy can be found on the ethics committee web page.

2. **Reporting**
   - The Coordinating Investigator will immediately report, in the specified format, anything which might warrant review of ethical approval of the project including any unforeseen events that might affect continued acceptability of the research.

     Serious adverse events (SAE) occurring to participants enrolled within Adventist HealthCare Limited must be notified to the Committee as soon as possible. The Coordinating Investigator must provide a summary of the events in the specified format including a comment as to the suspected causality, whether changes are required to the study.

     A suspected, unexpected serious adverse reaction (SUSAR) occurring to participants enrolled within Adventist HealthCare Limited must be notified to the Committee within 15 days of the occurrence. For fatal or life-threatening

events an initial report is required within 7 days with a follow-up report within 15 days. Reports must comment on how the event was related to the research, duration of treatment and outcome of the event and whether changes are required to the Participant Information Sheet & Consent Form.

A six-monthly summary safety report of SUSAR's occurring at all sites is required which comments on any planned action by the sponsor.

1. Amendments

- If there is an event requiring amendment/s to the approved research you should submit a request in the specified format.

Should you have any queries about the Adventist HealthCare Limited Human Research Ethics Committee's consideration of your project please contact the Research Officer on (02) 9487 9604 or ethics@sah.org.au. Report forms, in the specified format, can be found at http://www.sah.org.au/ethics-committee-forms.

The Adventist HealthCare Limited Human Research Ethics Committee wishes you every success in your research.

Yours faithfully,

Professor Ray Roennfeldt
Chairperson
Adventist HealthCare Limited Human Research Ethics Committee

Appendix 4.3: Publication License – Study IV

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Licensed Content Title	Prospective surveillance model in the home for breast cancer-related lymphoedema: a feasibility study
Licensed Content Author	Louise A. Koelmeyer et al
Licensed Content Date	Oct 1, 2020
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Circulation/distribution	1000 - 1999
Author of this Springer Nature content	yes
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Institution name	Macquarie University
Expected presentation date	Nov 2020
Order reference number	1
Requestor Location	Macquarie University Level 1, 75 Talavera Road Macquarie University Sydney, 2109 Australia Attn: Macquarie University
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Appendix 4.4: Participant Information and Consent Form – Study IV

MQ Health Lymphoedema Clinic

Department of Clinical Medicine

Faculty of Medicine and Health Sciences

MACQUARIE UNIVERSITY NSW 2109

Phone: +61 2 9812 2950

Fax: +61 2 9812 3600

Email: louise.koelmeyer@mq.edu.au

Chief Investigator's / Supervisor's Name & Title: Professor Catherine Dean

Participant Information and Consent Form

Name of Project: Home monitoring of breast cancer related lymphoedema using SOZO: A feasibility & usability study

You are invited to participate in a study which is partly sponsored by ImpediMed Limited (Brisbane, Australia), the manufacturers of the L-Dex® SOZO device. Before you agree to be a volunteer, it is important that you read the following information. Please ask as many questions as necessary to be sure you understand the study requirements.

When lymphoedema is present, fluids build up within the tissues, resulting in the swelling of the affected limb. This can be assessed by measuring low frequency currents that have been passed through the limb.

The L-Dex® SOZO device detects changes in extracellular fluid and is a tool used to detect lymphoedema. The purpose of the study is to determine whether or not using the SOZO device is a feasible and acceptable method for women at-risk of developing lymphoedema to monitor for this condition at home.

The study is being conducted by Louise Koelmeyer to meet the requirements of a Doctor of Philosophy (PhD) under the supervision of Prof Catherine Dean, Department of Health Professions, Faculty of Medicine & Health Sciences, Macquarie University and Prof John Boyages, Director, ALERT - Australian Lymphoedema Education, Research & Treatment Program, Faculty of Medicine & Health Sciences. If you have any questions about the purpose of the study and/or what participation will involve, please contact Louise Koelmeyer by phone (02 9812 2950 or e-mail: louise.koelmeyer@mq.edu.au).

This study is partly sponsored by ImpediMed Limited (Brisbane, Australia), the manufacturers of the L-Dex® U400 and SOZO devices. PhD student Koelmeyer is an experienced lymphoedema therapist and has been involved in research, education, training and clinical work with the Australian Lymphoedema Education, Research and Treatment (ALERT) program at Macquarie University. She has been an education consultant to ImpediMed on a casual basis for five years however has no further commitments whilst this study is being conducted. Measures will be put in place to avoid any perceived conflict of interest issues or coercion to study participants. The conduct, data collection, analysis and dissemination of results for this study will not involve ImpediMed and this arrangement has been formalised through a Macquarie University Collaborative research agreement. A research assistant will be trained to assist in data collection. Any problems with the ImpediMed devices will be reported to the study sponsor and ethics committee.

If you decide to participate, you will be asked to attend five 60-90 minute visits by a lymphoedema therapist (Louise Koelmeyer) or research assistant in your home. During the first visit, participants will complete some surveys assessing baseline health, demographic information and medical history. You will also be asked about any symptoms in your arm you may have and also questions relating to activity and exercises you complete. You will undergo weight, height, circumference measurements (using a tape measure) and L-Dex® measurements (including tissue analysis) using the SOZO device and the earlier model U400 device. The SOZO device will be set up in your home, and you will receive instruction on how to operate the SOZO device and how to monitor the fluid in your arm.

You will be given education about lymphoedema and strategies for reducing risk. You will be asked to use the SOZO device three times per week for twelve months at home.

Following the use of the SOZO device at home, you will attend follow-up visits at home every three months (four follow-up visits total). During each follow-up visit, you will be asked to complete a survey (either written or on-line) on your experience using the SOZO device at home. There will be an optional focus group at the conclusion of the study that you will be invited to attend to share experiences of others' using the SOZO device at home. The L-Dex® measurements take less than 5 minutes to complete, are painless and this study presents negligible risks. If you notice any symptoms of lymphoedema you will be advised to attend the MQ Health lymphoedema clinic for assessment and management.

Any information or personal details gathered in the course of the study are confidential, except as required by law. No individual will be identified in any publication of the results. All data collected will be de-identified and stored in locked filing cabinets (physical data) or on a secure, password-protected network. Only the researchers involved in this study will have access to the data. If you would like to receive a summary of the results of the study,

please inform the principal investigator (Prof Catherine Dean by emailing Catherine.dean@mq.edu.au) or any member of the research team.

Participation in this study is entirely voluntary: you are not obliged to participate and if you decide to participate, you are free to withdraw at any time without having to give a reason and without consequence. A decision to withdraw from the study will in no way affect the treatment that you receive or your relationship with your medical or allied health professionals.

I, *(participant's name*) have read *(or, where appropriate, have had read to me)* and understand the information above and any questions I have asked have been answered to my satisfaction. I agree to participate in this research, knowing that I can withdraw from further participation in the research at any time without consequence. I have been given a copy of this form to keep.

Participant's Name:_____

(Block letters)

Participant's Signature: _____ Date:_____

Investigator's Name:_____

(Block letters)

Investigator's Signature: _____ __ Date:_____

The ethical aspects of this study have been approved by the Macquarie University Human Research Ethics Committee. If you have any complaints or reservations about any ethical aspect of your participation in this research, you may contact the Committee through the Director, Research Ethics & Integrity (telephone (02) 9850 7854; email ethics@mq.edu.au). Any complaint you make will be treated in confidence and investigated, and you will be informed of the outcome.

(INVESTIGATOR'S [OR PARTICIPANT'S] COPY)

Appendix 4.5: Data Collection Form – Baseline Study IV

Baseline Case Report Form

Principal Investigator: Prof Catherine Dean

Study Contact: Louise Koelmeyer – + 61 2 9812 2950

Site location: MQ Health Lymphoedema Clinic, Suite 301, Building F10A, 2 Technology Place, Macquarie University

Date of Visit: ____/____/_____ (dd/mm/yyyy)

Informed Consent

Has written informed consent been obtained from the participant? *Note: Consent must be obtained prior to any study procedures.*

❍ Yes
❍ No

Participant Information

DOB: ____/____/_____ (dd/mm/yyyy)

Height (cm): _____
Weight (kg): _____

Demographic Information

Do you identify as being an Australian Aboriginal, Indigenous or Torres Strait Islander?

❍ Yes
❍ No

What is your marital status?

❍ Single, never married
❍ Married or De Facto
❍ Divorced
❍ Widowed
❍ Separated

What is the highest level of education that you have completed?

❍ Less than Year 10
❍ High School Certificate or equivalent
❍ Vocational / TAFE
❍ Undergraduate degree
❍ Postgraduate degree

What is your household income?

❍ Less than $50,000
❍ $50,000 to $99,000
❍ $100,000 to $150,000
❍ More than $150,000
❍ I prefer not to say

Are you currently working in paid employment?

- Yes
- No

If yes, are you working:

- Full-time
- Part-time
- Number of hours / week (Please specify): _____

If no, are you:

- Retired
- On leave due to breast cancer treatment
- Committed to home duties
- Committed to voluntary work
- Committed to caring for family members (elderly / children)
- Planning to resume paid employment in future
    - Full-time / Part-time

Medical History

Do you have a metallic surgical implant (e.g., total hip replacement, not including small implants such as sternal wires or surgical staples)?

❍ Yes. Location: _____
❍ No

Breast Cancer treatment (select all that apply):

- Surgery Type __Mastectomy __WLE __Reconstruction
- Radiation Location Breast / chest / Axilla / Supraclavicular
- Chemotherapy __Taxane based
- Hormone treatment e.g. Tamoxifen, Aromatase Inhibitor

If surgical removal of lymph nodes, what type of surgery?

- ❍ Sentinel Node
- ❍ Axillary Dissection

Number of lymph nodes removed____

Number positive____

What part of the body is at-risk of developing lymphoedema?

- ❍ Right arm
- ❍ Left arm

Dominant limb:

- ❍ Right arm
- ❍ Left arm

Measurements

Circumference					
	10cm	20cm	30cm	40cm	50cm
Right arm					
Left arm					

	L-Dex reading
Lying	

	L-Dex reading
Standing	

	Reading
Standing	Completed Y /N

Lymphoedema Symptom Intensity and Distress Survey-Arm Version 2.0

For each symptom below, circle yes or no to indicate whether you have had this symptom *DURING THE PAST WEEK*. If you circle yes, please rate how intense this symptom was using the 1 to 5-point scale. Also rate how distressed you were by this symptom using the 1 to 5-point scale.

Ridner SH, Dietrich MS (2015) Development and validation of the Lymphedema Symptom and Intensity Survey-Arm. Supportive Care Cancer 23(10):3103-3112. doi:10.1007/s00520-015-2684-

Symptom	Yes/No	Intensity	Distress
1. Heaviness in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
2. Tightness in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
3. Stabbing pain in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
4. Cramping pain in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
5. Pain in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
6. Numbness in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
7. Achiness in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
8. Swelling in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
9. Hardness in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
10. Tingling in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
11. Pins and needles in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
12. Difficulty in raising arm above head	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
13. Difficulty in moving arm side to side	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
14. Sadness	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
15. Anger	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
16. Lack of confidence in self	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
17. Lack of confidence in your insurance provider	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
18. Concerns about how you look	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
19. Feeling misunderstood by spouse/significant other	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
20. Feeling less sexually attractive	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5

21. Frustration with your insurance company	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
22. Loss of confidence in your body	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
23. Fatigue	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
24. Difficulty sleeping	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
25. Lack of interest in sex	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
26. Partner having lack of interest in sex	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
27. Inability to complete hobbies or leisure activities you used to do	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
28. Consistently decreased social activities	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
29. Decreased level of physical activities	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
30. Decrease in sexual activity	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5

Incidental and Planned Exercise Questionnaire (IPEQ)

Merom D, Delbaere K, Cumming R, Voukelatos A, Rissel C, Van Der Ploeg HP, Lord SR (2014) Incidental and Planned Exercise Questionnaire for seniors: validity and responsiveness. Med Sci Sports Exerc 46 (5):947-954. doi:10.1249/MSS.0000000000000196

The next questions are exploring what you do in regards to physical activity and exercise.

In the **last week**, how often have you been on **walks specifically for exercise**? i.e., walking in the park, in the streets, cross-country walking, walking the dog, etc.

- o Every day
- o 3-6 times per week
- o Twice per week
- o Once per week
- o Less than once per week
- o Never

In these **walks for exercise**, how long did you walk for?

- o Less than 15 mins per day
- o 15 mins to less than 30 mins per day
- o 30 mins to less than 1 hour per day
- o 1 hour to less than 2 hours per day
- o 2 hours to less than 4 hours per day
- o 4 or more hours per day

In the **last week**, how often have you **attended exercise classes?**

- o Every day
- o Six times
- o Five times
- o Four times
- o Three times
- o Twice
- o Once
- o Never

How **long** did these exercise classes last per session?

- o Less than 30 mins
- o 30 mins to less than 45 mins
- o 45 mins to less than 1 hour
- o 1 hour to less than 2 hours
- o 2 hours to less than 4 hours
- o

In the **last week**, how often have you **undertaken home activities for exercise**?

Examples of activities: stationary bicycle, stretching, etc.

- Every day
- Six times
- Five times
- Four times
- Three times
- Twice
- Once
- Never

How **long** was your home exercise session on average per session?

- Less than 30 mins
- 30 mins to less than 45 mins
- 45 mins to less than 1 hour
- 1 hour to less than 2 hours
- 2 hours to less than 4 hours

In the **last week**, how often have you undertaken **other types of activities for exercise?**

Examples of other activities: bowls, golf, tennis, swimming, dancing, jogging, bicycling, etc.

- Every day
- Six times
- Five times
- Four times
- Three times
- Twice
- Once
- Never

In these activities for exercise, how **long** was each session?

- Less than 30 mins
- 30 mins to less than 45 mins
- 45 mins to less than 1 hour
- 1 hour to less than 2 hours
- 2 hours to less than 4 hours

During the **last week**, how often have you been on **walks NOT specifically for exercise?**

For example, walking to the general practitioner, pharmacy or store.

- o Every day
- o 3-6 times per week
- o Twice per week
- o Once per week
- o Less than once per week
- o Never

In these other walks, how **long** did you walk for?

- o Less than 15 mins per day
- o 15 mins to less than 30 mins per day
- o 30 mins to less than 1 hour per day
- o 1 hour to less than 2 hours per day
- o 2 hours to less than 4 hours per day
- o 4 or more hours per day

During the **last week**, in **addition** to the walking you mentioned previously, **how much time did you spend each day outdoors doing other physical activity** such as house maintenance, gardening and community work?

Excluding activities inside the house.

- o Never
- o Less than 15 mins per day
- o 15 mins to less than 30 mins per day
- o 30 mins to less than 1 hour per day
- o 1 hour to less than 2 hours per day
- o 2 hours to less than 4 hours per day
- o 4 or more hours per day

During the **last week**, how **many hours** did you **spend on your feet each day indoors at home** doing tasks like housework, self-care or care for another person?

- o Never (living in hostel, assisted living)
- o Less than 15 mins per day
- o 15 mins to less than 30 mins per day
- o 30 mins to less than 1 hour per day
- o 1 hour to less than 2 hours per day
- o 2 hours to less than 4 hours per day
- o 4 or more hours per day

Lymphoedema Self-management

Please list which lymphoedema risk minimization or self-management activities you do and its frequency to assist in managing your condition

Self-management strategy	**Tick if used**	**Frequency Daily/ weekly/ ad-hoc (specify)**
Self-manual lymphatic drainage massage (MLD)		
Exercise (please specify)		
Compression therapy (garment, bandages, wraps)		
Pneumatic compression pump		
Skin care		
Laser		
Kinesiology taping		
Other – please list		

Willingness and Confidence Scale (Modified)

Ridner SH, Bonner CM, Doersam JK, Rhoten BA, Schultze B, Dietrich MS (2014) Bioelectrical Impedance Self-Measurement Protocol Development and Daily Variation Between Healthy Volunteers and Breast Cancer Survivors with Lymphedema. Lymphatic Research and Biology. doi:10.1089/lrb.2013.0020

Please rate to what extent you agree with the following statements:

I am confident I can use the device at home to measure my arms.

Strongly agree | Agree | Neither agree / disagree | Disagree | Strongly disagree

I know how to set up the device for use at home.

Strongly agree | Agree | Neither agree / disagree | Disagree | Strongly disagree

I know how to set up the tablet for use at home.

Strongly agree | Agree | Neither agree / disagree | Disagree | Strongly disagree

I know how to prepare for taking a measurement using the device.

Strongly agree | Agree | Neither agree / disagree | Disagree | Strongly disagree

I know where to place my hands and feet for taking a measurement using the device.

Strongly agree | Agree | Neither agree / disagree | Disagree | Strongly disagree

I know how to use the device to take measurements of both my arms.

Strongly agree | Agree | Neither agree / disagree | Disagree | Strongly disagree

I am able to read the measurement results on the tablet and record them on paper (Protocol Observance and Measurement Log):

Strongly agree | Agree | Neither agree / disagree | Disagree | Strongly disagree

I am willing to contact the study team by telephone or by email if I need help using the device at home.

Strongly agree | Agree | Neither agree / disagree | Disagree | Strongly disagree

I am willing to use the device to measure my arm at home without help.

Strongly agree	Agree	Neither agree / disagree	Disagree	Strongly disagree

I am willing to use the device to measure my arm at home with help if I need it.

Strongly agree	Agree	Neither agree / disagree	Disagree	Strongly disagree

Appendix 4.6: Data Collection Form – Follow-up Study IV

Follow Up Case Report Form

Principal Investigator: Prof Catherine Dean

Site location: MQ Health Lymphoedema Clinic, Suite 301, Building F10A, 2 Technology Place, Macquarie University

Date of Visit: ____/____/_____ (dd/mm/yyyy)

Participant Information

Weight (kg): _____

What part of the body is at-risk of developing lymphoedema?
❍ Right arm
❍ Left arm

Dominant limb:

❍ Right arm
❍ Left arm

Measurements

Circumference					
	10cm	20cm	30cm	40cm	50cm
Right arm					
Left arm					

U400	L-Dex reading
Lying	

SOZO	L-Dex reading
Standing	

SOZO Tissue Analysis	Reading 1
Standing	Completed Y /N

Lymphoedema Symptom Intensity and Distress Survey-Arm Version 2.0

For each symptom below, circle yes or no to indicate whether you have had this symptom *DURING THE PAST WEEK*. If you circle yes, please rate how intense this symptom was using the 1 to 5-point scale. Also rate how distressed you were by this symptom using the 1 to 5-point scale.

Ridner SH, Dietrich MS (2015) Development and validation of the Lymphedema Symptom and Intensity Survey-Arm. Supportive Care Cancer 23 (10):3103-3112. doi:10.1007/s00520-015-2684-y

Symptom	Yes/No	Intensity	Distress
1. Heaviness in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
2. Tightness in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
3. Stabbing pain in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
4. Cramping pain in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
5. Pain in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
6. Numbness in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
7. Achiness in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
8. Swelling in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
9. Hardness in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
10. Tingling in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
11. Pins and needles in your arm	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
12. Difficulty in raising arm above head	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
13. Difficulty in moving arm side to side	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
14. Sadness	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
15. Anger	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
16. Lack of confidence in self	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
17. Lack of confidence in your insurance provider	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
18. Concerns about how you look	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
19. Feeling misunderstood by spouse/significant other	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
20. Feeling less sexually attractive	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5

21. Frustration with your insurance company	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
22. Loss of confidence in your body	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
23. Fatigue	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
24. Difficulty sleeping	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
25. Lack of interest in sex	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
26. Partner having lack of interest in sex	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
27. Inability to complete hobbies or leisure activities you used to do	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
28. Consistently decreased social activities	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
29. Decreased level of physical activities	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 1 2 3 4 5
30. Decrease in sexual activity	Yes No	Slight Severe 1 2 3 4 5	Slight Severe 2 2 3 4 5

Incidental and Planned Exercise Questionnaire (IPEQ)

Merom D, Delbaere K, Cumming R, Voukelatos A, Rissel C, Van Der Ploeg HP, Lord SR (2014) Incidental and Planned Exercise Questionnaire for seniors: validity and responsiveness. Med Sci Sports Exerc 46 (5):947-954. doi:10.1249/MSS.0000000000000196

The next questions are exploring what you do in regards to physical activity and exercise.

In the **last week**, how often have you been on **walks specifically for exercise**? i.e., walking in the park, in the streets, cross-country walking, walking the dog, etc.

- o Every day
- o 3-6 times per week
- o Twice per week
- o Once per week
- o Less than once per week
- o Never

In these **walks for exercise**, how long did you walk for?

- o Less than 15 mins per day
- o 15 mins to less than 30 mins per day
- o 30 mins to less than 1 hour per day
- o 1 hour to less than 2 hours per day
- o 2 hours to less than 4 hours per day
- o 4 or more hours per day

In the **last week**, how often have you **attended exercise classes?**

- o Every day
- o Six times
- o Five times
- o Four times
- o Three times
- o Twice
- o Once
- o Never

How **long** did these exercise classes last per session?

- o Less than 30 mins
- o 30 mins to less than 45 mins
- o 45 mins to less than 1 hour
- o 1 hour to less than 2 hours
- o 2 hours to less than 4 hours

In the **last week**, how often have you **undertaken home activities for exercise**?

Examples of activities: stationary bicycle, stretching, etc.

- o Every day
- o Six times
- o Five times
- o Four times
- o Three times
- o Twice
- o Once
- o Never

How **long** was your home exercise session on average per session?

- o Less than 30 mins
- o 30 mins to less than 45 mins
- o 45 mins to less than 1 hour
- o 1 hour to less than 2 hours
- o 2 hours to less than 4 hours

In the **last week**, how often have you undertaken **other types of activities for exercise?**

Examples of other activities: bowls, golf, tennis, swimming, dancing, jogging, bicycling, etc.

- o Every day
- o Six times
- o Five times
- o Four times
- o Three times
- o Twice
- o Once
- o Never

In these activities for exercise, how **long** was each session?

- o Less than 30 mins
- o 30 mins to less than 45 mins
- o 45 mins to less than 1 hour
- o 1 hour to less than 2 hours
- o 2 hours to less than 4 hours

During the **last week**, how often have you been on **walks NOT specifically for exercise?**

For example, walking to the general practitioner, pharmacy or store.

- o Every day
- o 3-6 times per week
- o Twice per week
- o Once per week
- o Less than once per week
- o Never

In these other walks, how **long** did you walk for?

- o Less than 15 mins per day
- o 15 mins to less than 30 mins per day
- o 30 mins to less than 1 hour per day
- o 1 hour to less than 2 hours per day
- o 2 hours to less than 4 hours per day
- o 4 or more hours per day

During the **last week**, in **addition** to the walking you mentioned previously, **how much time did you spend each day outdoors doing other physical activity** such as house maintenance, gardening and community work?

Excluding activities inside the house.

- o Never
- o Less than 15 mins per day
- o 15 mins to less than 30 mins per day
- o 30 mins to less than 1 hour per day
- o 1 hour to less than 2 hours per day
- o 2 hours to less than 4 hours per day
- o 4 or more hours per day

During the **last week**, how **many hours** did you **spend on your feet each day indoors at home** doing tasks like housework, self-care or care for another person?

- o Never (living in hostel, assisted living)
- o Less than 15 mins per day
- o 15 mins to less than 30 mins per day
- o 30 mins to less than 1 hour per day
- o 1 hour to less than 2 hours per day
- o 2 hours to less than 4 hours per day
- o 4 or more hours per day

Lymphoedema Self-management

Please list which lymphoedema risk minimization / self-management activities you do and its frequency to assist in managing your condition

Self-management strategy	**Tick if used**	**Frequency Daily/ weekly/ ad-hoc (specify)**
Self-manual lymphatic drainage massage (MLD)		
Exercise (please specify)		
Compression therapy (garment, bandages, wraps)		
Pneumatic compression pump		
Skin care		
Laser		
Kinesiology taping		
Other – please list		

Willingness and Confidence Scale (Modified)

Ridner SH, Bonner CM, Doersam JK, Rhoten BA, Schultze B, Dietrich MS (2014) Bioelectrical Impedance Self-Measurement Protocol Development and Daily Variation Between Healthy Volunteers and Breast Cancer Survivors with Lymphedema. Lymphatic Research and Biology. doi:10.1089/lrb.2013.002

Please rate to what extent you agree with the following statements:

I am confident I can use the device at home to measure my arm

Strongly agree	Agree	Neither agree / disagree	Disagree	Strongly disagree

I know how to set up the device for use at home.

Strongly agree	Agree	Neither agree / disagree	Disagree	Strongly disagree

I know how to set up the tablet for use at home.

Strongly agree	Agree	Neither agree / disagree	Disagree	Strongly disagree

I know how to prepare for taking a measurement using the device.

Strongly agree	Agree	Neither agree / disagree	Disagree	Strongly disagree

I know where to place my hands and feet for taking a measurement using the device.

Strongly agree	Agree	Neither agree / disagree	Disagree	Strongly disagree

I know how to use the device to take measurements of both my arms.

Strongly agree	Agree	Neither agree / disagree	Disagree	Strongly disagree

I am able to read the measurement results on the tablet and record them on paper (Protocol Observance and Measurement Log):

Strongly agree	Agree	Neither agree / disagree	Disagree	Strongly disagree

I am willing to contact the study team by telephone or by email if I need help using the device at home.

Strongly agree	Agree	Neither agree / disagree	Disagree	Strongly disagree

I am willing to use the device to measure my arm at home without help.

Strongly agree	Agree	Neither agree / disagree	Disagree	Strongly disagree

I am willing to use the device to measure my arm at home with help if I need it.

Strongly agree	Agree	Neither agree / disagree	Disagree	Strongly disagree

10. Home monitoring interview Guide

a. Please describe when you have been using the SOZO device at home?

b. How easy has it been to use the SOZO at home?

c. What do you think are the perceived advantages of using SOZO at home?

d. What do you think are the perceived disadvantages of using SOZO at home?

e. Please list any positive feedback you have for using the SOZO device at home?

f. Please list any difficulties or concerns that have arisen in using the SOZO device?

g. Would you use the SOZO device at home for monitoring your arm for lymphoedema? If yes, how often would you use it?

h. Would you be interested in purchasing a SOZO device? If yes, how much would you be willing to pay for it?

i. Do you have any other comments about your experience with using the SOZO device?

Appendix 4.7: TIDIER Checklist – Study IV

TIDIER checklist

TIDieR Criteria	Experimental intervention
Item 1: Brief name or phrase that describes the intervention.	Prospective surveillance model of care in the home
Item 2: Rationale, theory, or goal of the elements essential to the intervention	A prospective surveillance and early intervention model of care has been recognized as an optimal framework for the early detection and management of sub-clinical lymphoedema [14,13,15]. Using prospective surveillance model in clinical practice enables the early identification and intervention for lymphoedema, sometimes in a subclinical stage, where intervention can prevent progression to a chronic condition [16-19]. Recommended practice for the prospective surveillance model requires that individuals at-risk of lymphoedema regularly attend clinics on a 3-6 monthly cycle according to their risk factors and treatment pathway for three years to have their arm monitored for lymphoedema by either using bioimpedance spectroscopy (BIS) or circumference measurements [16,13]. This study assessed the feasibility of delivering a prospective surveillance model of care in the home to participants who were aged between 18-85 years with a histologically confirmed node positive invasive breast cancer after undergoing an axillary lymph node dissection or sentinel lymph node biopsy, were able to speak and read English and were capable of giving informed written consent participated in the study. They were excluded if they had implantable devices such as pacemaker or other inbuilt stimulator, were pregnant, reported having a previous history of breast cancer or arm lymphoedema, if they had a health condition that may affect body fluid status or if they reported having a psychiatric illness that would limit their compliance with study requirements. The intervention consisted of a package including BIS monitoring, education, and support to promote self-management and physical activity over a six-month period.
Item 3: What (Materials): any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers.	1) BIS monitoring involved the use of a BIS stand-on device. The stand-on device used was a commercially available impedance device (SOZO®, ImpediMed Limited, Brisbane, Australia) with demonstrated validity and reliability [26]. This device is portable and can be operated easily by an individual completing self-measurements within a home environment with access to power and a wireless internet network. 2) Electronic scales were used so that the participant could take their weight prior to a BIS measurement. 3) The education component focussed on risk minimisation and included provision of the *Australian Cancer Council Understanding Lymphoedema* fact sheet [29]. 4) Self-management strategies included skin care, exercise, self-lymphatic drainage massage, compression and the use of pneumatic compression. Information about these strategies was provided to participants by research team and included in the *Australian Cancer Council Understanding Lymphoedema* fact sheet [29]. 5) To facilitate understanding of their own condition, participants were asked to record their L-Dex measurement and relevant comments (e.g. weather changes, activity, air travel, changes in treatment) in the home measurement log form.
Item 4: What (Procedures): the procedures, activities, and/or processes used in the	Women were screened via the telephone and eligible participants were scheduled for a baseline assessment in their home three months' after breast cancer surgery. Measurements were taken at baseline, three and six months in the

intervention, including any enabling or support activities.	home by trained measurers following standardised protocols. Intervention was provided at the conclusion of each measurement session. The stand-on BIS device was set up within the home (bedroom, bathroom, study or living area) and training was provided of how to take measurements and how to record and interpret results. Participants were advised to take the measurement three times a week, in the morning after waking and voiding. Participants were advised to contact research team if their L-Dex score increased by >+6.5 points or more (defined as sub-clinical lymphoedema) from baseline result or if they had any lymphoedema related symptoms or concerns. The device is controlled with an Android tablet pre-installed with the SOZOapp (ImpediMed Limited, Brisbane, Australia). All user accounts, measurement data, and other calculated measures and trends were stored in the secure MySOZO cloud (ImpediMed Limited, Brisbane, Australia) and BIS measurements were monitored remotely by the research team through this secure connection. Research personnel contacted participants by telephone or email if their L-Dex score increased above normal or if they observed any clinical or technical issues relating to lymphoedema or the study. At any time, participants who had an increase in extracellular fluid or lymphoedema symptoms were referred to a qualified lymphoedema therapist for standard clinical care, and this did not affect their ability to remain on study.
Item 5: Who provided, their expertise, background and any specific training given.	The prospective surveillance model of care in the home was delivered by a qualified occupational and lymphoedema therapist, registered with the appropriate professional body with support for data collection and liaison with participants by a trained research assistant.
Item 6: Modes of delivery (e.g. Face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	The prospective surveillance model of care in the home was provided individually: 1) Face-to-face provision of the intervention program 2) Telephone calls and email communication to participants for any study related or technical support.
Item 7: Where, the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	The prospective surveillance model of care was delivered in the home environment. The BIS stand-on device and electronic scales were loaned to the participant for the duration of the study and wipes for infection control and dampening the electrodes were supplied by study team.
Item 8: When and how much. A description of the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	The prospective surveillance model of care was standardized to a six-month program. Participants were advised to take the BIS measurement three times a week, in the morning after waking and voiding. Measurements were taken at baseline, three and six months in the home by trained measurers following standardised protocols.
Item 9: Tailoring, if the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	The prospective surveillance model of care was standardised, however at any time, participants who had an increase in extracellular fluid or lymphoedema symptoms were referred to a qualified lymphoedema therapist for standard clinical care, and this did not affect their ability to remain on study.
Item 10: Modifications. If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	No modifications were made to the standardized protocol after participant recruitment began. Further training and education to participants on the importance of good contact between the skin and electrodes reduced further technical errors when using the stand-on device to take an accurate measurement.
Item 11: How well (Planned) If intervention adherence or fidelity was assessed, describe how	1) Audit of documentation to assess provision of the prospective surveillance model of care within the home 2) Participant recorded details of the number of BIS measurements taken in the home measurement log form

and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	3) Double entry and external checking of all data inputted into electronic database
Item 12: How well (Actual) If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	To facilitate understanding of their own condition and participation in the prospective surveillance model of care, participants were asked to record their L-Dex measurement and relevant comments (e.g. weather changes, activity, air travel, changes in treatment) in the home measurement log form.

Appendix 4.8: Photographs of SOZO at home – Study IV of this thesis have been removed as it may contain sensitive/confidential content