UNIVERSITY OF CANBERRA

THE EFFICACY AND COSTS OF COMPRESSION THERAPY TO PREVENT RECURRENT LOWER LIMB CELLULITIS IN ADULTS WITH CHRONIC OEDEMA

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Bachelor of Applied Science (Physiotherapy) (Hons1)

Master of Public Health

A thesis submitted for the degree of Doctor of Philosophy at the

University of Canberra in 2022

Discipline of Physiotherapy, Faculty of Health

Abstract

Cellulitis is a common bacterial infection of the skin and subcutaneous tissue, which usually occurs in the legs. It is often recurrent, with up to 47% of patients experiencing one or more repeat episodes within three years. Cellulitis is potentially serious, resulting in morbidity and financial burden for the patient, as well as substantial costs to the healthcare system. It is the third most common reason to present at an emergency department within Australia, with the infection often developing on the background of unmanaged risk factors such as tinea, wounds and oedema.

Chronic oedema refers to swelling which has persisted for three or more months. It is a strong risk factor for initial and recurrent cellulitis infections, and the relationship between chronic oedema and cellulitis is cyclical. Expert consensus recommends chronic oedema is managed using compression therapy to prevent recurrent cellulitis infections, however there is little research and no randomised trials to support this theory. Therefore, this project sets out to investigate the efficacy of compression therapy to prevent lower limb recurrent cellulitis in adults with chronic oedema. Additionally, the costs of compression therapy and cellulitis are calculated and compared to assess the cost-effectiveness of the intervention.

Studies 1 and 2 comprise the protocol and outcomes of a randomised controlled trial (RCT) which assessed the efficacy of compression therapy to prevent recurrent cellulitis. The single centre, randomised trial with cross-over planned to include 162 adults with lower limb chronic oedema and a history of two or more episodes of cellulitis in the same leg in the two years prior to trial referral. Randomisation was stratified based on prophylactic antibiotic use. Concealed allocation was used to assign participants in a 1:1 ratio to receive lower limb compression therapy and education on cellulitis prevention (experimental group) or the education alone (control group). Follow-up of participants was planned to occur 6-monthly for up to three-years or until 45 episodes of cellulitis occurred across the trial cohort. An interim analysis was planned to occur after the 23rd episode of cellulitis, with pre-specified stopping rules agreed on. Following an episode of cellulitis, participants in the control group were crossed over to the experimental group to receive compression therapy. Neither the assessors or patients were blinded for logistical and ethical reasons. Survival analysis was used to assess the primary outcome of time to the first episode of cellulitis. Other secondary outcomes included the impact of compression therapy on cellulitis-related hospital admissions, leg volume and quality of life.

During the trial, a total of 183 participants were screened, and 84 were enrolled, with 41 participants being assigned to the experimental group and 43 to the control group. Following the 23rd episode of cellulitis, the interim analysis was conducted by an external statistician. A log-rank test showed a highly significant ($p<0.001$) group difference in favour of the experimental group, resulting in the early cessation of the trial for efficacy. In the experimental group, 6 (15%) participants experienced recurrence, compared to 17 (40%) participants in the control group. Based on time to recurrence, the hazard ratio was 0.23 (95% CI, 0.09 to 0.59), showing a 77% decrease in recurrent cellulitis risk for the intervention group compared to the control group. The relative risk was 0.37 (95% CI, 0.16 to 0.84; P = 0.02), and number needed to treat to prevent one episode of cellulitis was 4 (95% CI, 2 to 15). During the trial, 3 (7%) participants in the experimental group were hospitalised for cellulitis, compared to 6 (14%) in the control group (hazard ratio, 0.38; 95% CI, 0.09 to 1.59). Over 12-months, mean leg volume between the ankle and knee was reduced by 181ml in the experimental group and increased by 60ml in the control group, giving an intergroup difference of 241ml (95% CI, 117 to 365). Changes measured in quality of life were not clinically significant. No adverse outcomes occurred during the trial.

Study three is a cost-analysis which was conducted during the RCT to measure and compare the cost of compression therapy and cellulitis from both patient and health service perspectives. A clinical audit and patient survey were used to measure patient and health service resource use for (1) compression therapy over 18-months and (2) the most recent episode of cellulitis. Australian reference costs were applied to the measured resources to calculate mean compression therapy and cellulitis costs and, subsequently, the mean total expenditure across both the experimental and control groups during the RCT. Of the 84 RCT participants, the survey and audit were completed for 40 participants on resource use for compression therapy and 43 participants on resource use for cellulitis. The mean cost of compression therapy over 18 months per participant was $421 from a patient perspective and $1905 from a health service perspective. For an episode of cellulitis, the mean cost of a hospitalised and non-hospitalised infection was $4496 and $1320 from a patient perspective and $9071 and $506 from a health service perspective. Across the duration of the RCT, the mean annual cost per participant was $4,972 in the experimental group, compared to $26,382 in the control group. Therefore, the provision of compression therapy produced an annual cost saving of $21,483 (95% confidence interval, $3,136 to 48,176) per participant.

This is the first RCT and cost-analysis to demonstrate that for patients with lower limb chronic oedema and recurrent cellulitis, compression therapy is not only efficacious in preventing cellulitis, it is also cost-saving. The implications for these patients are clear: oedema management using compression therapy should become standard practice for the prevention of recurrent cellulitis. The health and financial benefits demonstrated by this research provide strong justification for health services and policy makers to advocate for, and invest in, oedema management services for these patients.

Trial registration: ACTRN12617000412336 (Australia New Zealand Clinical Trials Registry

Publications relating to this thesis

2019 Webb E, Neeman T, Gaida J, Bowden FJ, Mumford V, Bissett B. Impact of Compression Therapy on Cellulitis (ICTOC) in adults with chronic oedema: a randomised controlled trial protocol. BMJ Open. 2019;9(8):e029225.

2020 Webb E, Neeman T, Bowden FJ, Gaida J, Mumford V, Bissett B. Compression Therapy to Prevent Recurrent Cellulitis of the Leg. The New England Journal of Medicine. 2020;383(7):630-9.

2020 Webb E, Bowden FJ, Bissett B. Letter to the editor: Compression Therapy to Prevent Recurrent Cellulitis of the Leg. The New England Journal of Medicine. 2020;383(19):1891-1892.

2021 Webb E. Compression Counters Cellulitis (feature article). Pathways: Canada's Lymphedema Magazine. Canadian Lymphedema Framework; March 2021.

2021 Webb E. Compression Counters Cellulitis. Lymph Exchange. Australasian Lymphology Association; February 2021.

2021 Webb E. Compression Counters Cellulitis: How compression therapy substantially reduces the recurrence of cellulitis. News & Views. British Lymphology Society; 2021.

2022 Webb E, Bissett B, Neeman T, Bowden F, Preston E, Mumford V. Compression Therapy Is Cost-Saving in the Prevention of Lower Limb Recurrent Cellulitis in Patients with Chronic Edema. Lymphatic Research and Biology. Online ahead of print 23 Aug 2022. doi: 101089/lrb20220029.

Awards relating to this thesis

2018 Best Higher Degree Research Paper, ACT Australian Physiotherapy Association Symposium.

2019 Best Research Paper, ACT Australian Physiotherapy Association Symposium

2019 Three-minute Thesis Winner, University of Canberra.

2019 Best Overall Paper Award, the Cancer, Palliative Care and Lymphoedema Stream, Australian Physiotherapy Association Conference

2022 Nominated for Research Excellence, ACT Health Allied Health awards.

2022 Delegate's Choice Best Oral Presentation, Australasian Lymphology Association Conference.

Grant applications and sponsorship agreements relating to this thesis

2017 Sponsorship Agreement with Haddenham Healthcare to the estimated value of $40,000-$70,000.

2018 Australian Physiotherapy Association Project Grant ($16,000); applied.

2019 Australian Physiotherapy Association Seeding Grant ($10,000); shortlisted.

2020 Australasian Lymphology Association Research Grant ($10,000); applied (unfortunately not eligible after advice to the contrary).

Presentations relating to this thesis

2022 Invited webinar: 'Application, costs and benefits of compression therapy to prevent recurrent cellulitis', Thrive Webinar Series, Australian Physiotherapy Association, Australia.

2022 Presentation: 'Compression therapy prevents cellulitis, but is it cost-effective', Australasian Lymphology Association Conference, Hobart, Australia.

2022 Invited national speaker: Australian Physiotherapy Association Conference, Brisbane, Australia.

- Presentation: 'Application, Costs and Benefits of Compression Therapy to Prevent Recurrent Cellulitis' (cancelled due to COVID).
- Half day workshop: 'Chronic oedema, the hidden epidemic, and its relationship with cellulitis' (cancelled due to COVID).

2020 Invited Webinar: 'Putting Research into Practice for Chronic Oedema/Cellulitis', Haddenham Healthcare, Australia.

2020 Invited webinar: 'Cellulitis and Compression Therapy', Midday and Adriana and Andrea, Essity, Australia.

2020 Radio: Interview with Bernie Bissett on 2CC regarding research results, Canberra, Australia.

2020 Lecture: 1-hour lecture to emergency department registrars on the relationship between cellulitis and chronic oedema and undertaking research, Calvary Public Hospital Bruce, Canberra, Australia.

2020 Presentation: 'Keeping the pressure on: Does compression reduce cellulitis? Results of a randomised controlled trial', Australasian Lymphology Association Conference, Hobart (virtually), Australia.

2020 Presentation: 'Keeping the pressure on: Does compression reduce cellulitis? Results of a randomised controlled trial', European Wound Management Association Conference, London, England (accepted to speak however conference was postponed due to COVID-19).

2019 Invited speaker presentation: 'Lymphoedema and Cellulitis', Wounds Australia Symposium, Canberra, Australia.

2019 Presentation: ‘Keeping the pressure on: Does compression reduce cellulitis? Results of a randomised controlled trial’, Australian Physiotherapy Association Conference, Adelaide, Australia.

2019 Asia-Pacific 3MT final: ‘Keeping the Pressure ON’, Brisbane, Australia.

2019 University of Canberra 3MT Presentation: Keeping the Pressure ON, Canberra, Australia.

2019 Presentation: ‘Keeping the pressure on: Does compression reduce cellulitis? Results of a randomised controlled trial’, Australian Physiotherapy Association Symposium, Canberra, Australia.

2019 Presentation: ‘Keeping the pressure on: Does compression reduce cellulitis? Results of a randomised controlled trial’, Canberra Health Research Meeting, Canberra, Australia.

2018 Presentation: ‘Keeping the pressure on: Does compression reduce cellulitis? Protocol and preliminary data for a randomised controlled trial’, Australian Physiotherapy Association Symposium, Canberra, Australia.

2018 Radio: Interview on ABC Canberra to advertise the Impact of Compression Therapy Randomised Controlled Trial to ACT and local NSW residents, Canberra, Australia.

2018 Presentation: ‘Keeping the pressure on: Does compression reduce cellulitis? Protocol and preliminary data for a randomised controlled trial’, Australasian Lymphology Association Conference, Brisbane, Australia.

2018 Presentation: ‘Lymphoedema, Oedema & Obesity and Calvary’s drive for Excellence’, Grand Rounds, Calvary Public Hospital Bruce, Canberra, Australia

2017 Presentation: ‘Keeping the pressure on: Does compression reduce cellulitis? Canberra Health Annual Research Meeting, Canberra, Australia

Acknowledgements

First and foremost, I have to thank my PhD supervisors. I could not have asked for a better support team! Bernie, you inspired me to initiate this research project and seek external expert advice, and your ongoing encouragement, guidance and support made it happen. You have always been incredibly generous with your time and provided efficient, quality and targeted feedback. You have been a true mentor to me, and your infectious enthusiasm was always a source of motivation when needed. You made my PhD experience a pleasure, and quite simply, there is nothing I could write that would give justice to how valuable you have been throughout this process. Terry, before this project became a PhD, you opted to help me out of pure goodwill and a strong commitment to helping clinicians to conduct quality research. Without your expertise and guidance, this project would have looked vastly different and certainly would not have produced the meaningful results which are now evident. Your kindness and patience, coupled with your dedication to building my research and analytical skills, have been invaluable to me. Virginia, I am incredibly fortunate to have stumbled upon your expertise. Your patient guidance allowed me to add another valuable dimension to the research project and stretched me to learn and apply new concepts. Frank, despite your pending retirement and busy schedule, you still took the time to listen to me and to support this project through your medical, research and editing expertise. Lis, although you were a late addition to my panel, your eye for detail and editing skills were immensely useful to me. My sincere thanks go to all of you for making my PhD such a positive experience.

This project has only been possible due to the generous support of the Calvary Physiotherapy Department. In particular, I would like to express my gratitude to my lymphoedema team (Gemma Arnold, Marie Coulombe, Caitlin Aspden, Emma May, Abby Benton, Alicia Palmer, Joshua Pogson, Nievelle Chand, Ashlee Cashion, Sarah Toohey and Bhavleen Singh), as it has been your ongoing commitment to conducting quality research that has enabled this project to happen. To Gemma Arnold, thank you for believing in this project right from the start and for ensuring I had the time and support required to see it through. Marie Coulombe, aside from being a truly wonderful colleague and friend, you helped to conceive this project and navigate the necessary logistics to make it feasible. To Jennifer Azurin, thank you for valuing and supporting research within the department.

This project has been financially supported through sponsorship from Haddenham Healthcare, for which I am sincerely thankful. Without sponsorship in the form of compression garments, it would have been incredibly difficult to recruit an adequate number of participants. Helen, you have always been a pleasure to work with, and I am pleased this research provides further evidence to support the many benefits of compression therapy.

To Megan Carters, Jessica Pink, Katie Thurber, Sarah Demery and Tahnee Carters, I cannot express my gratitude and appreciation for your friendship. I am incredibly fortunate to have such a wonderful group of friends around me, listening, understanding, and providing advice and laughs. I look forward to being more present in your lives.

Lastly, none of this could have happened without the support of my wonderful family. Mum and Dad, thank you for your persistent encouragement and particularly for taking Adriana on Fridays to give me the time I needed to complete this thesis. Noreen, thank you for your unwavering dedication to family, travelling regularly to look after Adriana and supporting us in whatever we needed. Matt, it has been a big few years- getting married, moving house, managing the property, two pregnancies, one toddler and another on the way. Despite competing priorities, I always had your unconditional love and support, for which I am deeply thankful. I particularly have to thank you for being my on-call IT and emotional support, and for always making my days a little brighter! Adriana, you have been my greatest distraction and source of joy, which has always helped me to keep everything in perspective. I look forward to having a little more freedom to spend time with you all.

Keywords

Cellulitis, recurrence, oedema, lymphoedema, compression, compression garment, cost.

Ethics Approvals

Calvary Public Hospital Bruce: 53-2016

Australian Capital Territory Health: ETH.4.17.092

University of Canberra: cross-institutional approval.

Australia New Zealand Clinical Trials Registry

Trial registration: ACTRN12617000412336

Use of Images

Consent has been gained for the use of all patient photos within this thesis.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

ADLs	Activities of daily living
AR-DGR	Australian refined diagnosis related groups
BMI	Body mass index
CCL	Compression class
EQ-5D	EuroQol Five Dimension Scale
HRQoL	Health related quality of life
ICC	Intraclass correlation coefficient
IHPA	Independent Hospital Pricing Authority
LOS	Length of stay
LYMQOL	Quality-of-life measure for limb lymphoedema
QOL	Quality of life
RCT	Randomised controlled trial
95% CI	95% Confidence interval

CHAPTER 1: Introduction

Rationale

Cellulitis is an acute and often recurrent bacterial infection of the skin and underlying tissue[1,2]. It contributes physical, psychological, and financial burden to the patient, as well as substantial cost to the health care system. Cellulitis can occur on any area of the skin; however, the leg is the most common site of infection, accounting for 68-84% of infections[3-6]. It is very common, being the third most common principal diagnosis within Australian emergency departments in 2017-2018, leading to 128,129 emergency presentations, of which over half required hospital admission[7,8]. These large figures likely only account for a small proportion of cellulitis cases within Australia, with research in the Netherlands showing only 7% of patients with cellulitis require hospital admission[9]. A challenge of cellulitis management is its recurrent nature, with up to 47% of patients experiencing one or more recurrent episodes within three years[10].

Chronic oedema, which is swelling persisting for three or more months[11], is a primary risk factor for cellulitis and cellulitis recurrence[5,6,10,12]. The relationship between cellulitis and chronic oedema is cyclical[10,13], with oedema increasing the risk of infection, and cellulitis infections damaging lymphatic vasculature and subsequently producing or increasing residual oedema and hence the risk of future infections[10,13,14]. Chronic oedema is also very common; however, it is considered to be a hidden epidemic as it is poorly recognised and diagnosed by the medical community[15]. Unfortunately, the prevalence of chronic oedema, and subsequently cellulitis, is likely to increase as our population becomes older and more obese[16-19].

Management of local factors predisposing to cellulitis, such as chronic oedema, has long been recommended to prevent cellulitis recurrence[20,21], however, there are no randomised trials to support this advice[22]. To date, the only intervention to prevent recurrent cellulitis that has been investigated using randomised trials is prophylactic antibiotics[22]. Although prophylactic antibiotics are effective[22], their use can be problematic: their benefit diminishes once treatment is ceased[23]; they do not specifically target the underlying pathogen, which is usually unknown[2,24]; they can cause adverse side effects such as nausea and diarrhoea[22]; and they have been found to be less effective in patients with oedema, obesity (body mass index ≥33), and a history of three or more cellulitis

episodes[23]. Research into the best non-antibiotic prophylactic interventions for cellulitis should be a high priority[25], as identified by a cellulitis research priority-setting partnership undertaken by health professionals and patients in the United Kingdom[25]. With the known cyclical relationship[10,13] between cellulitis and chronic oedema and the likely increase in chronic oedema prevalence resulting from changes in the population demographics[16-19], research into the efficacy and costs of chronic oedema management to prevent cellulitis is warranted.

The aim of this project is to determine if chronic oedema management is effective in preventing lower limb recurrent cellulitis episodes in adults with chronic oedema, and to explore and compare the costs related to cellulitis and oedema management from both patient and healthcare perspectives. To ensure this research was achievable within limited public health resources, the scope of this research was narrowed to only investigate the impact of oedema management on cellulitis of the lower limb and only within patients at a higher risk of cellulitis recurrence. This research expands the body of knowledge on best practice for the management of cellulitis and provides insight into the cost-effectiveness of preventing cellulitis recurrence through oedema management.

Due to the scarcity of research in this area, a review of the literature gleaned so few trials related to preventing cellulitis through risk factor management that a systematic review was not feasible. Further, at the start of this project, a formal Cochrane Review specifically addressing "*the beneficial and adverse effects of antibiotic prophylaxis or other prophylactic interventions for the prevention of recurrent episodes of cellulitis in adults aged over 16*" was near completion and published in 2017[22]. Of note, this review did not identify any publications related to non-antibiotic interventions[22]. Therefore, the first chapter of this thesis is a narrative review which gives a detailed description of the current knowledge and literature relating to recurrent cellulitis, chronic oedema, and the relationship between the two. Specifically, the review will describe cellulitis and chronic oedema and provide detail on their prevalence, risk factors, impact on quality of life (QOL), associated financial burden, and current treatment recommendations. Lastly, the review will specify and provide justification for the research questions and provide an outline of the thesis.

Recurrent Cellulitis

Overview of cellulitis

Cellulitis is a common acute bacterial infection of the dermis and subcutaneous tissue that tends to recur [2,24,26]. The infection will often arise from a fissure or break in the skin, such as a wound, ulcer, insect bite, or dermatosis[2]. As laboratory tests are non-specific for cellulitis, diagnosis is mainly based on clinical features and patient history[24]. Clinical features include poorly demarcated and spreading erythema, heat, oedema and tenderness local to the involved area[2,24], with possible accompanying fever and malaise[2,27,28]. Other possible clinical signs include inflamed lymphatics (lymphangitis) proximal to the infection, lymphadenopathy, bullae formation, and swollen and dilated skin lymphatics giving a peau d'orange appearance of the skin[24]. Erysipelas is an infection of the superficial dermis and lymphatics which presents with well demarcated erythema[24], and is at times considered a type of cellulitis[2,24]. As cellulitis and erysipelas have similar presentations, aetiology and treatment approaches[24], most clinical research does not differentiate between them, and for the purpose of this thesis, they will be considered as one entity. Cultures of needle or biopsy aspirate often do not detect the underlying pathogen and are not routinely indicated[2,24]. The most commonly detected microorganisms are gram-positive, including staphylococcus aureus and group A or B streptococci, and as such, beta-lactam antibiotics which target these are usually recommended[2].

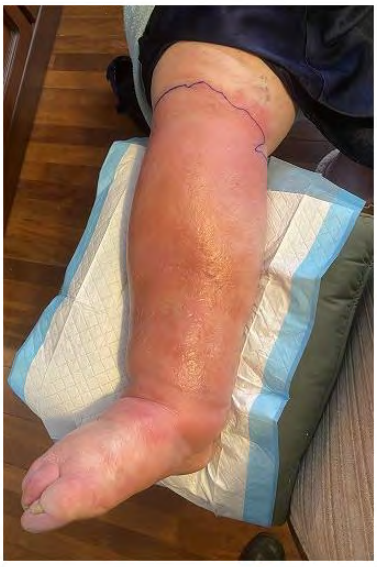


Figure 1: Cellulitis of the Lower Limb

Cellulitis can occur on any area of skin but most commonly occurs in the leg and is almost always unilateral[29]. The leg is the location of cellulitis in 68-84% of cases[3-6], with the head or face (9-10%), upper limb (6-14%) and trunk (1.4-8%) being other common sites[4,6]. Although cellulitis is often mild, it can be life-threatening and may require hospital admission for management. The reported mortality rate of hospitalised patients ranges 1-2.5%[29,30]. Serious complications of cellulitis include bacteraemia, sepsis and rarely necrotising fasciitis[10], while other common consequences include recurrent infections, chronic oedema and skin ulceration[10].

Cellulitis has been labelled as 'a disease with no home'[26], as it is managed by a range of clinicians across a variety of settings, including both hospital and community settings. Clinicians managing cellulitis include dermatologists, general practitioners, and general medical, infectious disease, emergency department and vascular physicians. With such a broad range of practitioners managing cellulitis, consistent diagnosis and management is challenging. Diagnosis of cellulitis can be difficult, with many other conditions presenting with similar characteristics. Two studies have found cellulitis to be misdiagnosed in 31% of cases[31,32] with common mimics being deep vein thrombosis, congestive heart failure, gout, and inflammatory dermatoses of the lower limb, such as lipodermatosclerosis, eczema, contact dermatitis and acute venous stasis dermatitis[31,32]. Many cellulitis mimics present bilaterally in the legs, whereas cellulitis is almost always unilateral, and therefore a diagnosis of bilateral leg cellulitis should raise alarm bells for misdiagnosis. Despite the complexities surrounding cellulitis diagnosis, accurate diagnosis is critical to ensure patients receive appropriate treatment, particularly given the high prevalence of this often debilitating infection.

Prevalence of cellulitis

In Australia in 2017-2018, cellulitis accounted for 128,129 emergency department presentations[7], 72,150 hospital admissions[8], and consequently 275,653 bed days[33]. This made cellulitis the 3rd most common principal diagnosis for emergency department presentations and the 4th most common principal diagnosis that required subsequent hospital admission[7]. Further, hospital rates for cellulitis are rising. From 2014-2015 to 2017-2018, hospital admissions for cellulitis increased by 9% nationally, and by 18% for Aboriginal and Torres Strait Islander people[33].

Cellulitis infections recur in a high proportion of patients, with 22-49% of hospitalised patients reporting a prior episode[5,10,12]. Within a three year time frame, cellulitis has been found to recur one or more times in 29-47%[4,10,34] of patients and two or more times in 13% of patients[34]. Unfortunately, compared to initial infections, recurrent cellulitis infections require longer hospital admissions and are more severe with an increased inflammatory response[5,35].

Within Australia, cellulitis was the 4th most common cause of potentially preventable hospitalisations in 2017-2018, behind only chronic obstructive pulmonary disease, urinary tract infections, and dental conditions[36]. The term 'potentially preventable hospitalisations' refers to admissions which may have been prevented through the "*provision of appropriate preventative health interventions and early disease management in primary care and community-based care settings (including by general practitioners, medical specialists, dentists, nurses and allied health professionals)*"[37]. Thus, these admissions reflect the accessibility and effectiveness of primary health, and are influenced by sociodemographic and lifestyle factors[33,38]. From this perspective, early signs of cellulitis, and factors predisposing to cellulitis, such as wounds, oedema and fungal infections, need to be better recognised and managed to avoid preventable hospitalisations.

Within Australia, rates of cellulitis vary considerably based on age, location and sociodemographic status. The annual rate for cellulitis hospitalisations is up to 15.5 times greater in the area with the highest rate (1,393 per 100,000) compared to the lowest rate (90 per 100,000)[33]. Hospital admissions for cellulitis are more common in remote areas and generally increase with socioeconomic disadvantage[33]. In 2017-18, the rate of hospitalisation for cellulitis was three times higher for Aboriginal and Torres Strait Islander people (727 per 100,000) than for other Australians (242 per 100,000)[33]. Older people also have a higher risk of hospitalisation for cellulitis, with those over 65 years being three times more likely to be admitted compared with younger adults[33]. As such, addressing the social determinants of health and improving primary health care access is pertinent to reducing cellulitis infections in Australia[33]. Other strategies suggested to address the high rate of potentially preventable hospitalisations for cellulitis include improved management of diabetes, a risk factor for cellulitis, and improved access to podiatry and lymphoedema services [33].

While we know the rates of cellulitis-related hospital admissions in Australia, there is very little data nationally and internationally on the prevalence of cellulitis managed by primary health care. An audit of 28,000 patients with cellulitis in the Netherlands found only 7% required hospital admission[9], and similarly, an audit from insurance data in the United States found that of 7438

infections, 6% required in-patient care, 21% were managed in an acute setting (emergency department, acute outpatient service), and 74% were seen in outpatient healthcare settings[9,39]. Given that over 72,000 patients with cellulitis are managed in Australian hospitals annually[8], and this number likely only accounts for approximately 7% of all cases[9], there may be over 1 million cellulitis cases diagnosed annually in Australia.

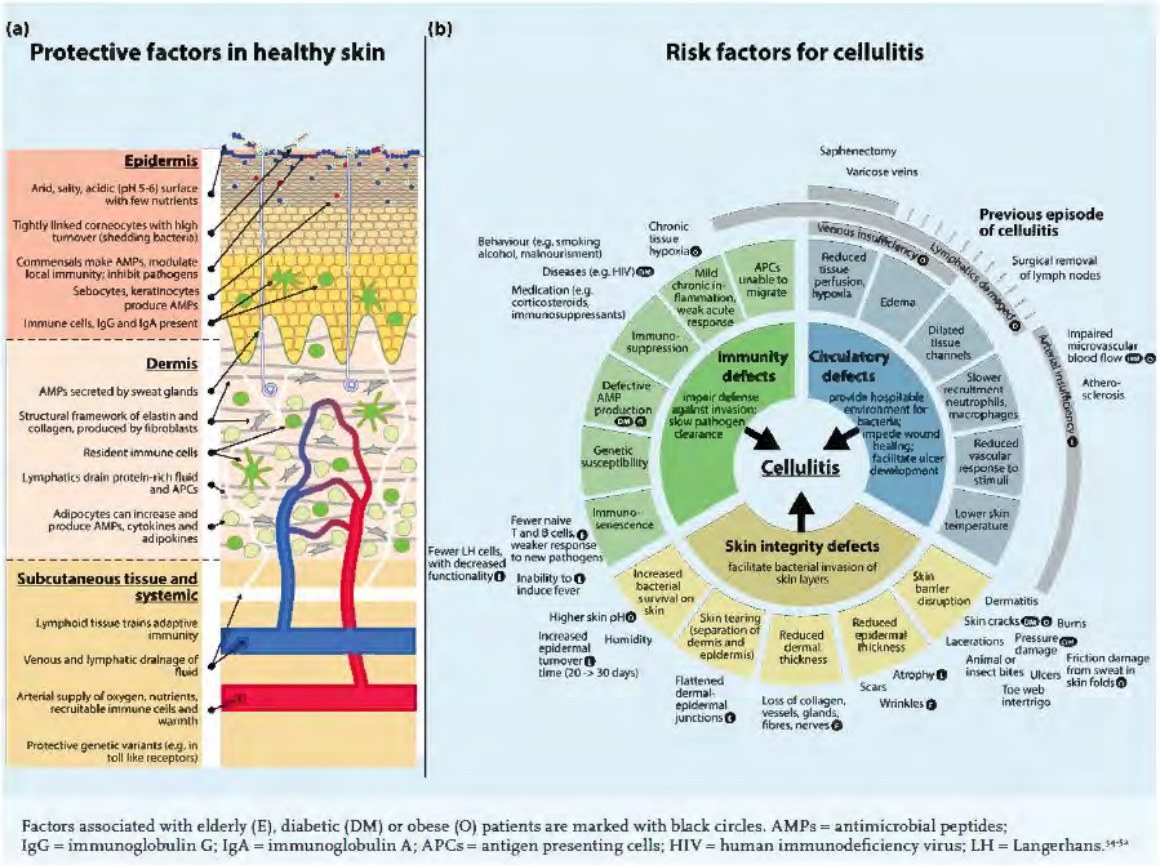
Risk factors for cellulitis

Conditions which impair skin integrity, vasculature or immune function can predispose individuals to cellulitis[40] (see Figure 2). The skin provides a physical barrier which prevents the invasion of pathogens, while the immune system defends against and clears pathogens, and intact vasculature is required to maintain skin integrity and support the immune system by maintaining homeostasis and transporting nutrients and immune cells[40]. Thus, risk factors for cellulitis involve a deficiency in one or more of these areas.

The main systemic risk factor for cellulitis is obesity[5,12,41], although age is also thought be a predisposing factor[40] due to its impacts on vasculature, skin integrity and immune function. Local risk factors include oedema (lymphoedema or chronic oedema)[5,12,41], previous cellulitis[14,41], venous insufficiency[12], toe-web infection (e.g. tinea)[12,41], and skin barrier disruption (e.g. dermatitis, wounds, ulcers, trauma)[5,6,12,41]. The risk factors for cellulitis recurrence are similar, being lymphoedema[4,6,10], previous cellulitis[14,41], venous insufficiency[4,6], obesity[4,6], a history of malignancy[6] and a previous operation[4,6] or trauma[4]. Chronic oedema is the most prominent risk factor for cellulitis recurrence[6,40], with 60-66%[10,23] of patients with recurrent cellulitis having oedema.

Seasonal variability also impacts cellulitis risk[40]. In cold countries such as Norway, cellulitis is more likely to occur in winter[42], whereas in warmer regions such as Australia, cellulitis is more common in summer. In contrast, in tropical areas where there is less variability in temperature, cellulitis incidence remains stable across the year[43]. The increased incidence of cellulitis measured over winter in colder counties is proposed to be due to increased indoor time and crowding, which subsequently increases exposure to certain bacteria[43]. Whereas, in warmer counties, the increased incidence of cellulitis in summer is thought to be due to heat exacerbating some cellulitis risk factors such as tinea and venous insufficiency and greater outdoor activity with open footwear increasing the risk of cuts and breaks of the skin[43].

With changes in the Australian population demographic, cellulitis may be a growing issue. The population is getting older[16] and more obese[17], and as such chronic oedema and venous insufficiency and their sequelae (e.g. venous ulcers and eczema) will also increase. Therefore, it is reasonable to expect that as the risk factors for cellulitis become more common, cellulitis infections may also become more prevalent.



Factors associated with elderly (E), diabetic (DM) or obese (O) patients are marked with black circles. AMPs = antimicrobial peptides; IgG = immunoglobulin G; IgA = immunoglobulin A; APCs = antigen presenting cells; HIV = human immunodeficiency virus; LH = Langerhans.[34-54]

Figure 2: An aetiological approach to factors protecting against (a) or predisposing for (b) cellulitis[40]

Impact of cellulitis on quality of life

Evidence relating to the impact of cellulitis infections on QOL is scarce. A multi-centre randomised controlled trial (RCT), assessing the impact of prophylactic antibiotics (penicillin) on cellulitis recurrence, conducted a within-trial cost-effectiveness analysis for which two QOL measures were used, being the EuroQol EQ-5D-3L and the Dermatitis Life Quality Index[44]. For this trial, the impact of cellulitis on QOL was a secondary outcome, with change in QOL being measured over 10 days of infection resolution[44]. Participants completed the two QOL outcome measures during a screening appointment and again 10 days later, with the aim to capture participants during, and after resolution of an infection[44]. However, as the infection had already resolved for the majority of participants prior to their screening appointment, the change in QOL due to cellulitis was only able to be measured for 71 of the 200 participants who had active infection upon completing the initial QOL assessment[44]. The group with active infection displayed a statistically and clinically significant improvement in QOL over 10 days, with the EQ-5D finding a 26.3% improvement and the Dermatitis Life Quality Index measuring an improvement of almost 10 points out of a total of 30[44]. Unfortunately, the pre-determined 10-day time frame for the QOL assessment likely meant participants were at various stages of the infection and/or recovery at the specified assessment times. Further, as cellulitis can cause long term morbidity, particularly acutely after the infection, it is likely many patients were still recovering from their infection during the follow-up QOL assessment.

No other studies have directly measured the impact of cellulitis on QOL, nor have they assessed whether interventions preventing or treating cellulitis have affected QOL[22,45]. However, in 2007 Carter et al. completed semi-structured group and individual interviews to qualitatively assess 24 patients' views on their cellulitis management within the hospital setting[46]. Some themes that emerged from this paper included: pain is a cause of distress and almost universal across patients with cellulitis; flu-like symptoms delay recognition; health information and communication are inadequate at times; outpatient care is desirable with adequate support; and more education is required regarding the cause of the infection and how to prevent future infections[46]. Although this study did not provide a quantitative measure of the impact of cellulitis on QOL, the interviews provided insight into patient priorities and what leads to satisfaction or dissatisfaction with their care.

There is a need for further research on the impact of cellulitis on QOL. The only two studies that shed light on this topic were based in a hospital setting in either the United Kingdom or Ireland. Further research should include patients managed in different settings, assess patients over a longer timeframe, and include baseline (pre-infection) QOL measures if possible.

Financial burden of cellulitis on patients and healthcare services

Cellulitis causes considerable financial burden for both health services and patients. Australia's Independent Pricing Authority data shows that in the 2017-2018 financial year, there were 19,912 hospital admissions for cellulitis of major complexity (Australian refined-diagnosis related group (AR-DRG) J64A) costing an average of $7,799 per episode; and 52,238 hospital admissions for cellulitis of minor complexity (AR-DGR J64B) costing an average of $3,292 per episode[8]. Additionally, that year there were 128,129 presentations to the emergency department for cellulitis[7], which cost an average of $705 per presentation[47]. Based on these figures, in 2017 to 2018, cellulitis related emergency department presentations and hospital admissions cost the Australian health system approximately $90 million and $327 million AUD, respectively. A retrospective cohort study conducted in Australia in 2012-2013 compared the cost of patients managed in an inpatient versus home based setting (Hospital in the Home) and found that average admissions costs were in fact higher for Hospital in the Home patients ($5873 versus $5196 per admission) due to their longer length of stay (mean of 7.5 versus 5.8 days)[48]. Other factors associated with an increased length of stay (LOS), such as chronic oedema[49] and admission for recurrent cellulitis infections[35] may also increase admission costs.

As research on cellulitis-related costs has predominantly focused on hospitalised patients from a healthcare perspective, there is very little information on healthcare costs for community-managed cellulitis or the personal expense to patients suffering cellulitis. To estimate the cost of cellulitis in the community, not only do we need to know the associated costs, but we also need to know the incidence of infections. As discussed above in 'prevalence of cellulitis', an audit of 28,000 patients in the Netherlands found that although only 7% of patients treated for cellulitis required hospital admission, they accounted for 83% of healthcare expenditure related to cellulitis[9]. Based on this, we would expect the majority of cellulitis cases in Australia are managed in the community and account for a small proportion of the total healthcare expenditure on cellulitis, however, further research within Australia is required to make accurate estimates. Further, research and data relating to

patient costs for cellulitis management appears to be non-existent. As patients with cellulitis require medical management, antibiotics, and often pain relief, time off work and assistance with activities of daily living (ADLs), it is reasonable to assume there are also substantial personal costs for patients. This deserves further exploration as it should inform healthcare budget priorities at local and national levels.

Chronic Oedema

As described above, chronic oedema is the most prominent risk factor for cellulitis recurrence[6,40]. Due to the cyclical relationship between chronic oedema and cellulitis, it is valuable to provide a detailed description of chronic oedema.

Overview of chronic oedema

Oedema occurs when there is an imbalance between capillary filtration and lymphatic drainage. Previously, our concept of interstitial fluid formation was guided by Starling's law, which proposed that the net fluid flow in and out of capillaries was determined by the total difference in opposing pressures across the capillary wall[50,51]. According to this theory, there is filtration of fluid out of the arterial end of the capillary, with reabsorption occurring at the venular end and only a small portion of fluid (approximately 10%) being drained by the lymphatic vessels[50-52]. However, we have since learned that in peripheral tissues, there is an outflow of fluid from the capillaries with no reabsorption, and the lymphatic vessels drain the excess interstitial fluid, thus playing a pivotal role in maintaining interstitial volume homeostasis[51].

The National Lymphoedema Partnership defines chronic oedema as "*a term used to describe a group of conditions characterised by the presence of swelling within tissues of the body, caused by the accumulation of excess fluid within the interstitial space of the affected area. Oedema most commonly affects the lower or upper limbs but may also affect midline structures such as the head and neck, trunk, breasts or genitalia"*[53]. The NLP outlines that while 'chronic' usually refers to oedema persisting for more than three months to differentiate from acute causes of oedema, the term should not be used restrictively as clinically it may be possible to identify early on when acute swelling is likely to persist and require long term management[53]. The term itself does not specify the underlying cause(s) of the oedema[50].

Chronic oedema is a relatively new public health definition that was developed to define a population, thus allowing research and advocacy for a neglected global healthcare issue[50]. The terms lymphoedema and chronic oedema are often used interchangeably; however, historically, lymphoedema has been used to define chronic swelling which has arisen from either a primary fault in lymphatic development or from damage to the lymphatic vessels, which impaired lymphatic flow[50]. Unfortunately, this definition fails to accommodate for swelling resulting from other

conditions such as venous hypertension, obesity, immobility and heart disease. With recent advances in our knowledge of microvascular fluid exchange, we know that the lymphatic system is always implicated in oedema, whether it is due to increased capillary filtration overwhelming lymphatic drainage, reduced lymphatic drainage, or a combination of both[50,52]. Therefore, chronic oedema has been proposed as an umbrella term for persistent swelling, regardless of the underlying aetiology.

Chronic oedema is a clinical diagnosis based on physical examination and medical history[54], and determining the underlying cause(s) is important to guide management[55]. Chronic oedema results for a range of conditions, and many patients with chronic oedema have multiple factors contributing to their oedema. Cancer has long been thought to be the most common cause of chronic oedema, however, a cross-sectional study found cancer was only implicated in 3% of cases[56]. Common causes of chronic oedema include venous disease[57], obesity[18,19], heart failure[18,19], and reduced mobility[18,58]. Unfortunately, patients with non-cancer related oedema are at high risk of delayed diagnosis and misdiagnosis[59], and often have limited access to oedema management due to discriminatory variances in service access criteria and availability[60,61], predisposing them to long-term health sequelae[59].

Prevalence of chronic oedema

Information on the prevalence of chronic oedema in the broader population is lacking. As chronic oedema has no specific diagnostic codes (e.g. International Classification of Diseases (ICD-10) or Australian Refined Diagnosis Related Groups (AR-*DRGs*)), and is poorly recognised and underdiagnosed by healthcare professions[56], accurate data collection for research is difficult. In the past 5 years, a large international prevalence study 'LIMPRINT' (Lymphoedema IMpact and PRevalence –INTernational Lympoedema Framework) has vastly improved our knowledge on the topic; however, much of their data are drawn from healthcare settings and specific populations (e.g. chronic wound services and hospitals) in which chronic oedema is more prevalent, reducing the generalisability of the results to the general population.

In 2019, LIMPRINT published data on the prevalence of chronic oedema from 222 patients across four different settings within Australia[62]. The first setting included three residential care facilities, of which 54% (20/37 participants) had oedema, and the second setting was a community-delivered aged care service in which 24% (4/17) of participants had oedema[62]. Setting three was an acute care

hospital, in which 27% of inpatients (31/113) had oedema, and the last setting was a wound treatment centre for which 100% (55/55) of patients had oedema[62]. The oedema was not related to cancer in 95% of participants with swelling, and the leg was the most common site of oedema, with only 6% (2/31) of acute hospital patients having swelling located elsewhere[62]. Although this data provides useful information for specific populations, the small sample sizes and the specific study population mean the results give little insight into the prevalence of chronic oedema in the broader Australian population.

Between 2000 and 2012, two studies in the UK studied the prevalence of chronic oedema in the broader community[11,56]. Health professionals prospectively identified patients with chronic oedema across multiple sites in a catchment area to measure prevalence[11,56]. Sites included community and acute hospitals, general practices, outpatient and community nursing services and residential homes, giving a broad patient sample[11,56]. In the first study in 2000, Chronic oedema prevalence was 1.33 per 1000, increasing to 5.4 per 1000 for those over 65 years[11]. Of those with chronic oedema, 36% had not received treatment for it, and one-third had not been informed of their diagnosis[11,63]. In the second study in 2012, chronic oedema prevalence was higher, being 3.93 per 1000, increasing to 28.75 per 1000 for those aged 85 or more[56]. Prevalence was higher in women (5.37 per 1000 versus 2.48 per 1000), and of those with chronic oedema, it was located in the leg in 84% of patients and only related to a cancer diagnosis in 3%[56]. The higher prevalence found in 2012 may reflect increasing prevalence, but also might be due to better recognition and identification of chronic oedema[56]. Poor understanding and knowledge of chronic oedema results in frequent underdiagnosis[15] and patients are often not referred on for treatment. Thus, these figures are likely to underestimate the true prevalence of chronic oedema. Based on these conservative figures and the Australian population, the prevalence of chronic oedema in Australia in 2022 is likely between 34,580 and 102,180.

Risk factors for chronic oedema

Chronic oedema arises when capillary filtration exceeds lymphatic return. Therefore, any condition which increases capillary filtration or impairs lymphatic return can increase the risk of lymphoedema. Lymphatic impairment may be from a congenital lymphatic abnormality or from damage to the lymphatics post birth.

Lymphatic filariasis, which damages lymphatic vessels, is the most common cause of lymphoedema, with the World Health Organisation estimating there are over 15 million people with lymphoedema and a further 25 million men with hydrocele related to the parasitic disease[64]. Cancer and cancer treatment are known causes of chronic oedema, although the level of risk varies depending on disease and treatment-related factors. Factors that impact the risk of cancer-related chronic oedema risk include more extensive surgery (i.e. the number of lymph nodes removed)[65,66], radiation to regional lymph nodes[65-67], development of post-operative seroma[66], chemotherapy[66], the number of metastatic lymph nodes[66] and obesity[66,67].

There are several other conditions that increase the risk of developing chronic oedema, and many patients will have multiple factors contributing to their oedema[50,63]. Venous disease[57], obesity[18,19], heart failure[18,19], reduced mobility[18,58], ethnicity[19] (Caucasian), renal failure[68,69], medication side effects[70], hypoproteinaemia[68,69], surgery or trauma[68], cellulitis[10] and older age[18,19] all increase risk of developing chronic oedema. With the forecast growth of our aging[71] and obese populations[72] and the associated comorbidities, chronic oedema is likely to be an increasingly common problem.

Impact of chronic oedema on quality of life

Research on the impact of chronic oedema on QOL predominantly focuses on female patients with upper limb and cancer-related lymphoedema[73,74], with a lack of research relating to the lower limb and the broader concept of chronic oedema[75]. A systematic review assessing the psychosocial impacts of lymphoedema included 23 studies published between 2004-2011; of these, only 4 included participants with lower limb oedema, and 19 focussed on breast-cancer related lymphoedema[73]. Therefore, most QOL research is not generalisable to patients with non-cancer related chronic oedema or chronic oedema in other areas of the body, such as the lower limbs. This is surprising when we consider that as little as 3% of chronic oedema is related to cancer[56].

In more recent years, a few studies investigating the impact of chronic oedema on QOL have included participants with chronic oedema affecting differing body parts and arising from various aetiologies[75-77]. However, in all of these studies, cancer was still the most common cause of chronic oedema among the participants [76,77]. This is likely because the study samples were drawn from lymphoedema services and networks[75-77], which have established and well known referral pathways for cancer patients[62], while the diagnosis and referral for patients with non-cancer related chronic oedema is often delayed or missed. These studies showed that chronic oedema negatively affects

QOL, with significant effects on psychological, physical and social functioning[76,77]. A large, international, multi-centre study prospectively assessed health related quality of life (HRQoL) in 1094 adults with chronic oedema using a disease specific (LYMQOL) and generic (EuroQol Five Dimension Scale (EQ-5D)) tool. In this study, the mean self-reported health of participants measured using the EQ-5D visual analogue scale ranked below the 25th percentile for the general public in almost all available countries[76]. Poorer QOL scores were associated with being older, obese and female, and having lower function and mood, as defined by the LYMQOL QOL assessment[76]. A cross-sectional multi-centre study in Sweden also assessed HRQoL 129 adults with chronic oedema using a condition specific (Lymphoedema Quality of Life Inventory) and generic (SF-36) tool. They found patients with chronic oedema have significantly lower general health, social functioning and vitality compared to the general Swedish population[77]. In both of these studies, patients with lower limb chronic oedema reported their condition had a greater impact on HRQoL compared to those with upper limb chronic oedema[76,77]. Another quantitative descriptive study in Ireland assessed QOL in 122 adults with lower limb chronic oedema using a condition specific (LYMQOL) tool. They found adults with lower limb chronic oedema suffered physical problems, including pain, weakness and heaviness, and had difficulties with activities such as bending and walking. They experienced irritability, tension and anxiety, with 55% of participants reporting their oedema impacted their engagement in leisure activities and their social functioning[75]. Chronic oedema is clearly detrimental to QOL, however, further research into its impact on patients with lower limb and non-cancer related oedema is warranted.

Financial burden of chronic oedema on patients and health systems

There are substantial costs related to chronic oedema for individuals, health systems and our broader society. Costs arise from lost wages and productivity due to inability to work, care requirements, management of the condition itself (e.g. outpatient appointments, compression garments, bandages), and increased healthcare utilisation for sequelae such as cellulitis[63,75,78]. Resource use varies based on the stage of the chronic oedema[78], with more severe chronic oedema requiring more intensive treatment and also increasing the risk of complications such as immobility or infection[63,79].

There is very little research on the economic burden of chronic oedema. Two trials in the United Kingdom (England and Wales) have assessed the financial benefits of lymphoedema health services from a health perspective[63,78]. Both trials used pre-post methods, surveying or interviewing patients with chronic oedema on their health service utilisation during the 6-month period before and 6–12-month period after commencing care at a lymphoedema service[63,78]. The prospective cohort trial in England included 107 participants and found the cost per patient was £502 and £176 in the 6-month period before and 6-12 month period after attending the lymphoedema service, respectively[63]. The trial population and costs were well-defined, however the costs included were limited to key resources (bandaging, hosiery and inpatient/outpatient service utilisation)[63]. The trial in Wales included 50 participants across seven lymphoedema services and found the cost per patient was £4,859 and £2,217 (UK pounds) in the 6-month periods pre and post attending their service, respectively[78]. They also found that the cost per patient rose with increasing chronic oedema severity and complexity[78]. The Wales trial had a poorly defined population, with no demographic information provided, and although it appears they measured a broad range of resources (33 items), the specific resources and associated costs which were included are unclear[78]. Both trials indicate total health service utilisation for patients with chronic oedema reduces with appropriate management of the condition, however as the total costs calculated differ substantially (baseline cost £502 versus £4,859), it is difficult to draw many conclusions from these values. Further research with more detailed information regarding resource use and assessing costs from patient and societal perspectives is necessary to improve knowledge of the financial burden of chronic oedema.

The Relationship between Cellulitis and Chronic Oedema

The relationship between cellulitis and chronic oedema is a vicious cycle[10,13] (Figure 3), with chronic oedema being a strong risk factor for cellulitis[5,12,41] and cellulitis recurrence[6,10,80], and cellulitis increasing the risk of developing or exacerbating chronic oedema[10]. Compromised lymphatic drainage from chronic oedema not only leads to oedema but also impaired immune function[81], increasing susceptibility to infection, while cellulitis infections damage lymphatic vessels, impairing lymphatic drainage[82] and thereby increasing residual oedema and risk of future cellulitis infections[13]. Thus, worsening chronic oedema is not only a consequence of cellulitis but also increases the risk of recurrent infections.

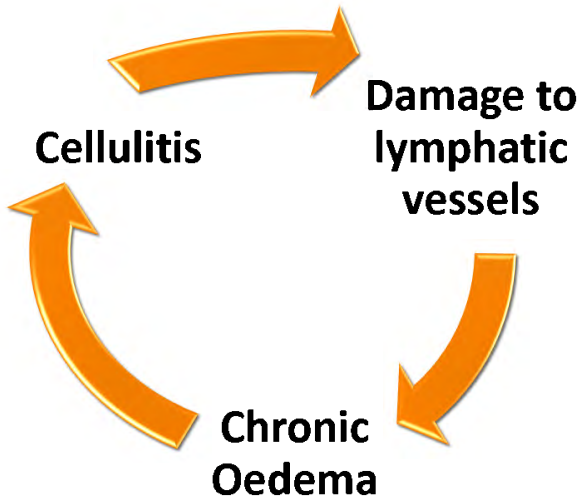


Figure 3: The cyclical relationship between chronic oedema and cellulitis

Data on the prevalence of cellulitis in patients with chronic oedema, and chronic oedema among cellulitis patients, is lacking. Two double-blind randomised controlled trials conducted across 28 sites in the UK and Ireland between 2006 and 2011 assessed the efficacy of low dose penicillin versus placebo for cellulitis prophylaxis. They found that 66% of patients with lower limb recurrent cellulitis (n=274) had concurrent oedema, while 58% of patients with an initial episode of lower limb cellulitis (n=97) or a recurrent episode but who had declined 12 months of antibiotic prophylaxis (n=27), also had oedema[23,83]. From another perspective, an international cross-sectional study that included 40 sites across nine countries between 2014-2017 found that of 7,477 patients with lower limb oedema, 16% had suffered a cellulitis infection in the past year, and 38% had experienced an episode during their lifetime[79]. Further, an epidemiological study in the UK, including 823

participants with chronic oedema, found that of 218 participants that were interviewed, 29% had experienced an acute infection in the affected area in the past year, with almost one third (n=17/64) requiring hospital admission for intravenous antibiotics[11]. Thus, both chronic oedema and cellulitis are common comorbid conditions.

Multiple studies have found that for patients with lower limb unilateral recurrent cellulitis, both their affected and unaffected leg often show evidence of impaired lymphatic drainage. Soo et al. conducted lymphoscintigraphy, a gold standard assessment method for detecting lymphatic abnormalities, on 15 patients four or more weeks after recovering from unilateral cellulitis[84]. They found that 87% of the participants had abnormal scans indicating impaired lymphatic drainage, with the abnormality being bilateral and thus involving the non-cellulitic limb for 53%[84]. Similar findings were also demonstrated by Damstra et al. who conducted lymphoscintigraphy in 40 patients with a history of one to three episodes of erysipelas in one leg (unilateral)[82]. Of the 40 participants, 83% (n=33) had impaired lymphatic drainage in their post-cellulitic limb, with 79% (n=26) of those also having impaired lymphatic drainage in their non-cellulitic limb[82]. This phenomenon suggests that abnormal lymph drainage likely often precedes cellulitis infections[82,84]. It also indicates that chronic oedema, including sub-clinical oedema, may predispose patients to cellulitis. Conversely, a retrospective observational study assessing risk factors, complications and treatment in 171 lower limb cellulitis patients found that of the 46% (n=77) of patients with oedema, it was worse in the post-cellulitic leg in 77% (n=69)[10]. Additionally, they found oedema was more common among patients who had experienced multiple versus single episodes of cellulitis (60% versus 32%)[10]. Although this doesn't indicate if the lymphatic impairment originated before or after the infection, it does imply that cellulitis caused or aggravated oedema[10]. Finding from these studies suggest that oedema often precedes and predisposes patients to cellulitis and that cellulitis infections cause or exacerbate oedema, thus supporting the concept of the vicious cycle. As such, identification and treatment of oedema among patients with cellulitis is likely to play an important role in preventing recurrence and worsening lymphatic function[82,84].

There are many theories as to why chronic oedema increases the risk of cellulitis and cellulitis recurrence. The lymphatic system plays a critical role in detecting and clearing pathogens[85]. However, in the presence of chronic inflammation, as occurs in chronic oedema, changes to the lymphatics can lead to an altered immune response[85]. A possible mechanism is that decreased lymphatic drainage and altered lymphatic function increase the risk of cellulitis through an impaired immune response to pathogens (due to poor trafficking of antigens and immune effector cells)[85,86].

Additionally, chronic oedema may predispose to cellulitis as it provides an excellent medium for bacterial growth[87,88], and can impair skin integrity[89], increasing susceptibility to entry of bacteria via the skin[87]. Therefore, managing chronic oedema may reduce cellulitis risk through improved immune response, reducing the medium for bacterial growth, improving the barrier function of the skin, and acting as a physical barrier to protect the skin.

For many years, it has been widely believed that chronic oedema management plays an important role in preventing initial and recurrent cellulitis infections[2,10,13,82,84,87,90], however, the evidence to support this theory is scarce. From 2006 to 2009, Arsenault et al. conducted a small prospective case-control (before-after) trial to assess the impact of oedema management, using complete decongestive therapy[1], on the cumulative incidence rate of hospitalisations for cellulitis[91]. They included patients with chronic oedema and a history of recurrent cellulitis requiring hospital admission. Although complete data were only gained for 10 of 21 participants, the results were promising. In the 24 months prior to enrolment, the participants had a cumulative incidence rate of 8.5 cellulitis episodes per year, but following the intervention, only one participant was hospitalised for cellulitis during the 18 month follow-up period, equating to an absolute risk reduction of 7.83[91]. However, the trial results were not significant and have substantial methodological and generalisability limitations due to the small sample size, pre-post trial design and the participant's high pre-intervention hospitalisation rate for cellulitis being non-representative of the target population. Another before-after trial of 299 patients, which assessed the impact of complete decongestive therapy on limb volume in patients with lymphoedema, incidentally found that the number of infections per patient per year reduced from 1.1 to 0.65[92] post intervention. Unfortunately, as the change in infection rate was not a research objective or specific to cellulitis infections, the findings must be interpreted with caution. Although both these trials are methodologically fraught, their findings support the theory that oedema management may prevent cellulitis and cellulitis recurrence.

[1] Complete decongestive therapy is described in paragraph one of 'Current treatment recommendations for chronic oedema'.

Current treatment recommendations for preventing recurrent cellulitis

The majority of guidelines addressing cellulitis management are specific to acute treatment and do not address preventing cellulitis recurrence. Within Australia, the Therapeutic Guidelines recommend addressing cellulitis prevention by managing common predisposing factors such as lymphoedema, lymphatic malformation, tinea and fissured dermatitis[21]. For patients with *"persistent risk factors for recurrent cellulitis*" they recommend antibiotic prophylaxis, being phenoxymethylpenicillin 500mg daily for 6 months before review[21]. The Australasian Lymphology Association's position statement on the 'Management of Cellulitis in Lymphoedema' recommends antibiotic prophylaxis is "*offered to lymphoedema patients who have two or more attacks of cellulitis in a 12 month period, despite diligent skin care and treating all contributing risk factors*"[20]. They recommend prescribing phenoxymethylpenicillin 500mg daily for the first year, and in those for whom prophylaxis is successful, reducing the dose to 250mg after 12 months and ceasing use after two years[20]. For patients who experience recurrence following two years of prophylactic antibiotics and skin care, antibiotic prophylaxis may need to be lifelong[20]. The Australasian Lymphology Association's position statement also recommends optimal management of local cellulitis risk factors including wounds, dermatitis, weeping lymphangiectasis, and interdigital scaling; and management of systemic risk factors such as obesity, diabetes and poor mobility[20]. Further, they note that oedema control is important[20].

In 2017, Cochrane published a systematic review on 'Interventions for the prevention of recurrent erysipelas and cellulitis'[22]. This review specifically assessed "*the beneficial and adverse effects of antibiotic prophylaxis or other prophylactic interventions for the prevention of recurrent episodes of cellulitis in adults aged over 16*"[22], negating the need for a systematic review on this topic as part of this thesis. The review included six trials, of which five assessed the impact of prophylactic antibiotics on recurrent cellulitis of the legs[22]. Across the six trials, there were 573 participants with an average age between 50-70 and an average of 1-4 prior episodes of cellulitis. The review found there was moderate-certainty evidence that antibiotic prophylaxis was effective in preventing cellulitis recurrence compared to no treatment or placebo, reducing the risk of cellulitis by 69% (risk ratio 0.31, 95% confidence interval (CI) 0.13 to 0.72; n = 513; P = 0.007), the incidence rate by 56% (risk ratio 0.44, 95% CI 0.22 to 0.89; four trials; n = 473; P value = 0.02) and the rate until next episode by 49% (hazard ratio 0.51, 95% CI 0.34 to 0.78; three trials; n = 437; P = 0.002)[22]. However, the protective effect of antibiotic prophylaxis diminished after treatment was stopped[22]. Common side effects of antibiotic therapy included nausea, rash, diarrhoea and thrush[22]. No trials assessed

the impact of other commonly recommended interventions to target cellulitis risk factors, such as skin care or chronic oedema management[22].

Of the trials included in the Cochrane review on interventions to prevent recurrent cellulitis, the largest was a multi-centre double-blind RCT that assessed the impact of 12 months of antibiotic (penicillin) prophylaxis in 274 participants with recurrent cellulitis[22,23]. The trial found antibiotics were effective in preventing cellulitis during active therapy (hazard ratio, 0.55; 95% CI, 0.35 to 0.86; P=0.01), however pre-existing oedema, a high body mass index (BMI) (≥33), and a history of three or more episodes of recurrent cellulitis were all significantly associated with antibiotic prophylaxis failure[23]. As antibiotic prophylaxis is only effective during active therapy[22,23]; many patients with recurrent cellulitis have one or more risk factors for antibiotic prophylaxis failure (BMI ≥33, pre-existing oedema or history of three of more cellulitis episodes)[23]; and there is little research into prophylactic interventions other than antibiotics; further research into other commonly recommended preventive interventions is warranted.

Current treatment recommendations for chronic oedema

To manage chronic oedema effectively, a combination of techniques are recommended[55,93]. The key elements of treatment include compression therapy, manual lymphatic drainage, exercise and skincare. Together, these treatment strategies are referred to as Complete Decongestive Therapy or Decongestive Lymphatic Therapy[55,93]. Education, psychosocial support and pain management are also considered to be important treatment components[55,93]. Management is often considered to have two stages, firstly a period of intensive treatment involving compression bandaging, manual lymphatic drainage, skin care and exercise to achieve oedema volume reduction, followed by a maintenance phase which aims to retain the reductions achieved through daily wear of compression garments, skin care, exercise and possibly self-manual lymphatic drainage [94]. The appropriate duration of the intensive treatment is not known, but treatment typically lasts between 1-4 weeks, with the greatest volume reductions occurring in the first week[93].

Management of chronic oedema is considered to be effective if there is an initial volume reduction with intensive treatment, and the maintenance phase controls symptoms, improves patient and carer engagement in self-management, and prevents an increase in oedema or deterioration in skin condition, tissue density or limb shape[55]. However, evidence supporting the efficacy of different components of complete decongestive therapy in the management of chronic oedema is deficient. A

Cochrane systematic review on 'Physical therapies for reducing and controlling lymphoedema of the limbs' concluded that to determine the best approach for lymphoedema management, further well-designed RCT's assessing various interventions needs to be completed[95]. Another limitation of complete decongestive therapy research is that it is predominately conducted on women with upper limb, unilateral, breast cancer related lymphoedema[95], with the results being extrapolated to the legs and various body parts.

The inclusion of manual lymphatic drainage in complete decongestive therapy is controversial as, despite it being a commonly recommended treatment technique, the evidence to support its use is lacking. Currently, there are no RCTs investigating the efficacy of manual lymphatic drainage specifically in lower limb chronic oedema, with the vast majority of research being conducted on women with unilateral, breast cancer related lymphoedema[96,97]. Further, many trials are limited by methodological issues such as lack of assessor blinding or concealed allocation, short follow-up duration, and small sample sizes[96-98]. Two recent multi-centre RCTs with blinded assessors investigated the benefit of manual lymphatic drainage in addition to complete decongestive therapy in patients with breast cancer related lymphoedema, with both finding manual lymphatic drainage to have no additional benefit[99,100]. A systematic review in 2013 that included ten trials also had the same conclusion[97]. A more recent (2021) systematic review on the topic found that 1 high-quality and three low-quality trials all reported that manual lymphatic drainage provided no additional benefit to complete decongestive therapy. However, one high-quality trial did find that the addition of manual lymphatic drainage to complete decongestive therapy was beneficial in patients with mild lymphoedema, but not for patients with moderate to severe lymphoedema[96]. Of note, the trials included in this systematic review reported trained therapists conducting between five to 54 sessions of manual lymphatic drainage, lasting between 15-80 minutes in length[96]. Considering the time and labour-intensive nature of this treatment and the evidence of its limited efficacy, it can be argued that manual lymphatic drainage should not be a primary treatment for chronic oedema, particularly in patients with moderate to severe chronic oedema.

Exercise and skin care are recommended as part of complete decongestive therapy throughout the intensive and maintenance phase. Poor skin integrity is common in patients with chronic oedema[55], as oedema can cause deep skin folds, skin thickening and reduced tissue compliance, all of which increase susceptibility to infection[55]. Additionally, many patients with chronic oedema have vascular disease which also causes poor skin integrity[57]. Maintaining good skin integrity to optimise the skin's barrier function to prevent infection is therefore considered a priority[55]. Research regarding the

effect of exercise on limb volume largely relates to patients with cancer and upper-limb breast cancer related lymphoedema[101]. In this population, exercise is safe, and a systematic review has concluded it may lead to a small reduction in limb volume[101]. Although the impact of exercise on the lymphatic system is unclear, the known benefits it has on the cardiovascular, cardiorespiratory and musculoskeletal systems, and its demonstrated benefit on QOL and symptom control (pain, fatigue), justify its inclusion in all chronic oedema treatment regimes[101].

Despite compression therapy being considered the cornerstone of treatment for chronic oedema, there is very little high-quality evidence to support its efficacy. Only one low-quality RCT published in 1995 has assessed the efficacy of compression garments[102]. The trial randomised 25 women with breast cancer related oedema to either wear a compression sleeve day and night, or to a control group[102]. Although the author concluded compression was beneficial[102], the small sample, high drop-out rate and lack of trial details mean the results must be interpreted with caution. Despite the paucity of high-quality research investigating the impact of compression, the potential benefit of compression has been indicated in many RCTs where compression therapy was provided as the baseline treatment to both groups, with an experimental treatment being provided to only one group[100,103-106]. In these studies, the significant improvement in oedema volume demonstrated in both trial groups with no inter-group differences[100,103-106] could be consistent with compression therapy being effective in reducing and controlling oedema. Similarly, oedema reduction and control has been demonstrated in patients with lower limb chronic oedema in pre-post trials[92]. However, none of these studies provide sufficient or robust evidence for the efficacy of compression therapy alone.

To date, only one RCT has assessed the additional benefit of compression bandaging prior to daily wear of compression garments in patients with lower limb oedema[95]. Badger et al. randomised 83 participants with lower or upper limb lymphoedema to receive either compression garments or 18 days of daily compression bandaging to reduce limb volume followed by compression garments[107]. After 24 weeks of follow-up, the participants who received the additional compression bandaging had approximately double the limb volume reduction (31% versus 15.8%) compared to those who received compression garments alone[107]. Two other RCTs assessing the added benefit of compression bandaging to standard care in patients with breast cancer related lymphoedema also reported similar findings[108,109]. More recently, a multi-centre, randomised prospective trial comparing the daily application of traditional multi-layer compression bandages to Coban-2[110] (a contemporary 2-layer cohesive compression bandage) applied two, three or five times per week

found that coban-2 applied twice weekly resulted in the greatest volume reduction[111]. In participants with lower limb chronic oedema, volume reduction was 18.7% for those who received Coban-2 applied twice weekly compared to 10.9% in participants who received daily application (5-days per week) of traditional bandages[111]. This evidence supports the use of compression bandaging in addition to compression garments to reduce limb volume, with the twice weekly application of a contemporary 2-layer bandaging systems achieving the greatest volume reduction, and likely also increasing the efficiency of treatment which reduces patient and healthcare costs and burden.

Based on the current evidence for oedema management techniques, it can be argued that a more contemporary and efficient treatment approach involves only compression therapy, skin care, exercise and education. As the labour-intensive nature of manual lymphatic drainage results in a time and cost burden to both the healthcare system and patients, it is difficult to justify without evidence of benefit, particularly in public healthcare setting where there is competition for limited resources. Based on the knowledge that compression therapy is likely the most efficient and effective treatment technique for chronic oedema, it has been chosen as the primary chronic oedema intervention to research in this body of work. The following section provides a detailed overview of compression therapy, its mechanisms of action, and barriers to its use.

Overview of Compression Therapy

Compression therapy is used for the long term management of chronic oedema and refers to both compression bandaging (Figure 4) and compression garments (Figure 5). Generally, compression bandages are applied regularly during the intensive phase of lymphoedema management to reduce oedema. Compression garments worn daily, or day and night, are used to control oedema and maintain reductions achieved during intensive treatment. Compression bandaging may not be required for patients who are starting to develop oedema, have mild chronic oedema or minimal reducible oedema (minimal pitting oedema and/or low bioimpedance ratios), and instead compression garments may be used as first line treatment. For patients with chronic oedema, continuous compression is required as oedema will recur if compression is ceased[93]. Compression garments are also used to prevent the development of oedema in certain patient groups who are at greater risk of developing chronic oedema[112,113].

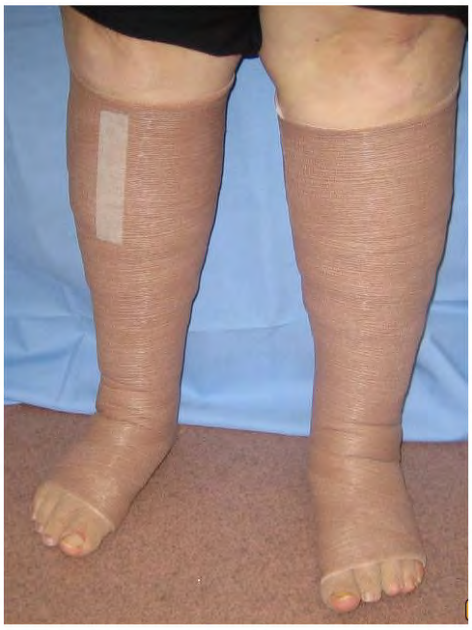


Figure 4: Compression bandaging for chronic oedema

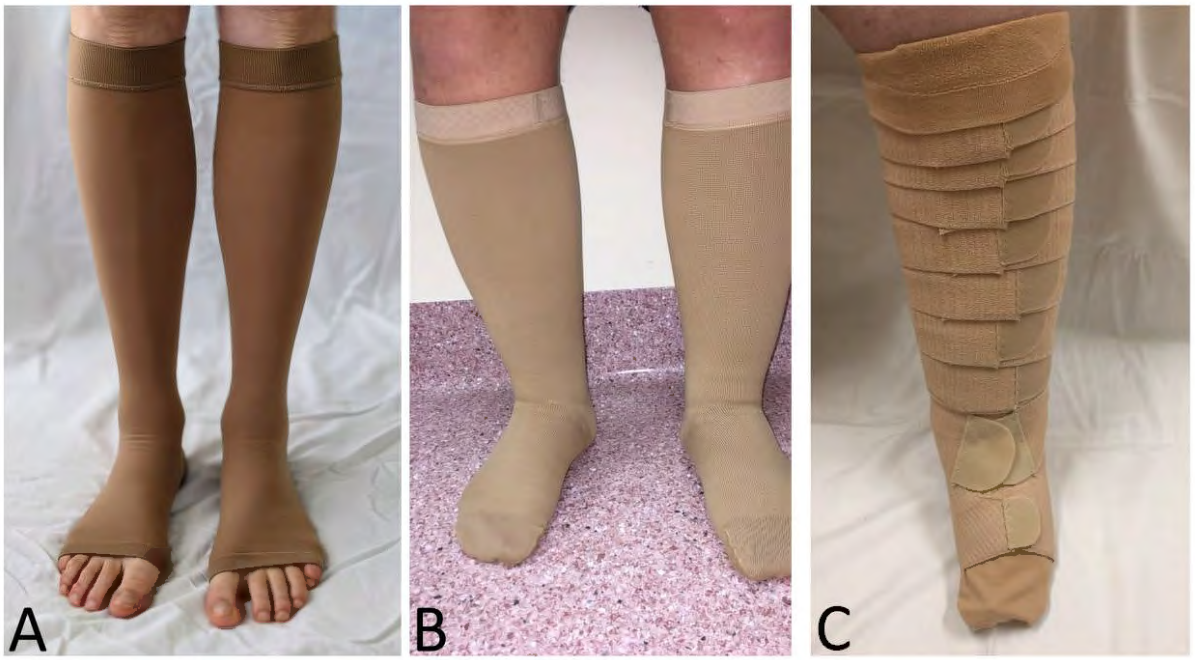


Figure 5: Image A shows round-knit compression stockings; Image B shows flat-knit compression stockings; Image C shows lower leg and foot compression wraps

Mechanism of compression therapy

Compression therapy acts by exerting external pressure on the limb or body part. This external pressure achieves several effects: it increases interstitial pressure, which reduces capillary filtration and lymph production; it increases reabsorption of lymph and stimulates lymphatic contractions; it promotes fluid to shift from compressed to uncompressed areas; and it enhances the efficiency of the venous muscle pump to improve venous return and reduce venous reflux[114-116].

The efficacy of compression therapy is dependent on the pressure applied to the limb, known as the sub-bandage pressure. Laplace's Law will predict sub-bandage pressure, with the pressure increasing with higher compression tension and smaller limb circumference[116]. Tension is influenced by the force with which the bandage is applied, but the ability of a bandage or garment to sustain the tension is governed by the elastomeric properties of the compressive material used[116]. Extensibility is the ability of a material to increase in length in response to applied force, and this impacts the amount of force developed at 'rest' or at 'work'[116]. Resting pressure is the constant sub-bandage pressure applied while the limb is at rest, whereas working pressure is a temporary increase in pressure generated inside the limb when muscles contract and expand, pressing against external resistance[55] (Figure 6). Materials with a higher working pressure are thought to be more effective in reducing oedema, while those with lower resting pressures are better tolerated by the wearer[93,114]. Thus, as materials with lower extensibility achieve both higher working pressures and lower resting pressures, they are preferred for oedema management due to their improved comfort and efficacy in reducing oedema[55,93,114,116].

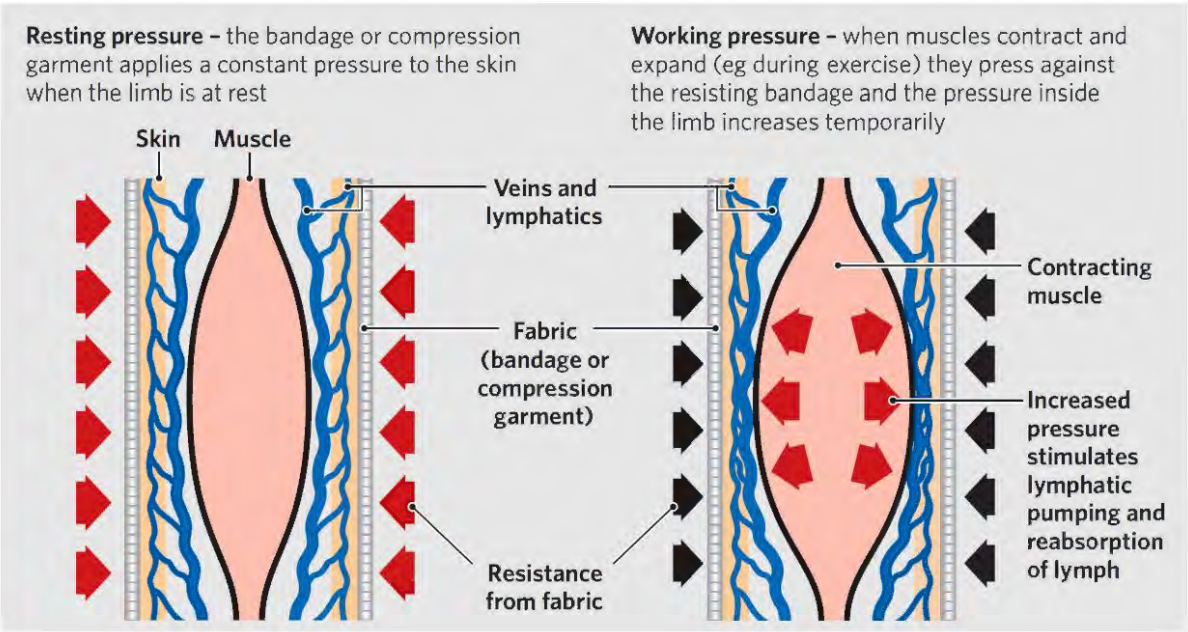


Figure 6: Resting and working pressures[55]

Compression Characteristics

A wide range of compression garments with various characteristics are available to meet patient needs. Appropriate prescription is essential for compression garments to achieve their purpose of controlling oedema and maintaining limb volume. Both patient and condition-specific factors heavily influence prescription. Patient factors include lifestyle, mobility, continence, co-morbidities, psychosocial status, cognition, comfort, preference, compression tolerance, access to assistance/carers, and ability to apply and remove garments[55,114]. Condition-specific factors include oedema severity, limb shape, skin integrity and presence of wounds[55,117].

The following characteristics are commonly used to categorise compression garments:

- Fabric Type:
    - Circular knit garments are made from fabric continuously knitted on a cylinder and therefore have no seam[55]. These garments are usually thinner and more cosmetically pleasing. However, they are less adaptable to fit distorted limb shapes and are more prone to cutting into a limb[55,114]. (See Figure 5: image A).
    - Flat knit garments are made from thicker material which is knitted as a flat fabric. The garment shape is created by adding or removing needles (to adjust fabric width), before stitching it together at the seam[55]. Flat knit garments are generally stiffer (lower extensibility) compared to circular knit garments, less likely to cut in, better able to bridge skin folds, and are better tolerated[55,114]. Custom made garments are more likely to be flat knit as the manufacturing process better accommodates limb shape distortion[55,114]. (See Figure 5: image B).
    - Compression wraps are made from fabric sheets with limited extensibility. The wrap is shaped to fit the limb and is secured in place by velcro fastenings. For the wearer, the velcro fastenings can increase ease of application and removal and allow adjustment of tension as required. Wraps can be more suitable for patients with poor skin integrity or wounds, as unlike compression stockings, there is no sheer force created from pulling the garment on and off a limb which can cause tissue damage. However, wraps are bulkier than other compression garments which makes them less aesthetically pleasing and can impact the fit of clothing and footwear. (See Figure 5: image C).
- Custom made or ready-to-wear:
    - Custom made garments are made specifically to the measures of the patient.
    - Ready-to-wear garments are pre-made according to a specified size range.

- Compression Class:
    - The compression class (CCL) of a compression garment refers to the amount of pressure (mmHg) it applies to the ankle at its smallest circumference[114]. There are four compression classes, however the pressure range used to define each class varies between different standards (e.g. the British and German standard)[114]. In Australia, the German standard is used most commonly, with CCL1 being 18-21mmHg, CCL2 being 23-32mmHg, CCL3 being 34-46mmHg and CCL4 being >49mmHg[114]. The CCL prescribed will vary depending on factors such as patient vascular status, oedema severity, compression tolerance, and ability to apply and remove garments.

Barriers to compression therapy

Compression therapy is the primary and long-term treatment modality for chronic oedema. However, there are many health service and patient factors that influence access to, and adherence with, compression therapy. Although the barriers to compression therapy in patients with chronic oedema are widely recognised, most research on the topic pertains specifically to patients with venous disease/ulcers and to a lesser extent patients with upper limb breast cancer related lymphoedema. For patients with venous disease, pain and discomfort, psychosocial issues, knowledge deficit, physical limitations, and financial issues are key themes for non-compliance with compression therapy[118]. Although venous ulcers generally cause more pain than chronic oedema, these barriers reflect those experienced by patients with chronic oedema.

The above key themes relating to poor patient adherence with compression therapy could be expanded upon at great length. Poorly fitting or incorrectly applied hosiery can cause discomfort and may worsen oedema or cause tissue damage[119]. Difficulty with garment application and removal, and lack of access to assistance or support services, can limit garment use[119]. Ease of garment application is often impacted by poor hand strength, dexterity, mobility (ability to reach feet) and cognition, while garment type and compression class also influence application difficulty[119]. Garment aesthetics and patient choice and involvement in prescription may impact motivation to wear hosiery[119], and understanding how and why compression therapy is beneficial may also influence treatment adherence[119]. Thus, oedema management and compression prescription by qualified, skilled lymphoedema practitioners is important to assist patients to overcome these challenges.

Access to appropriate health services, qualified practitioners and funding schemes are also major barriers to patients accessing compression therapy. Barriers to patient care include limited access to qualified clinicians; poor awareness of chronic oedema among the general public, health professionals and policy makers; inadequate service funding; and deficiency in state and federal level data collection (e.g. diagnosis related codes) and policy relating to chronic oedema [56,61,120,121]. As a consequence of these barriers, many patients will live with unmanaged chronic oedema and the related health sequelae.

Research Justification

Due to the known relationship between cellulitis and chronic oedema, the logical theory that treating cellulitis risk factors will reduce recurrence, and the anecdotal and low-quality research indicating oedema management prevents cellulitis[91,92], further research investigating the impact of oedema management on cellulitis recurrence is warranted. With cellulitis already being the 3rd most common reason to visit an emergency department[7], and the 4th most common reason for both hospital admissions[7] and for potentially preventable hospitalisations[36], and with recurrence of cellulitis occurring in up to 50% of patients within three years[10], finding effective preventative strategies should be a research priority. This is especially true with the current changes in the Australian population demographic meaning cellulitis risk factors and cellulitis incidence may be on the rise.

The need for research on the efficacy of compression therapy in the prevention of lower limb cellulitis was highlighted in 2017 by the results of a James Lind Alliance Priority Setting Partnership which set out to identify priority research areas relating to cellulitis diagnosis, treatment and prevention[25]. Determining the best non-antibiotic interventions for cellulitis prevention was found to be a research priority, being listed as the top priority in an online survey of health professionals and patients[25].

To enable successful high-quality research on this topic within limited public health service resources, the scope of this research was narrowed. Thus, the current research focuses primarily on preventing the recurrence of lower limb cellulitis in patients at high risk of further infections. Further, this research specifically investigates the effect of compression therapy rather than the multiple components of complete decongestive therapy. As cost is a major driver of change in the healthcare sector, determining the cost-effectiveness of compression therapy to prevent cellulitis was also deemed an important component of this project.

Outline of the Thesis

This thesis comprises three publications which together describe the research methods and outcomes of an RCT and concurrent cost analysis investigating the efficacy, cost and cost-savings of using compression therapy to prevent recurrent lower limb cellulitis in patients with chronic oedema.

Paper one is the research protocol for an RCT assessing the impact of compression therapy on cellulitis in adults with chronic oedema. The protocol details the planned method of recruitment, allocation, stratified randomisation, follow-up, interim analysis, and statistical analysis, as well as the interventions provided to the participants. The methods to measure the primary outcome of time to cellulitis recurrence, and the secondary outcomes of change in limb volume, QOL and rate of cellulitis-related hospital admissions, are also explained in detail.

Paper two is an RCT of the impact of compression therapy on cellulitis recurrence in adults with lower limb chronic oedema. This trial demonstrates the efficacy of compression therapy in preventing recurrent lower limb cellulitis, as well as its impact on cellulitis related hospital admissions, leg volume and QOL.

Paper three outlines the method and results of a cost analysis that was undertaken during the RCT (paper two). The cost analysis calculates and compares the cost of an episode of cellulitis, and the cost of compression therapy over 18 months, from both patient and health service perspectives. Further, the mean expenditure across the RCT experimental and control groups is calculated and compared to determine if the provision of compression therapy to prevent recurrent cellulitis is cost saving.

To conclude, the results of these studies will be discussed in context with current practice and the existing literature, and recommendations for future research will be made.

CHAPTER 2: Paper One

Impact of Compression Therapy on Cellulitis (ICTOC) in adults with chronic oedema: a randomised controlled trial protocol

This chapter has been peer reviewed and published as original research in the journal BMJ Open (Appendix E):

https://pubmed.ncbi.nlm.nih.gov/31420389/

Webb E, Neeman T, Gaida J, Bowden FJ, Mumford V, Bissett B. Impact of Compression Therapy on Cellulitis (ICTOC) in adults with chronic oedema: a randomised controlled trial protocol. BMJ Open. 2019;9(8): e029225

BACKGROUND AND RATIONALE

Cellulitis is a common acute bacterial infection of the skin and subcutaneous tissue[2]. The majority of cellulitis episodes (69-81%) occur in the lower limbs[4,6,122]. In Australia lower limb cellulitis is associated with significant health costs due to frequent hospital admissions and high levels of morbidity. In 2014-2015 there were 59,466 hospitalisations for cellulitis[123], with the average admission lasting 4.3 days[124]. In 2013-2014 cellulitis was the third leading cause of potentially preventable hospital admissions, with over half of all admissions for cellulitis being considered potentially preventable[124,125]. Erysipelas is an infection similar to cellulitis, which typically affects more superficial tissues. As the terms erysipelas and cellulitis are often used interchangeably and most clinical studies do not differentiate between them, this paper will consider them as one entity.

Recurrence of cellulitis is common and represents a significant proportion of the disease burden. In a 3 year time frame cellulitis has been reported to recur in 29-47% of patients[10,34], with a case series in Sweden finding that 13% of patients admitted for cellulitis developed two or more recurrences within 3 years[34]. In light of the significant recurrence rates, effective interventions which reduce recurrence could limit the disease burden and improve patient outcomes.

Oedema occurs when capillary filtration overwhelms the available lymphatic drainage[52]. Lymphoedema specifically refers to persistent oedema resulting from lymphatic drainage failure[50]. Chronic oedema is an umbrella term that refers to oedema resulting from insufficient lymphatic drainage, where the principle cause of the oedema may be increased capillary filtration and/or lymphatic drainage failure[50]. As such, the term chronic oedema encompasses oedema of various aetiologies, including lymphoedema. For the purpose of this trial, we will use the term chronic oedema.

Lymphoedema and chronic oedema are potent risk factors for developing lower limb cellulitis, and for its recurrence[5,6,10,12]. It is broadly accepted that the relationship between cellulitis and chronic oedema is a vicious cycle[10,13]. Chronic oedema predisposes individuals to cellulitis and with each episode of cellulitis, the lymphatic system is further impaired, increasing residual oedema and heightening risk of future cellulitis infections[13]. Thus chronic oedema is not only a result of cellulitis but also increases risk of recurrence[13].

The standard treatment for chronic oedema includes compression therapy and skin care[126]. Compression bandaging can be used to reduce oedema in a limb, and daily wear of compression garments is used to control oedema. There is general consensus that in addition to antibiotic prescription, compression to manage oedema should be an adjuvant treatment for patients with chronic oedema who are experiencing cellulitis recurrence[2,10,13,90]. Despite this common recommendation and the strong evidence supporting the relationship between oedema and cellulitis, there is a paucity of evidence to support the use of compression to manage chronic oedema to prevent cellulitis recurrence.

The time-intensive nature of compression therapy, and the fact that measuring meaningful outcomes requires lengthy assessment periods, probably contribute to the lack of research in this field. Only one study has been conducted on the impact of oedema management on cellulitis recurrence[91], with a second study incidentally observing a reduction in 'infection' among patients receiving oedema management, although this was not a research objective[92]. While both studies support the hypothesis that oedema management decreases cellulitis recurrence, their conclusions are hampered by methodological limitations, including pre-post intervention methods, small sample sizes and change in infection rate not being specified a research objective[91,92]. Whilst research regarding compression therapy to prevent cellulitis recurrence is scarce, there is high quality evidence to support the use of prophylactic antibiotics. A multi-centre, double-blind, randomised controlled trial found that use of prophylactic antibiotics in patients experiencing recurrent cellulitis is effective in preventing subsequent attacks, although the effect diminishes following prophylaxis cessation[23]. A 2017 Cochrane systematic review of interventions to prevent cellulitis identified 6 studies investigating prophylactic antibiotics, but no other randomised trials investigating other prophylactic measures such as oedema management or skin care[22]. Thus further research into the efficacy of prophylactic measures other than antibiotic is warranted[22].

The following protocol describes a randomised controlled trial (RCT) with cross-over to determine if the use of compression therapy for adults experiencing lower limb recurrent cellulitis and chronic oedema will delay cellulitis recurrence.

RESEARCH HYPOTHESES

The hypotheses are that compression therapy to control lower limb chronic oedema will delay recurrent lower limb cellulitis, reduce the rate of associated hospitalisations, minimise affected limb volume and improve the quality of life of this population.

RESEARCH OBJECTIVES

Primary objective

To determine if compression therapy delays the recurrence of lower limb cellulitis in adults with lower limb chronic oedema and recurrent cellulitis.

Secondary objectives

To determine if, in adults with lower limb chronic oedema and recurrent cellulitis, compression therapy; (1) reduces the rate of cellulitis-related hospital presentations; (2) reduces affected leg volume; and (3) improves quality of life (QOL).

TRIAL DESIGN

A randomised controlled trial with cross-over will be used to assess the impact of compression therapy on clinical outcomes (time to next episode of cellulitis, rate of cellulitis-related hospital presentations, QOL and leg volume). Participants will be randomised to the intervention or control group by block randomisation using sealed opaque envelopes. As prophylactic antibiotics have been shown to influence cellulitis recurrence[22,23,83], randomisation of participants will be stratified by prophylactic antibiotic use. Following an episode of cellulitis, participants in the control group will cross-over into the intervention group, whereas intervention group participants will remain in their original group and continue to receive compression therapy. Figure 7 shows the proposed participant allocation process.

The absence of high-quality evidence regarding the impact of compression therapy on recurrence of cellulitis means there is uncertainty as to whether it is an effective intervention, justifying the use of an RCT. While there is no high-quality evidence to support use of the compression therapy to prevent cellulitis in this patient population, it reflects the accepted expert opinion and the standard clinical practice of the institution conducting the trial. Therefore, the trial design crosses the control group participants over into the intervention group following the first episode of cellulitis to ensure no participant continues to experience recurrent cellulitis episodes without receiving the institution's standard intervention.

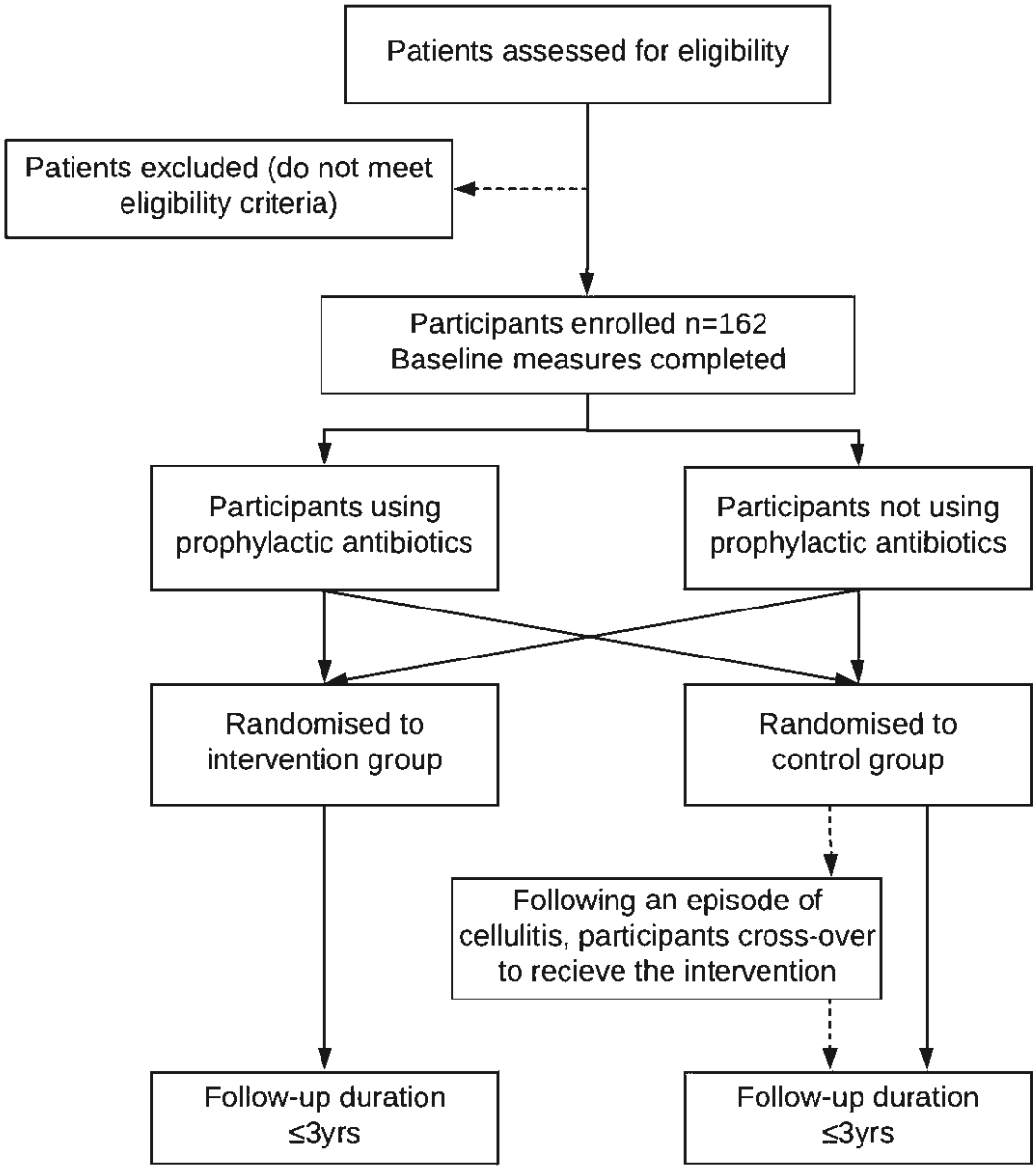


Figure 7: Anticipated participant flow through trial.

METHODS

Study setting and population

The trial will be conducted at the Calvary Public Hospital Bruce (CPHB) outpatient lymphoedema clinic. Adults with lower limb chronic oedema and a history of recurrent cellulitis who meet the eligibility criteria will be recruited from the two major ACT public Hospitals (CPHB and Canberra Hospital) and general practitioners servicing the ACT and nearby NSW residents.

Eligibility criteria

Inclusion criteria

- ≥ 18 years of age
- ≥ 2 episodes of cellulitis diagnosed in the same leg in the past 2 years (at the time of referral). Clinical diagnosis of cellulitis ideally will have been based on the presence of acute erythema, oedema, warmth and pain, with spreading involvement of the skin and subcutaneous tissues, malaise, and possibly fever[2,24,127].
- Chronic oedema (oedema persisting ≥ 3 months) in the leg/s that have had recurrent cellulitis diagnosed (presence of oedema confirmed by an accredited lymphoedema therapist through interview and physical examination, including a thorough medical history combined with limb palpation and visual assessment)
- Understanding of involvement in the study as per the participant information sheet
- Provision of informed consent
- Able to attend regular scheduled appointments for the duration of the study
- Has a valid Medicare number

Exclusion criteria

- Currently wearing effective compression garments (≥ compression class 2, or compression class 1 if considered effective by a lymphoedema therapist) regularly (≥ 5 days per week)
- Declines to participate or is unable to participate for whatever reason
- Receiving end of life care
- Medically unstable
- Chronic wound/ulcer, or a wound/ulcer requiring specialist treatment or treatment that prevents the use of compression garments
- Unable to wear compression (unable to don/doff garments or has a medical condition that contraindicates use of compression)

Interventions

All assessments, interventions and outcome measures will be conducted by a physiotherapist or occupational therapist who meets the registration requirements for category one of the Australian National Lymphoedema Practitioners Register[128].

At the initial appointment eligibility will be formally checked, and those who consent to participate will undergo stratified randomisation using sealed, opaque, and identical envelopes that are sequentially numbered. Prior to randomisation, baseline measures including number of episodes of cellulitis in the 2 years prior to referral, duration of chronic oedema, referral source and demographics will be captured. Presence of identified potential risk factors for cellulitis will also be recorded, including history of tinea or other fungal infections between toes, diabetes mellitus, obesity and chronic venous insufficiency[4,6,12,129,130].

At the initial appointment participants in both the control and intervention groups will receive education (verbal and written) regarding cellulitis and how to decrease the risk of recurrence. Education will include the benefits of skin care, prevention of tinea or other fungal infections between toes, maintaining a healthy body weight and regular exercise.

For the intervention group, the initial appointment will also be used to plan appropriate compression therapy which will be provided at subsequent appointments. Compression therapy will involve application of compression garments (compression stockings or wraps) and may or may not involve compression bandaging to minimise oedema prior to fitting of compression garments. The number of appointments necessary for provision of compression therapy will be individualised to meet participant requirements.

Participants in both groups will be followed for up to 3 years at 6 monthly intervals (Table 1) to complete outcome measures and to continue to receive the allocated treatment (education with or without compression therapy). At each appointment the therapist will inform each participant of changes in their limb volume, providing tangible feedback to support ongoing participant attendance. Throughout the trial, participants in the intervention group may require additional appointments for compression therapy (compression bandaging, and measure for and provision of compression garments). Intervention compliance (number of days per week garments are worn) and adverse effects will be captured by self-report.

Cross-over of control group participants will be triggered upon clinician identification of cellulitis. Recurrence of cellulitis will be checked at scheduled appointments, however if a participant reports a recurrence between scheduled assessments, they will be reviewed at an additional appointment to record outcome measures (Table 1), and to commence cross-over for control group participants. Date of cross-over will be defined as the day compression garments are initially fitted.

Outcome measures

Table 1 shows the timeline for completion of trial activities and outcome measures.

The primary outcome is 'observed time to first episode of cellulitis recurrence'. Cellulitis recurrence will only be assessed in a leg that has been assessed as having chronic oedema, thus if cellulitis occurs in a leg that was not previously identified as having chronic oedema, the infection will not be considered a recurrence. Cellulitis will be diagnosed by medical practitioners external to the study. Date of cellulitis recurrence (and associated hospitalisation) will be gained by participant self-report and may be verified using medical records from the hospitals and/or general practitioners.

Secondary outcomes include: (1) rate of cellulitis-related hospital admissions; (2) percent change in leg volume from baseline, measured using the perometer; (3) QOL, assessed using the LYMQOL and EuroQol Five Dimension Scale (ED-5D-3L). Occurrence of cellulitis-related hospital admissions will be measured in the same manner as cellulitis recurrence.

Percent change in leg volume will be measured using a perometer, an optoelectronic imaging device designed to measure limb volume[131]. The perometer has excellent intra-rater reliability (intraclass correlation coefficient [ICC]= 1.0, 95% CI: 0.99 to 1.00) and inter-rater reliability (ICC= 1.0, 95% CI: 0.97 to 1.00), is sensitive to changes in limb volume[132-134], and is a valid measure of knee volume[131]. Leg volume will be measured between 53mm and 400mm height from the ground using the perometer. Monthly calibration of the perometer will be conducted using a standardised object of known volume (875ml) to minimise instrument error, ensuring consistency of this measurement device across the duration of the trial. Use of this device will also prevent potential differential measurement bias arising from lack of therapist blinding.

Where limb volume cannot be measured using the perometer, due to impaired mobility of a participant or equipment failure, summated circumferential leg measurements will be used following expert clinical guidelines. Circumferential leg measures will be taken at the mid foot, oblique ankle and at 10, 20, 30 and 40cm intervals up the leg using a measurement board.

Circumferential limb measurement also has excellent intra-rater reliability (ICC=0.977-0.996, 95% CI: 0.960-0.998) and inter-rater reliability (ICC= 0.942- 0.994, 95% CI: 0.936-0.997)[135].

Quality of life will be measured using LYMQOL, a validated, condition-specific quality of life tool for people with lower limb lymphoedema[136], and the EQ-5D-3L, a generic preference-based measure of health related quality of life that comprises of five dimensions of health[137]. The EQ-5D can be used to calculate quality adjusted life years (QALYs) for the purpose of economic evaluation[137]. A systematic review has found the EQ-5D has good validity and responsiveness for people with skin diseases, although the tool has not been specifically validated within a population suffering cellulitis[137].

Exploratory analysis will be conducted to test the robustness of the trial hypotheses and may include assessment of cellulitis recurrence post cross-over, intervention compliance, participant demographics, risk factors, and per protocol analysis.

Sample size and duration of follow up

The sample size has been calculated for the primary objective of detecting a difference in time to cellulitis recurrence between the control and intervention groups. The sample size estimation is based upon the assumptions that the 3-year cellulitis recurrence rate in control participants is approximately 47%[10] and compression therapy will reduce the 3-year incidence of recurrent cellulitis by 50%[91,92]. Assuming that events occur at a constant rate, these assumptions correspond to a hazard ratio of 0.42. The eligibility criteria of two or more episodes of cellulitis in the same leg in the past 2 years has been used so that the trial cohort have an increased likelihood of cellulitis reoccurring during the follow up period.

It is assumed that patients will be recruited over a 2.5-year period, and the total study duration will be 3.5 years. Length of participant follow up will vary based on time of enrolment. Using a sequential design software package gsDesign in R[138], in order to detect a hazard ratio of 0.42 with 80% power and 2.5% (1-sided) type 1 error, a total of 45 cellulitis recurrences are needed. Under the present recruitment and recurrence assumptions, we plan to recruit 162 participants (81 per arm).

An interim analysis will be performed by a Data Monitoring Committee after 23 episodes of cellulitis. A log rank test will be used to assess group differences. If a nominal (1 sided) significance level of p=0.003 is detected, indicating a strong clinical effect, the study will be ceased. If the Data Monitoring Committee recommends that the study continue to 45 episodes of cellulitis, the final analysis will use a log rank test with (1-sided) significance level p=0.0238. These efficacy bounds

were derived using a Hwang-Shih-DeCani spending function with gamma = -4 to preserve an overall Type I error rate of 5%.

Recruitment and enrolment of participants

Recruitment will be conducted over a 2.5-year period. A multi-faceted recruitment strategy will be used. In order to capture acute patients (seen in CPHB and Canberra Hospital emergency departments and wards), all patients diagnosed with lower limb cellulitis during their hospital presentation will be sent information regarding the trial and how to contact the CPHB lymphoedema service if they would like to learn more information or self-refer. To recruit from the community, the study will be advertised via posters, radio and articles in various magazines and newspapers, providing information about the trial and encouraging self-referral. Education (in-services, faxes, newsletters, posters) and referral forms will be provided to recruitment sites (Canberra Hospital, CPHB, General Practices within the surrounding region) to encourage health professionals to refer patients. Patients from these sites must consent to referral to the CPHB lymphoedema service for the study, but do not need to consent to participating in the trial at time of referral.

After self-referral, a screening phone call will be conducted to check inclusion/exclusion criteria, and for those that appear to be eligible, an appointment at the service will be made with a lymphoedema therapist. At this appointment candidates will be provided with participant information and consent forms, a verbal explanation of the study and an opportunity to ask questions, prior to choosing to consent or decline to participate.

To promote participation in the study, a free set of compression garments will be offered by a secondary sponsor. Compression garments are expensive, which can provide a barrier to treatment compliance. Participants in the intervention group will receive the free garments at intervention commencement. Participants in the control group will receive the free garments following their first cellulitis recurrence (cross-over) or upon study completion for those who do not experience recurrence.

Patient and public involvement

A patient centred approach was utilised to design this study. The trial design replicates the institution's standard clinical practice as closely as possible, whilst aiming to minimise additional burden to participants. Patients from the participating clinical service were surveyed to assess acceptability of the model of care undertaken by the trial. As time required to attend appointments was identified as a potential burden, the trial was designed to minimise scheduled follow-up

appointments. Cost of compression therapy was identified as a likely financial burden which is minimised through provision of two sets of free compression garments and use of accessible funding schemes. Referral processes were developed to enable patients to self-refer to the trial. The cross-over design feature was chosen to ensure participants do not continue to experience episodes of recurrent cellulitis without receiving the institution's standard intervention.

Table 1: Timeline per patient for RCT outcome measures

Time Point	**Enrolment**	**Assessment post initial intervention**	**Assessment post cellulitis recurrence**	**Cross -over**	**6**	**12**	**18**	**24**	**30**	**36**
Body Mass Index	X		X	X	X	X	X	X	X	X
Perometer (limb volume)	X	X	X	X	X	X	X	X	X	X
Summated Limb Circumferences	X	X	X	X	X	X	X	X	X	X
ED-5D-3L	X					X		X		X
LYMQOL	X				X	X		X		X
Cellulitis recurrence date/s			X		X	X	X	X	X	X
Hospitalisation due to cellulitis (date, length of stay)			X		X	X	X	X	X	X
Verification of cellulitis recurrence and associated hospitalisation using medical record/general practitioner report			X		X	X	X	X	X	X
Intervention provided (type of garment, application of compression bandages)		X	X	X	X	X	X	X	X	X
Presence of fungal infections/tinea/ maceration or cracking of skin between toes			X		X	X	X	X	X	X
Adverse events			X		X	X	X	X	X	X
Intervention compliance			X		X	X	X	X	X	X
Occurrence of wounds/ulcers (acute/chronic)					X	X	X	X	X	X

Primary and secondary outcome measures have been underlined. Identified potential risk factors have been italicised[4,12].

Assignment of interventions and blinding

Participants will be assigned to the intervention or control group in a 1:1 allocation ratio using block randomisation, with a block size of 10. Sealed sequentially numbered opaque envelopes will be used to ensure concealed allocation. A computer-generated allocation sequence will be created and supplied by a consultant statistician and saved in a folder only accessible by administration staff. Administration staff will prepare the sealed sequentially numbered opaque envelopes, ensuring therapists involved in participant allocation have no premature access to the letters.

Therapists will not be blinded due to practicalities of providing the intervention within a small team of 4 specialised clinicians. Further, the visible nature of the treatment and lack of feasible sham interventions prevent effective blinding of both assessors and participants. Additionally, for ethical reasons, participants will be fully informed of both the potential interventions, prior to consenting to participate.

Data management and quality assurance

Prior to any involvement in the trial, therapists will receive training regarding trial implementation and completion of outcome measures. Refresher training will be provided to therapists annually and the trial protocol will be kept readily available.

For the duration of the study, data will be stored in identifiable form in both a locked office and on a secure access hard drive, accessible only by designated research staff. Data will be entered by a research officer or members of the research team. For quality assurance, data completeness will be reviewed annually, and all entered data will be cross-checked against written records at least once after initial entry. Following trial conclusion and prior to data analysis, all data will be de-identified. Data will be stored for a minimum of 7 years as per CPHB policy, however data may be retained for longer for identified new, ethically approved ancillary studies. A contract with the secondary sponsor ensures they will have no involvement in the study design, in the collection, analysis, and interpretation of data, in the writing of the manuscript, or in the decision to submit the manuscript for publication.

Participant retention

Once a participant is enrolled in the study, every effort will be made to ensure they are followed up as per the protocol. Where participants cannot attend a scheduled appointment, a phone call assessment may be completed to gain the primary outcome measure. Phone call assessment will not allow for completion of limb volume or QOL measures but will capture date of cellulitis recurrence and cellulitis-related hospitalisation.

Participants can withdraw from the study at any point. For participants that withdraw, the medical record and/or general practitioner report may be checked according to the schedule for cellulitis recurrence and cellulitis-related hospitalisation.

Termination criteria

Participants will be withdrawn from the study in the case of death, withdrawal of consent or if they develop a wound or lymphorrhea requiring compression for effective management[139].

Proposed methods for data analysis

For the main outcome measure of 'time to first episode of recurrent cellulitis', survival analysis will be undertaken. Kaplan-Meier plots will be used to visualise patterns of time to first cellulitis recurrence between the groups, with a log rank test being used to determine if there is a statistically significant difference between the groups. Cox proportional hazards regression may also be used to adjust for important risk factors. Right censoring will be used for participants who are lost to follow up. Intention to treat analysis will be used, with all enrolled participants being assessed according to their randomisation, regardless of protocol adherence.

For the secondary outcomes of percent change in limb volume and QOL, measures will be taken at multiple time points. Therefore, groups will be compared using a linear mixed model or using a repeated measures analysis. A generalised linear model will be used to assess rate of cellulitis-related hospital admissions.

MINIMISING BIAS

Selection and attrition bias

Use of randomisation will minimise selection bias and confounding. Stratification will ensure use of prophylactic antibiotics is not confounded with treatment assignment. Presence and distribution of other known potential confounding factors will be measured and reported. Intention to treat analysis will be used to prevent attrition bias that may occur through loss to follow up of participants.

Internal validity

Use of an RCT and validated measurement tools support the internal validity of this research. The lack of blinding of therapists and participants has the potential to induce surveillance and recall bias and lead to differential measurement error in the reporting of cellulitis recurrence. To minimise this, accuracy of self-report of recurrence may be cross-checked with the participant's general practitioner or medical record (from CPHB and Canberra Hospital). Diagnosis of cellulitis by doctors external to the study and use of perometry to measure limb volume will reduce the risk of measurement bias and thus differential measurement error. Calibration of the perometer will be performed to prevent non-differential measurement error that could result from machine error.

Control and intervention group participants have the same appointment schedule throughout the duration of the trial, however participants in the intervention group may attend more appointments than the control group. This systematic difference in clinician contact could influence participant's perceived benefit, allowing potential bias in self-reported measures (LYMQOL, EQ-5D).

Participants enrolled in the trial have a history of 2 or more episodes of cellulitis diagnosed by medical practitioners independent to the trial. As misdiagnosis of lower limb cellulitis is not uncommon[31], the trial may include incorrectly diagnosed participants leading to non-differential misclassification.

ANALYSIS OF COSTS

A within-trial cost-analysis assessment will be conducted. Data obtained from the trial and participant medical records will be used to assess the cost of oedema management and the cost of an episode of cellulitis from both an individual and a health systems perspective. Upon completion of the RCT, the cost-effectiveness and cost-utility of chronic oedema management to prevent recurrent cellulitis may be assessed.

ETHICS AND DISSEMINATION

Ethics approval has been granted for these studies by three institutional committees:

1. Calvary Public Hospital Bruce Human Research Ethics Committee ETH.4.17.092
2. Australian Capital Territory Health Human Research Ethics Committee (53-2016)
3. University of Canberra Human Research Ethics Committee (cross-institutional approval)

Regardless of the outcome of the trial, the findings are planned to be submitted for publication in relevant peer-reviewed journals and for presentations at national and international conferences. Key findings will be disseminated to identified stakeholders, including primary contact clinicians for patients experiencing cellulitis (doctors and health professionals in acute and community settings), clinicians who manage chronic oedema and professionals who may be involved in developing relevant policy and practice. Upon request, participants will be provided with a copy of the trial results.

DISCUSSION

Although current expert consensus recommends compression therapy to prevent the recurrence of cellulitis in patients with lower limb chronic oedema, the evidence supporting this recommendation is lacking. This study aims to review the efficacy of compression therapy to allow for better informed practice and policy. Given the high incidence of cellulitis within Australia and around the world, reducing cellulitis recurrence will significantly decrease cost to the healthcare system and reduce financial and personal burden of sufferers. Further, should compression therapy reduce the recurrence of cellulitis this may limit the dependence and widespread prescription of prophylactic antibiotics. This trial will be performed on adults receiving healthcare services in the Australian Capital Territory, however the results will be relevant to cellulitis management throughout Australia and internationally.

CHAPTER 3: Paper Two

Compression Therapy to Prevent Recurrent Cellulitis of the Leg: a randomised controlled trial

This chapter has been peer reviewed and published as original research in the New England Journal of Medicine (Appendix F):

https://pubmed.ncbi.nlm.nih.gov/32786188/

Webb E, Neeman T, Bowden FJ, Gaida J, Mumford V, Bissett B. Compression Therapy to Prevent Recurrent Cellulitis of the Leg. *N Engl J Med.* 2020;383(7):630-639

INTRODUCTION

Cellulitis is a common bacterial infection of the skin and subcutaneous tissue, which mostly occurs in the legs and is associated with healthcare costs[1] and morbidity[90]. Recurrence of cellulitis is common, with up to 47% of patients experiencing a repeat episode within 3-years[10]. Penicillin prophylaxis is effective in preventing cellulitis recurrence, although a trial published in the *Journal* in 2013 showed that the protective effect diminishes progressively once the antibiotic is discontinued[23]. A Cochrane review of interventions to prevent cellulitis identified 6 studies investigating prophylactic antibiotics but no randomised trials of other measures such as oedema management[22]. The efficacy of non-antibiotic measures to prevent cellulitis has not been well studied[22,25].

Chronic oedema refers to swelling that persists for 3 months or longer and encompasses various and often mixed causes of swelling. The principal cause of oedema may be increased capillary filtration or failure of lymphatic drainage[50,52]; other causes include lymphoedema, venous hypertension, immobility, obesity, and heart failure. Chronic oedema is a risk factor for cellulitis of the leg and for recurrent cellulitis[5,6,10,12].

Compression therapy has been used to reduce and control chronic oedema. This treatment involves the daily wearing of compression garments such as stockings, with or without a short period of compression bandaging to reduce swelling before compression garments are fitted. Compression garments and bandages exert the greatest degree of compression at the ankle and gradually apply less pressure proximally along the limb. By exerting this type of graduated pressure on the leg, compression therapy reduces the formation and accumulation of interstitial fluid and shifts fluid proximally, away from the lower leg[93]. Guidelines have suggested the use of compression therapy to prevent recurrent cellulitis in patients with chronic oedema of the leg, and compression therapy is widely used by clinicians[2,10,13,90]; however, there are limited data from trials to support this practice. We conducted a randomised, controlled, single centre trial to determine whether compression therapy would prevent the recurrence of cellulitis of the leg in adults with chronic oedema of the leg.

METHODS

Trial design and Oversight

Assessors and participants were aware of the trial-group assignments. Participants were randomly assigned in a 1:1 ratio to receive either compression therapy plus education regarding prevention of cellulitis (compression group) or education alone (control group). Randomisation was stratified according to prophylactic antibiotic use (yes or no), with a planned maximum follow-up of 3 years. Participants in the control group crossed over to the compression group when they had an episode of cellulitis.

The trial was conducted at Calvary Public Hospital Bruce (Canberra, Australia). The protocol (available with the full text of this article at NEJM.org) was approved by three institutional human research ethics committees. Participants provided written informed consent before the trial. The authors designed and implemented the trial and collected and analysed the data. The first author wrote the first draft of the manuscript, and all authors contributed to subsequent drafts. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. Haddenham Healthcare manufactured and provided the compression garments but had no involvement in the design, conduct, analysis, or reporting of the trial and did not have access to the trial data.

Participants

Participants were recruited at one of two primary public hospitals or were referred by general practitioners servicing the local region. Patients were eligible to participate if they had a history of two or more episodes of cellulitis in the same leg in the 2 years before referral to the trial and had oedema lasting longer than 3 months in one or both legs, with recurrent cellulitis. Full inclusion and exclusion criteria are provided in the protocol. The presence of oedema was confirmed by means of interview and physical examination by specialist lymphoedema physiotherapists. Patients were excluded from the trial if they were younger than 18 years of age, were already wearing effective compression garments 5 or more days per week, were receiving end-of-life care, had a clinically unstable condition, or had a chronic wound or a wound requiring specialist treatment, or if compression therapy was contraindicated.

Compression garments are categorised by manufacturers into four numbered classes according to the pressure they exert at the ankle[114]. If patients were already wearing garments of compression class 2 or higher (providing 23 to 32 mm Hg of pressure), the garments were considered to be effective and the

patients were excluded from the trial. Patients who were wearing class 1 garments (providing 18 to 21 mm Hg of pressure) were excluded if a lymphoedema therapist determined that this lower amount of pressure was effective for the patient.

Interventions and Assessments

All assessments and interventions were performed in the outpatient department of the hospital by specialist lymphoedema physiotherapists who were aware of the trial-group assignments. Baseline measures, including demographic characteristics, leg volume, and quality of life, were recorded before randomisation. Cellulitis was diagnosed by general medical practitioners or by hospital physicians who were not otherwise involved in the trial; the diagnosis was confirmed by trial assessors. Trial assessors verified the dates of recurrence and hospitalisation with the use of medical records. Participants were encouraged to report episodes of cellulitis at the time that they occurred. In addition, participants were interviewed at the 6-month follow-up appointments to determine whether there had been unreported recurrences of cellulitis. If a recurrence was reported between scheduled follow-up appointments, participants were seen for an additional appointment with a lymphoedema therapist to record outcome measures (date of cellulitis diagnosis and associated hospitalisation); participants in the control group commenced crossover to the compression group at this time. An episode of cellulitis was recorded only if it occurred in a leg in which chronic oedema had been identified at baseline; in the case of oedema in both legs, recurrence of cellulitis was recorded as a single event if it occurred in either leg. Quality-of-life measures, leg volume, adherence to wearing garments in the compression group, and adverse events were assessed at the 6-month appointments. If participants could not attend their scheduled appointments, assessment was performed by means of telephone to check for cellulitis recurrence and associated hospital admission; quality-of-life assessments were obtained by means of mailed surveys.

Education about cellulitis prevention was provided to participants in the two trial groups at the initial appointment and at follow-up appointments and included information on the benefits of skin care, prevention of interdigital fungal infections, healthy body weight, and regular exercise. Participants assigned to the compression group were instructed to wear compression garments throughout the day and were provided information on use, safety, cleanliness, and application and removal of the garments. Two free sets of compression garments were provided to participants in the compression group at the beginning of the trial and to participants in the control group when they crossed over to the compression group.

When appropriate, a short period (typically 3 to 5 days) of therapist-applied compression bandaging to minimise oedema was provided immediately before the compression garments were fitted (Figure 10 in the RCT Supplementary Appendix). The majority of prescribed compression garments were knee-high compression stockings that included the foot, with or without the toes (Figure 11 in the RCT Supplementary Appendix); less often, leg-and-foot compression wraps were prescribed (Figure 12 in the RCT Supplementary Appendix). The number of appointments required to provide compression therapy was not prespecified and varied according to the individual needs of the participants.

The prescribed garment type and compression class were determined on the basis of oedema severity, leg shape, skin condition, and the ease of application and removal by the participants or their caregivers. If chronic oedema was present in both legs, compression therapy was provided for both legs. Replacement of compression garments was recommended after 6 to 12 months of wear, with no restrictions on the brand used.

Participants in the control group who had an episode of cellulitis crossed over to the compression group to receive compression therapy. The date of crossover was defined as the day that compression garments were initially fitted. Participation in the trial was terminated in the case of death, withdrawal of consent, or development of a wound or lymphorrhea for which management with compression therapy was advised and was supported by evidence[139]. No further outcome measures were obtained for participants who were withdrawn from the trial.

Outcomes

The primary outcome was the recurrence of cellulitis. Secondary outcomes were cellulitis-related hospital admission, change in leg volume, and quality of life measures. Leg volume was measured with the use of a perometer (an optoelectronic imaging device). Scanning was performed on the leg starting at a height of 5.3 cm from the bottom of the foot and extending up the leg to a height of 40.0 cm (Figure 13 in the RCT Supplementary Appendix). The perometer was calibrated to a standardised object every 2 weeks throughout the trial to ensure reliability.

Quality of life was assessed with the use of the quality-of-life measure for limb lymphoedema (LYMQOL)[136] and the EuroQol Group 5–Dimensions 3-Level scale (EQ-5D-3L)[140]. The LYMQOL consists of

two components that are assessed separately: a quality-of-life score (scores range from 0 to 10, with higher scores indicating better quality of life) and a combined score that encompasses four domains (symptoms, appearance, function, and mood), each scored at four levels (not at all, a little, quite a bit, or a lot; combined scores range from 4 to 16, with lower scores indicating better quality of life)[136]. The EQ-5D-3L also consists of two components that are assessed separately: a visual analogue scale that assesses the overall health state (scores range from 0 [worst imaginable health state] to 100 [best imaginable health state]) and a descriptive system that assesses five dimensions of quality of life (mobility, personal care, usual activities, pain and discomfort, and anxiety and depression) at three levels (no problems, some problems, or extreme problems; total scores for the descriptive system range from 5 to 15, with lower scores indicating better quality of life[140].

Adherence to the intervention in the compression group was determined on the basis of the number of days per week that garments were worn. Adverse effects were reported by participants during the 6-month assessments with therapists.

Statistical Analysis

Assuming that recurrence of cellulitis at 3 years would occur in 47% of participants in the control group (on the basis of previous reports[10,23]) and that there would be a 50% lower incidence of cellulitis in the compression group than in the control group[91,92], we calculated that 45 events of cellulitis would be needed to give the trial 80% power to detect a hazard ratio for recurrence of cellulitis of 0.42, at a one sided type I error rate of 2.5%. On the basis of these assumptions, we planned to recruit 162 participants (see the RCT Supplementary Appendix). Randomisation was stratified according to prophylactic antibiotic use, with the use of block sizes of 10. To prevent bias in assignment of participants to a particular group, sealed, opaque, sequentially numbered, identical envelopes were used to ensure concealment of trial-group assignments.

The statistical analysis plan prespecified that after 23 episodes of cellulitis had occurred, an independent data monitoring committee would review the results of the interim analysis and recommend whether the trial should stop early. A post hoc stopping rule for the time-to-event analysis was determined on the basis of a one-sided significance level of 0.003 with the use of a logrank test. If the trial continued until 45 episodes of cellulitis occurred, the final analysis would use a log-rank test with a one-sided significance level of 0.0238 to preserve an overall type I error rate of 5%.

Only data collected on or before the first interim analysis were used in the intention-to-treat analysis of the primary outcome and the secondary outcome of cellulitis-related hospital admission. Therefore, no data on outcomes for participants who crossed over to the compression group were included in the primary analysis. For the secondary outcomes of leg volume and quality of life, data for each participant in the control group were collected until crossover occurred, and data for participants in the compression group were collected until the last participant in the control group crossed over to the compression group.

Kaplan–Meier plots were used for the analysis of the primary outcome and for the analysis of the secondary outcome of cellulitis-related hospital admission. The log-rank test was used to test for between-group differences. Cox proportional-hazards regression was used to estimate the hazard ratios and to assess the contribution of other risk factors for cellulitis. The proportional-hazards assumption was assessed with the use of correlation of scaled Schoenfeld residuals and transformed survival time (cox.zph in the survival package of R software [R Project for Statistical Computing]). Data for participants who were lost to follow-up were censored at the time of the last contact. An episode of cellulitis was recorded only if it occurred in a leg in which chronic oedema had been identified at baseline.

Mixed-effects linear models were used to assess between-group differences in the change in leg volume and quality of life over time, with group and time as fixed effects and participant identification number as the random effect. The two components of each quality-of-life scale were analysed separately. Missing data were assumed to be missing at random. There was no plan for adjustment for multiple comparisons in the analyses of secondary outcomes, and no clinical conclusions can be made from these data. The statistical analysis plan is available with the protocol. All analyses were performed with the use of R software, version R 3.6.0[138].

RESULTS

Participants

A total of 183 patients were screened and 84 were enrolled from June 2017 through February 2019 (Figure 8). In September 2018, after nine events of cellulitis had occurred in 67 participants, lymphoedema therapists who were aware of the trial-group assignments noted that there may have been a large between group difference in recurrence. This potential difference between groups was

brought to the attention of the human research ethics committees overseeing the trial. The committees had advised the introduction of stopping rules to ensure that the trial population was not exposed to unreasonable risk. Therefore, in September 2018, an interim analysis plan with formal stopping rules was prepared and added as an amendment to the protocol. On March 26, 2019, the data monitoring committee advised, on the basis of the post hoc stopping rule, that the trial should be stopped for efficacy and recruitment should cease; the committee also recommended that crossover should commence to provide participants in the control group with compression therapy.

At the time that the trial was stopped, 41 participants had been assigned to the compression group, and 43 to the control group. During the trial, 2 participants (5%) in each group were lost to follow-up. Data for 3 participants (7%) in the compression group were censored because of death (1 [2%]), occurrence of a wound (1 [2%]), and relocation to a different state (1 [2%]). In the control group, 3 participants (7%) were withdrawn because of death (2 [5%]) and occurrence of a wound (1 [2%]) (Figure 8).

Baseline demographic characteristics were similar in the two groups (Table 2Table 2: Baseline characteristics of the participants). Two participants in each group were using prophylactic antibiotics at the time of enrollment and continued using them throughout the course of the trial. No other participants used prophylactic antibiotics before an episode of cellulitis during the trial. Before provision of compression garments, 24 participants in the compression group received therapist-applied compression bandaging to minimise leg oedema. Compression stockings were prescribed for all participants in the compression group, and a combination of compression stockings and compression wraps were prescribed for 3 participants.

At the time of the interim analysis, the follow-up time ranged from 0 to 511 days, with a median of 186 days. Participants who had not yet had their first 6-month follow-up at the time of the interim analysis were recorded as having had 0 days of follow-up. The median follow-up was 209 days in the compression group and 77 days in the control group. The median follow-up was short in the control group because of the participants whose data were censored after they had had an episode of cellulitis. Because data collection for leg volume and quality-of-life outcomes continued for participants in the control group until they crossed over to the compression group and continued for participants in the compression group until the last participant in the control group crossed over, the median follow-up was 336 days for those outcomes.

Before the interim analysis was performed, 88% of the participants in the compression group reported during a follow-up interview that they wore the garments 4 or more days per week, and 73% reported that they wore the garments 5 or more days per week. No adverse outcomes were reported in participants who wore compression stockings or compression wraps.

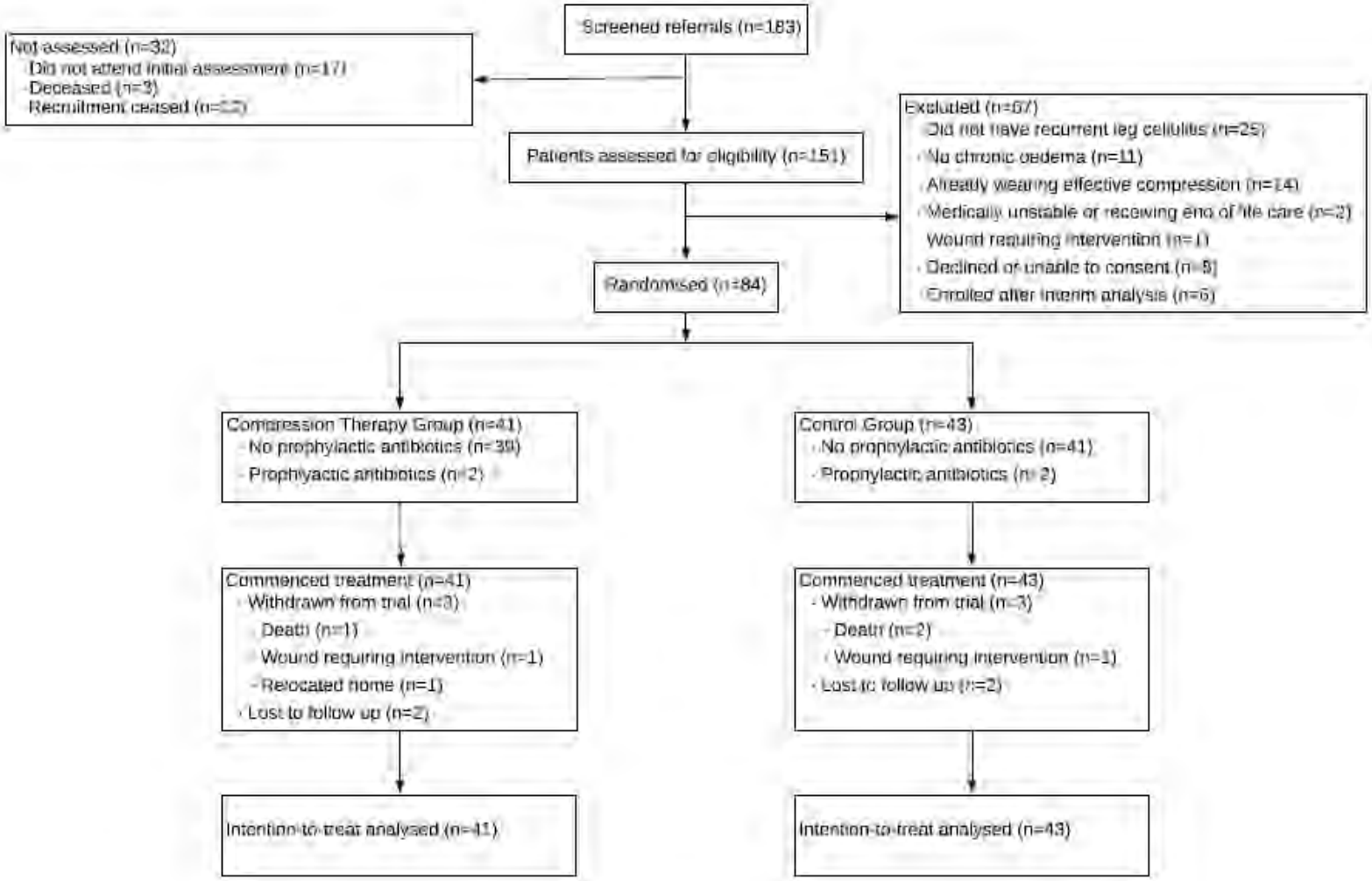


Figure 8: Eligibility, randomisation, and follow-up.

Table 2: Baseline characteristics of the participants

Characteristic	Compression (N=41)	Control (N=43)	Total (N=84)
Sex: Female – no. (%)	19 (46)	22 (51)	41 (49)
Age: Mean (SD)	65 (15.1)	64 (12.9)	64 (13.9)
Median (IQR)	68 (52-75)	66 (57-72)	66 (55-74)
Body Mass Index: Mean (SD)	39 (10.0)	42 (9.8)	41 (9.9)
Median (IQR)	39 (31-47)	41 (34-47)	40 (33-47)
Chronic oedema: Bilateral (%)	32 (78)	34 (79)	66 (79)
Duration of oedema: 1-5yrs (%)	14 (34)	17 (40)	31 (37)
>5yrs (%)	27 (66)	26 (60)	53 (63)
Episodes of cellulitis per leg in 2yrs prior to trial referral (both legs assessed): Mean (SD)	2 (1.5)	2 (1.4)	2 (1.5)
Median (IQR)	2 (0-2)	2 (1-2)	2 (0-2)
Hospital admission for cellulitis in 2yrs prior to trial referral: Mean (SD)	1 (0.9)	1 (1.5)	1 (1.2)
Median (IQR)	1 (0-2)	1 (0-1.5)	1(0-2)
Prophylactic antibiotics (%)	2 (5)	2 (5)	4 (5)
Factors contributing to chronic oedema (%):			
Obesity	26 (63)	27 (63)	53 (63)
Surgery/trauma	14 (34)	13 (30)	27 (32)
Venous Hypertension	15 (37)	11 (26)	26 (31)
Immobility	3 (7)	7 (16)	10 (12)
Primary Lymphoedema	3 (7)	2 (5)	5(6)
Cancer	0 (0)	1 (2)	1 (1)
Other	6 (15)	3 (7)	9 (11)
Comorbidities: Tinea pedis	13 (32)	17 (40)	30 (36)
Diabetes	10 (24)	14 (33)	24 (29)
Chronic venous insufficiency	12 (29)	11 (26)	23 (27)
Congestive Heart Failure	10 (24)	7 (16)	17 (20)

Note: It is assumed all participants had some degree of oedema related to prior cellulitis episodes.

Outcomes

At the time the trial was stopped, recurrence of cellulitis (the primary outcome) had occurred in 6 of 41 participants (15%) in the compression group and in 17 of 43 (40%) in the control group (hazard ratio, 0.23; 95% confidence interval [CI], 0.09 to 0.59; P = 0.002) (Table 3 and Figure 9). Because the proportional hazards assumption was not met, relative risk was calculated post hoc (relative risk, 0.37; 95% CI, 0.16 to 0.84; P = 0.02), and the results favored the compression group. Table 4 (in the RCT supplementary appendix) shows the results of the exploratory analysis of the influence of factors that are typically associated with recurrent cellulitis (body-mass index [BMI, the weight in kilograms divided by the square of the height in meters] ≥40, tinea pedis or toe-web intertrigo, ≥3 episodes of cellulitis in either leg in the 2 years before enrollment, or development of a wound during the trial)[4,12,23].

Hospital admission for cellulitis (a secondary outcome) occurred in 3 participants (7%) in the compression group and in 6 (14%) in the control group (hazard ratio, 0.38; 95% CI, 0.09 to 1.59) at the time of the interim analysis (Table 3). After 6 months, 1 participant (2%) in the compression group and 5 (12%) in the control group had been hospitalised for cellulitis (Figure 14 in the RCT Supplementary Appendix). After 12 months, the mean leg volume among participants in the compression group was 181 ml less than that at baseline; among participants in the control group, the mean leg volume had increased by 60 ml (between-group difference in change, −241 ml; 95% CI, −365 to −117) (Table 3, and Figure 15 in the RCT Supplementary Appendix).

At 12 months, the mean LYMQOL combined score had decreased (reflecting a better quality of life) by 0.5 points in the compression group and by 0.2 points in the control group (between-group difference in change, −0.3 points; 95% CI, −0.6 to −0.1) (Table 3). There were no substantial between-group differences in the LYMQOL quality-of-life score (between-group difference in change, 0.8 points; 95% CI, −0.1 to 1.7), the EQ-5D-3L visual analogue scale (between-group difference in change, 8 points; 95% CI, −5 to 16), or the score on the descriptive system of the EQ-5D-3L (between-group difference in change, 0.8 points; 95% CI, −0.4 to 2.1) (Table 3).

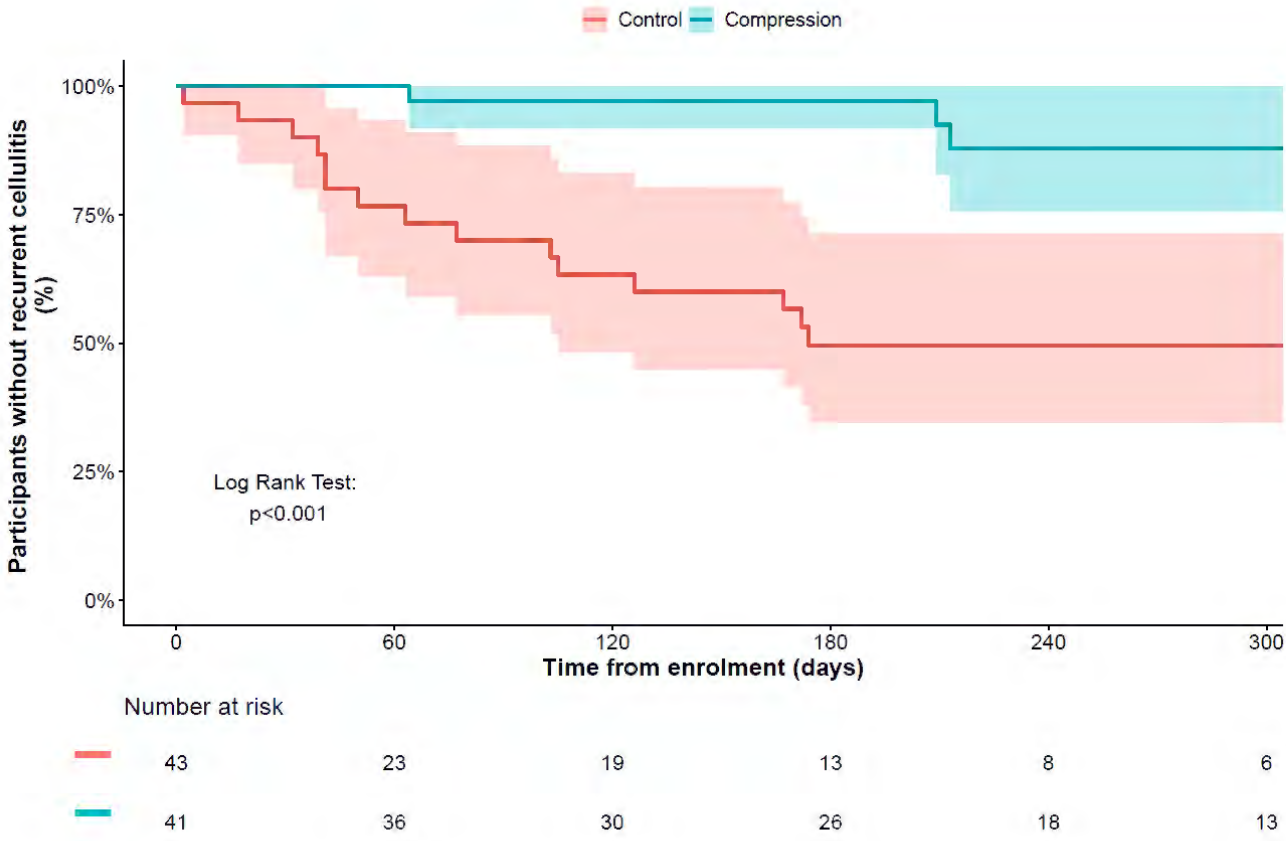


Figure 9: Freedom from recurrence of cellulitis over time. Shown are the Kaplan–Meier estimates of the freedom from recurrence of cellulitis in the compression group and the control group. The shaded areas indicate 95% confidence intervals.

Table 3: Primary and secondary outcomes

	Compression Group (n=41)	Control Group (n=43)	Hazard ratio or Difference
Cellulitis Recurrence			
Number (%)	6 (15)	17 (40)	11 (25)
Hazard Ratio (95% CI), p value	-	-	0.23 (0.09 to 0.59), 0.002
Relative Risk (95% CI), p value †	-	-	0.37 (0.16 to 0.84), 0.018
Hospitalisation for cellulitis recurrence *			
Number (%)	3 (7)	6 (14)	-
Hazard Ratio (95% CI)	-	-	0.38 (0.09 to 1.59)
Leg Volume (mean change over 12-months):*			
mL (95% CI)	-181 (-256 to -106)	60 (-38 to 159)	-241 (-365 to -117)
Percentage points (95% CI)	-4.3 (-5.8 to -2.9)	1.3 (-0.6 to 3.3)	-5.7 (- 8.1 to -3.2)
LYMQOL (mean change over 12 months)*			
Combined domains (range 4-16)	-0.5 (-0.6 to -0.4)	-0.2 (-0.3 to 0.02)	-0.3 (-0.6 to -0.1)
QOL (0-10)	0.5 (-0.1 to 1.1)	-0.3 (-1.1 to 0.4)	0.8 (-0.1 to 1.7)
EQ-5D-3L (mean change over 12 months)*			
VAS (0-100)	-1 (-9 to 7)	-9 (-20 to 2)	8 (-5 to 16)
Descriptive System (range 5-15)	-0.3 (-0.9 to 0.4)	-1.1 (-2.2 to 0.01)	0.8 (-0.4 to 2.1)

QOL= quality of life; VAS = visual analogue scale.

† Post hoc analysis on the basis that the proportional hazards assumption was not met.

*Confidence intervals for secondary outcomes are not corrected for multiple comparisons and no clinical inferences can be made from these data.

For cellulitis recurrence and hospitalisation for cellulitis recurrence, only data collected prior to the interim analysis is included in the analysis.

For leg volume, LYMQOL and EQ-5D-3L data collection occurred for control group participants until they initiated cross-over, and for compression group participants until the last control group participant initiated cross-over; the mean change (slope) has been estimated using mixed effects linear models that included baseline and all available follow-up data points.

Change in participant leg volume was calculated based on change from the original volume measure of the same leg at the initial assessment. The contralateral leg was not used as a comparison for ipsilateral oedema.

DISCUSSION

This single-centre, nonblinded, randomised trial, which was stopped early for efficacy, showed that compression therapy resulted in a lower incidence of recurrent cellulitis than conservative treatment in adults with chronic oedema of the leg. This result supports expert opinion, but data from trials are limited[2,10,13,90]. The results of the analyses of hospitalisation for cellulitis and of the change in leg volume from baseline were in the same direction as those of the primary outcome, but the lack of a prespecified plan for adjustment for multiple comparisons of secondary outcomes precludes clinical conclusions from these data. However, most quality-of-life measures did not differ substantially between the trial groups. Because the trial was stopped after the interim analysis, we were not able to report data on the 3-year effect of compression therapy on leg volume, as we had intended.

A Cochrane review showed that antibiotics were the only prophylactic treatments for cellulitis of the leg that have been supported by randomised trials[22]. However, patients with preexisting oedema, multiple previous episodes of cellulitis (≥3 episodes), or a high BMI (≥33) were less likely to benefit from antibiotic prophylaxis than other patients with cellulitis[23]. All participants in our trial had one or more risk factors that are predictive of antibiotic prophylaxis failure: all participants had preexisting oedema, 79% had a BMI of 33 or greater, and 26% had had three or more episodes of cellulitis in the 2 years before the trial. We found that compression therapy reduced cellulitis recurrence in this population at risk for failure of antibiotic prophylaxis.

Prevention of cellulitis by means of prophylactic antibiotics can cause side effects[22], and the bacterial species precipitating cellulitis is usually unidentifiable[141], which hinders targeted antibiotic prophylaxis[142]. In comparison, long-term use of compression therapy is recommended[114] and has shown benefits in controlling oedema in patients with chronic oedema[92,143,144]; in addition, its efficacy is not related to the causative bacterial species. Long term use of compression therapy has the additional potential advantages of managing chronic venous insufficiency[145], venous ulcers[139,146] and skin conditions (e.g., hyperkeratosis)[89,147] which are all common in patients with chronic oedema. Furthermore, compression therapy is the primary treatment for lipodermatosclerosis, a condition that is often misdiagnosed as cellulitis[148] and for which antibiotic treatment is ineffective.

The mechanism by which compression therapy prevents recurrent cellulitis is not known. The relationship between chronic oedema and cellulitis is considered to be multifactorial[87]: chronic oedema provides a medium for bacterial growth[87]; altered lymphatic function and decreased lymphatic drainage can impair the immune response to pathogens[85,86]; and chronic oedema can impair skin integrity[89], increasing susceptibility to entry of bacteria via the skin[87]. Compression therapy could potentially decrease the risk of cellulitis by lessening oedema, improving immune response and skin integrity, and providing physical protection for the skin. Future studies could further explore the role of these mechanisms in cellulitis associated with chronic oedema of the leg.

A potential source of bias in this trial is the fact that assessors and participants were aware of the trial-group assignments. Although the trial assessors, who were lymphoedema therapists, had no influence on making the diagnosis of cellulitis, medical practitioners external to the trial who diagnosed cellulitis could have been influenced by the participants, who were aware of their trial-group assignments. The trial assessors also requested an early review of trial results because they anecdotally reported outcomes that favored the compression group. With respect to measurement of leg volume, the calibrated perometer was used to mitigate the risk of bias because assessors were aware of the trial-group assignments. Difficulty in applying and removing compression garments is often a barrier to adherence to compression therapy; however, in our trial, 88% of the participants wore their garments 4 or more days per week. This high adherence may have been the result of support from experienced clinicians and may limit generalisability of our findings to other settings in which access to specialist lymphoedema physiotherapists is not available.

Other trial limitations include the short duration of follow-up and possible misdiagnosis of cellulitis by medical practitioners. Although misdiagnosis of cellulitis is common[32], this trial aimed to reflect standard clinical practice, and we accepted the diagnosis of cellulitis as determined by medical practitioners. The point estimates of differences in effect sizes between trial groups are imprecise because of the small size of the trial and because the trial was stopped early with post hoc stopping rules. The time to recurrence of cellulitis was reported by the participants; therefore, the precise time to recurrence may have varied by a few days or longer because the participants' recollection may not have been accurate.

This small, single-centre, unblinded trial showed that compression therapy prevented the recurrence of cellulitis in patients with chronic oedema and a history of two or more previous episodes of cellulitis. Larger and longer trials are necessary in order to determine the effect of compression therapy on the recurrence of cellulitis, especially in settings without access to specialized lymphedema services.

Sample Size and Interim Analysis Calculation (calculated using R 3.6.0):

```
library(gsDesign)

## Loading required package: xtable

## Loading required package: ggplot2

##Control 47% events after 3 years. Exp= 23.5% (50% reduction)
x47<-gsSurv(k=2, timing=c(0.5),lambdaC=log(.53)/-36, hr=0.42, hr0=1, minfu=12, T=42, beta=.2)

## Time to event group sequential design with HR= 0.42
## Equal randomization:       ratio=1
## Asymmetric two-sided group sequential design with
## 80 % power and 2.5 % Type I Error.
## Upper bound spending computations assume
## trial continues if lower bound is crossed.
##
##           ----Lower bounds----  ----Upper bounds-----
##  Analysis N  Z  Nominal p Spend+  Z  Nominal p Spend++
##         1 23 0.41   0.6603 0.0538 2.75   0.0030  0.003
##         2 45 1.98   0.9762 0.1462 1.98   0.0238  0.022
##     Total              0.2000            0.0250
## + lower bound beta spending (under H1):
##  Hwang-Shih-DeCani spending function with gamma = -2.
## ++ alpha spending:
##  Hwang-Shih-DeCani spending function with gamma = -4.
##
## Boundary crossing probabilities and expected sample size
## assume any cross stops the trial
##
## Upper boundary (power or Type I Error)
##          Analysis
```

```
##   Theta     1     2  Total E{N}
##  0.0000 0.0030 0.0209 0.0239 29.7
##  0.4289 0.2335 0.5665 0.8000 38.1
##
## Lower boundary (futility or Type II Error)
##          Analysis
##   Theta     1     2  Total
##  0.0000 0.6603 0.3158 0.9761
##  0.4289 0.0538 0.1462 0.2000
##            T        n  Events HR futility HR efficacy
## IA 1  27.39041 147.3215 22.23255      0.839      0.311
## Final 42.00000 161.3574 44.46510      0.552      0.552
## Accrual rates:
##     Stratum 1
## 0-30     5.38
## Control event rates (H1):
##      Stratum 1
## 0-Inf     0.02
## Censoring rates:
##      Stratum 1
## 0-Inf       0
```

```
summary(x47)
```

```
## [1] "Asymmetric two-sided group sequential design with non-binding futility bound, 2 analyses, time-to-event outcome with sample size 162 and 45 events required, 80 percent power, 2.5 percent (1-sided) Type I error to detect a hazard ratio of 0.42. Enrollment and total study durations are assumed to be 30 and 42 months, respectively. Efficacy bounds derived using a Hwang-Shih-DeCani spending function with gamma = -4. Futility bounds derived using a Hwang-Shih-DeCani spending function with gamma = -2."
```

Data Monitoring Committee Membership

Members:

The data monitoring committee was comprised of three independent academics who had no affiliation with the trial:

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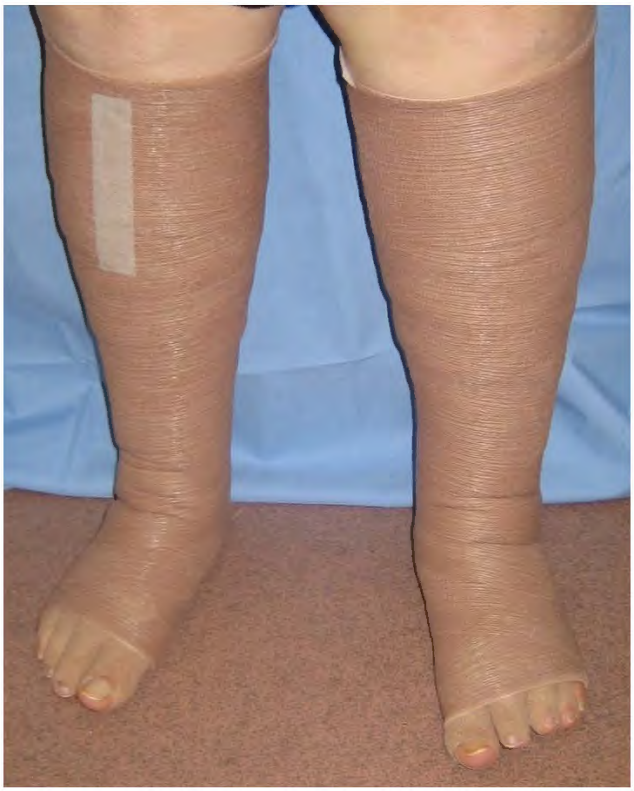

Figure 10: Compression bandaging

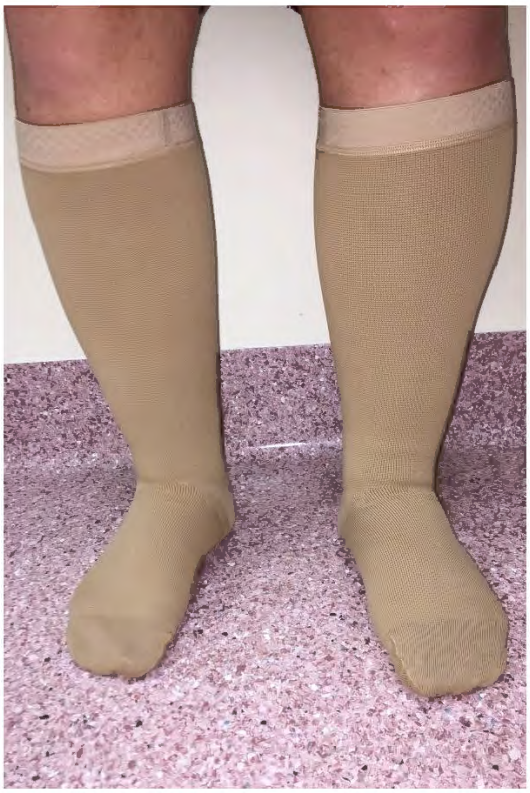

Figure 11: Knee high compression stocking

Figure 12: Compression wraps (foot and lower leg)

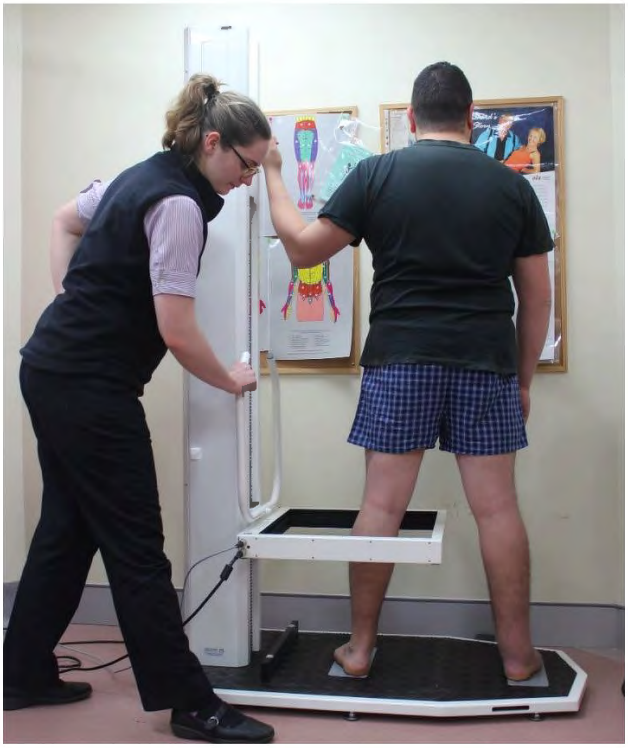

Figure 13: Perometer in use

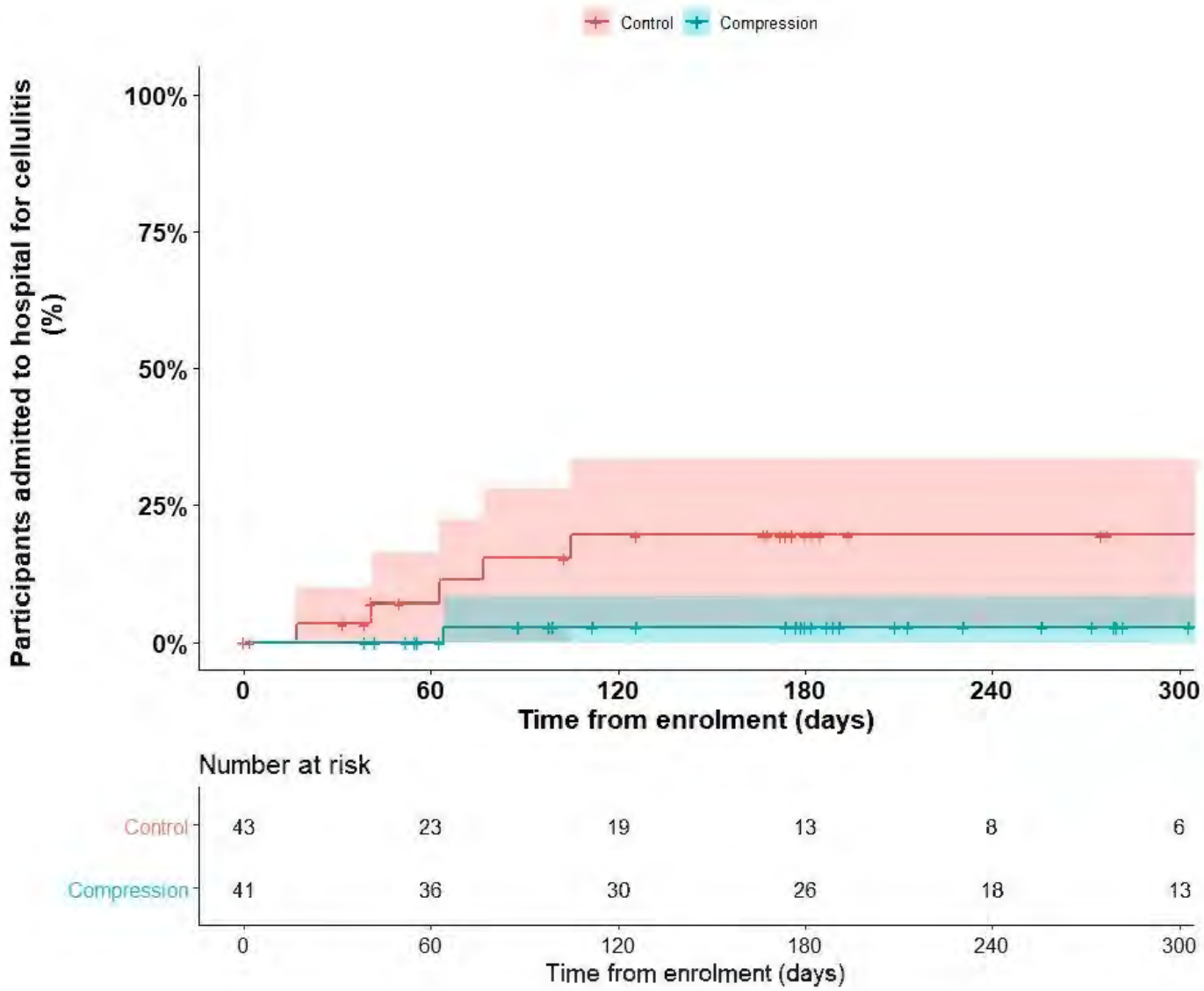

Figure 14: Percentage of participants admitted to hospital for cellulitis over time

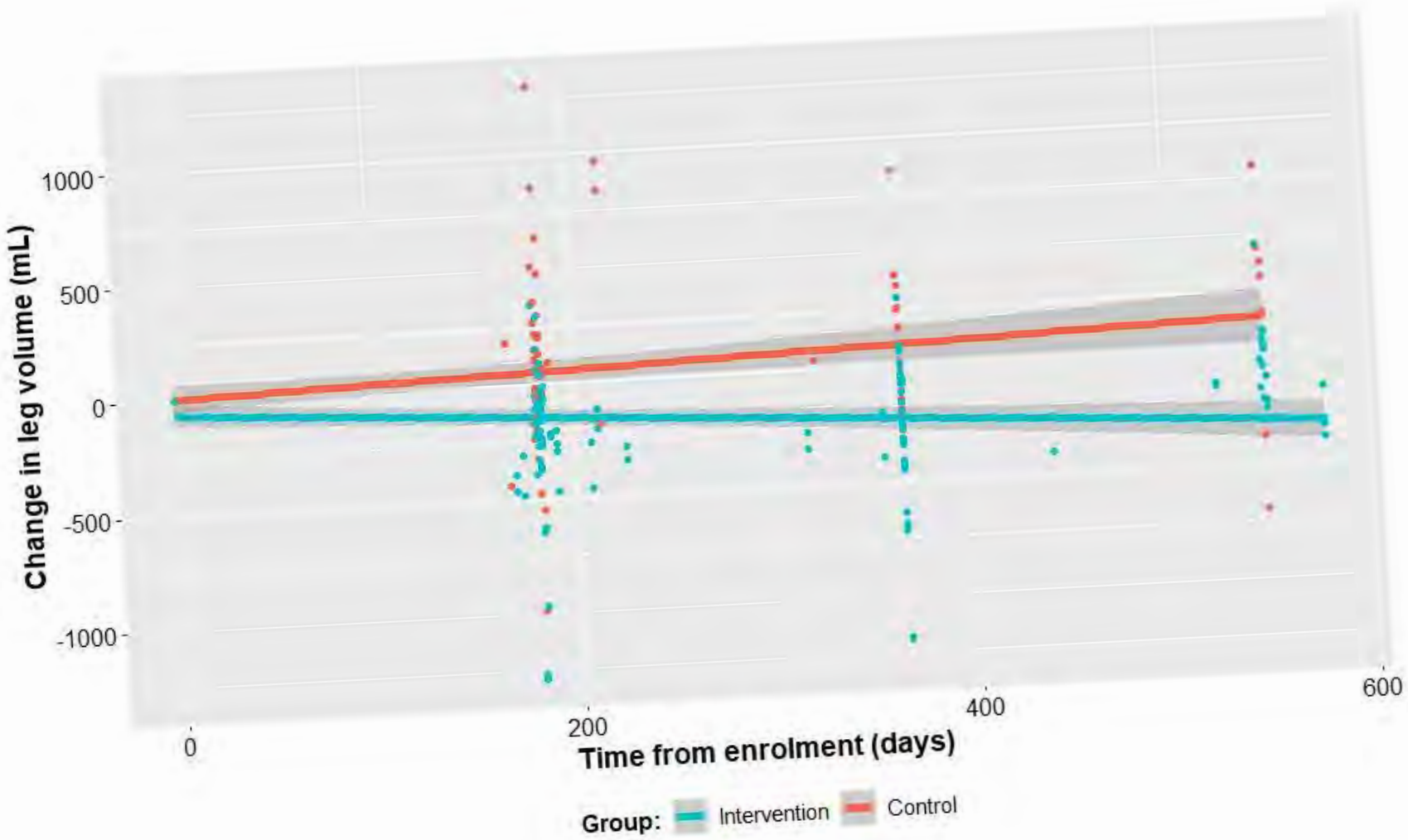

Figure 15: Change in leg volume over time

Table 4: Exploratory analysis of covariates that may contribute risk to cellulitis recurrence.

Covariate	Covariate present: number (%)		Hazard Ratio (95% CI)
	Compression Group (N=41)	Control Group (N=43)	
Baseline Body Mass Index ≥40	18 (44)	26 (60)	0.92 (0.38 - 2.20)
≥3 Episodes of cellulitis in the 2-years prior to trial referral	14 (34)	8 (19)	2.06 (0.77 - 5.56)
Tinea or toe web intertrigo reported or identified during course of the trial	19 (46)	12 (28)	0.70 (0.29 - 1.69)
Wound reported or identified during course of the trial (excluding wounds resulting from cellulitis)	1 (2)	5 (12)	2.61 (0.82 - 8.37)

CHAPTER 4: Paper Three

Compression Therapy is Cost-Saving in the Prevention of Lower Limb Recurrent Cellulitis in Patients with Chronic Oedema: a cost analysis

This chapter has been peer reviewed and published as original research in the journal of Lymphatic Research and Biology (Appendix G):

https://pubmed.ncbi.nlm.nih.gov/35997601/

Webb E, Bissett B, Neeman T, Bowden F, Preston E, Mumford V. Compression Therapy Is Cost-Saving in the Prevention of Lower Limb Recurrent Cellulitis in Patients with Chronic Edema. *Lymphat Res Biol.* Published online 23 Aug 2022. doi: 101089/lrb20220029.

INTRODUCTION

Cellulitis is a common bacterial infection of the skin and subcutaneous tissue. It frequently reoccurs, with up to 47% of patients experiencing another infection within three years[10]. Cellulitis causes considerable financial burden for both patients and health services. Within Australian emergency departments cellulitis is the 4th most common principal diagnosis, and the 3rd most common presentation requiring hospital admission[7]. In 2017-2018, there were 128,129 emergency department presentations[7] and 72,150 hospital admissions[149] for cellulitis, which cost the Australian health system approximately $90-million and $327-million AUD, respectively[47,149]. Although only 7-20% of cellulitis episodes require hospitalisation[9,150], it has been reported that 83% of medical expenditure for cellulitis is related to hospital admissions[9].

Chronic oedema, where swelling persists for three or more months, increases the risk of cellulitis and cellulitis recurrence[5,6,10]. There is a cyclical relationship between cellulitis and chronic oedema, whereby chronic oedema increases the risk of cellulitis, and cellulitis can cause or worsen chronic oedema[13]. An international cross-sectional study of patients with lower limb chronic oedema, observed the lifetime prevalence of cellulitis was 37%, with 16% suffering an episode in the past 12 months[79]. Further, controlled swelling was associated with reduced risk of cellulitis[79]. Two linked clinical trials investigating the impact of prophylactic penicillin on cellulitis recurrence found pre-existing oedema was present in 46% of participants with a history of cellulitis, and 59% of participants with recurrent cellulitis[23,83]. Thus, as both chronic oedema and cellulitis are common comorbid conditions, there is an urgent need to manage both conditions to improve health and relieve financial burden.

Compression therapy is the main modality used to manage chronic oedema. Our recent randomised controlled trial (RCT) demonstrated that for patients with lower limb chronic oedema experiencing recurrent cellulitis, compression therapy reduced the risk of further cellulitis episodes by 77% (hazard ratio, 0.23; 95% CI, 0.09 to 0.59; P=0.002)[151]. The RCT was designed to enrol 164 participants, however it was stopped for efficacy following a planned interim analysis. As such, the trial had a total of 84 participants with a median follow-up time of 186 days instead of the planned 3-years[151].

While we now know compression therapy is effective in preventing cellulitis, there is limited information on the associated costs involved. A retrospective cohort study conducted in Australia during the 2012-2013 financial year found the mean hospital admission cost for an episode of cellulitis was $5196 for

inpatient admissions and $5873 for hospital-in-the-home admissions. However, as patients hospitalised for cellulitis with concurrent oedema have longer admissions[49], hospital costs are likely to be higher in this population. While we have some knowledge of hospital admission costs for cellulitis, information on the broader health service and patient costs relating to cellulitis is scarce. Further, chronic oedema is considered a hidden epidemic, despite being very common, and the expense to the health system and patient are largely unknown. Improved knowledge of these costs is essential to guide policy and resource allocation.

Compression therapy can break the cycle of oedema and cellulitis, but there is no information on the cost-effectiveness of this intervention. As part of the clinical trial assessing the impact of compression therapy on cellulitis recurrence, a costs analysis was undertaken[152] with the aim to describe and compare the cost of a recurrent cellulitis episode and the cost of compression therapy (over 18-months) from both health service and patient perspectives. Further, the total costs arising in the experimental and control groups during the RCT were compared.

METHOD

During the RCT a cost analysis was undertaken to determine and compare the costs of cellulitis and compression therapy in patients with chronic oedema who are experiencing recurrent cellulitis. Cellulitis and compression therapy costs were measured from both health service and patient perspectives. These costs were then applied to the experimental and control RCT groups, allowing comparison of costs.

RCT Methods

The RCT protocol and results have been previously published[11,13] but are summarised briefly here. The primary outcome of the RCT was time to cellulitis recurrence. Following enrolment, participants were randomised to receive either education on the prevention of cellulitis (control group) or the same education plus compression therapy (experimental group)[13]. Trial group assignment was concealed, but after randomisation therapists and participants were not blinded to treatment allocation for ethical and logistical reasons. To replicate standard clinical practice, participants were followed up 6-monthly, with experimental group participants attending extra appointments to complete compression therapy with qualified lymphoedema physiotherapists. Following an episode of recurrent cellulitis, participants in the control group were crossed over to receive compression therapy. The trial was planned to continue for

3-years, or until 45 episodes of cellulitis occurred, and a planned interim analysis with stopping rules was completed after the 23rd episode of cellulitis. Although the trial was stopped early for efficacy, participants were followed up until 18-months post randomisation, allowing the cost of compression therapy to be measured across this time frame.

Participants

The cost-analysis included two subsets of participants from the RCT who were surveyed regarding resource use: one group in relation to their most recent episode of cellulitis (cellulitis group), and the other regarding the use of compression therapy over 18-months (compression group). Participants were excluded from the cellulitis group if their most recent episode of cellulitis was over a year before enrolment in the trial.

Participants met the inclusion criteria for the RCT which included having chronic oedema and a history of two or more episodes of cellulitis in the same leg in the two years prior to trial referral. Exclusion criteria comprised; being less than 18-years of age; being medically unstable; receiving end of life care; having a chronic wound or wound requiring specialist treatment; being unable to tolerate compression; or already wearing effective compression garments regularly.

Outcomes

The primary outcomes of the costs analysis were the cost of an episode of cellulitis, and the cost of compression therapy over 18-months. Costs were categorised as health service or patient expenses. Paper surveys were developed to measure participant resource use and piloted on relevant patients before use in the trial. Participants were also asked to complete the Self-Administered Comorbidity Questionnaire, and to provide demographic information to allow description and comparison of the samples.

The cellulitis group participants were surveyed consecutively following enrolment into the trial. The survey captured resource use relating to their most recent episode of cellulitis, including medical appointment attendances, health service utilisation, LOS in hospital, participant and family time away from work and leisure activities, duration that the participants required assistance with activities of daily living (ADLs), use of antibiotics and pain relief. Medical records were audited at both Australian Capital Territory (ACT) public hospitals to verify the details of reported hospital admissions. Participants' data

were excluded if they reported hospitalisation for cellulitis, but the medical record indicated their admission was primarily for another condition.

The compression group participants were consecutively surveyed during a scheduled follow-up appointment after 18-months of compression therapy. The survey obtained information regarding participant and family time away from work and assistance provided for ADLs that were related to their compression therapy. Medical records were audited to determine the cost of prescribed compression garments, the number of appointments attended, and the number of compression bandages applied.

Resource Costs

Australian national reference costs for the 2017/2018 financial year were applied to all resource items. Medications were costed using the Australian Pharmaceutical Benefit Scheme[153] (PBS) with the assumption that pension age participants (≥66years) paid the concession price with the PBS funding the surplus[154,155]. Health Information Services at the two local hospitals individually costed reported hospital admissions using the Australian Refined Diagnosis Related Groups[156] (AR-DRGs). For three reported hospital admissions that occurred outside of the ACT, admission costs were calculated using a standard algorithm that incorporates the 2017/2018 National Efficient Price, the average price weights for the two cellulitis AR-DRGs (J64A: Cellulitis, Major Complexity; and J64B: Cellulitis, Minor Complexity), and the hospital LOS. Emergency department presentations were costed based on the National Hospital Cost Data Collection Cost Report[47]. General practitioner appointment costs were based on the Medicare Benefits Scheme (MBS) prices[157], while hospital outpatient, pathology and allied health appointments were based on the Independent Hospital Pricing Authorities' (IHPA) Tier 2 Non-Admitted Services Classification prices[149]. The national average patient co-contribution was used for general practitioner and outpatient appointments[158]. Time off work was priced on the average Australian weekly earnings reported by the Australian Bureau of Statistics[159]. The National Disability Insurance Scheme price guide[160] was used to assign costs for assistance with activities of daily living (ADLs). For participants reporting they required both assistance with ADLs and family to take time away from work, family time off work was subtracted from the number of days ADL assistance was provided to avoid doubling up on costs. Travel for all appointments was assumed to be a 10 km round trip with the price per km based on the Australian Tax Office's work-related car expenses[161]. The compression bandage and compression garment costs were recorded for each participant. A full list of the resource costs can be found in Table 9 in the Cost Analysis Supplementary Appendix.

The health service perspective included all costs related to government funded health services, being hospital admissions, emergency department presentations, public outpatient services, and MBS and PBS rebates for appointments and medications. The patient perspective included all costs incurred by the participant and their family, including costs relating to appointments, travel, medications, assistance with ADLs, and the inability to work. Leisure time missed was recorded but not priced. Table 6 and Table 7 show which costs were assigned to either the health service perspective or the patient perspective.

Descriptive Analysis

Resource use and associated costs were reported as mean and standard deviation. Costs were calculated and presented using Australian reference costs for the 2017-2018 financial year, with high level costs being translated into US dollars (USD) using the average conversion rate for that financial year[162] to allow easier international comparison. Although some trial data collection and outcomes occurred before and after this time frame, due to the limited follow-up duration of the trial, discounting was considered redundant. Mean total costs for compression therapy were given over 18-months, as well as over 0-6 and 7-18-months to show how treatment costs change over time. Mean total costs for cellulitis were also presented separately for hospitalised and non-hospitalised participants due to the large difference in resource use for these participants. The sensitivity analysis assessed the impact of outlier values. Winsorisation was used, with all variable outliers over 3.29 standard deviations from the mean being replaced with the closest non-outlier value[163]. All analysis were performed using R software (version 3.6.0).

Application of measured costs to the RCT

The outcomes from the costs analysis were used to calculate the total cost of the intervention and the cellulitis episodes for each trial group during the RCT. For both the RCT groups (experimental and control), the intervention cost was calculated for each participant based on their individual follow-up time frame, prior to being censored for an episode of cellulitis or the trial's cessation. For the experimental group participants, their follow-up duration within the initial 6-month period, and the subsequent 7-18 month period were costed separately based on mean compression therapy costs for these periods, before being summated. For the control group, the intervention cost was based on the number of appointments attended for education on cellulitis prevention. Hospitalised and non-hospitalised episodes of cellulitis occurring during the trial were costed separately. Due to the large

discrepancy in follow-up time between the two trial groups arising from more control group participants being censored following cellulitis episodes, the trial costs were presented per participant per year to allow direct comparison. Due the small sample size and skewed data, non-parametric bootstrap sampling with 1000 samples was used to calculate the mean annual cost per participant for each trial group, and subsequently the mean intergroup difference and 95% confidence intervals.

RESULTS

Participant Characteristics

Data were obtained on the cost of compression therapy for 40 participants (compression group) and the cost of an episode of cellulitis for 43 participants (cellulitis group), with 18 participants contributing data to both groups. The majority of participants surveyed regarding compression therapy costs were those randomised to the experimental group, however three control group participants that completed 18-months of compression therapy following cross-over were also surveyed. Of participants surveyed on the cost of cellulitis, 21 were from the experimental group, and 22 were from the control group. The patient demographics of the compression and cellulitis groups in the cost analysis are shown in Table 5, and are similar to those of the RCT participants[151]. For both groups, the mean number of cellulitis episodes per leg in the two years before referral to the trial was two, the mean Self-Administered Comorbidity Questionnaire Score was 9 (out of a maximum score of 45), and obesity was the most common reported factor contributing to chronic oedema. For the compression group, the mean age and BMI were 66 (SD: 12.9) and 39 (SD: 9.9), respectively, and chronic oedema was bilateral in 78% of participants. The cellulitis group's mean age and BMI were 64 (SD: 14) and 42 (SD: 9.6), and 81% had bilateral chronic oedema.

Table 5: Baseline characteristics of the participants

Characteristic	Compression (N=40)	Cellulitis (N=43)
Female sex - no. (%)	19 (48)	17 (40)
Age: Mean (SD)	66 (12.9)	64 (14)
Median (IQR)	69 (55-75)	65 (52-73)
Pension age (≥66yrs) - no. (%)	23 (58%)	21 (48%)
Spousal status (single or de facto)		
Defacto - no. (%)	28 (70)	28 (65)
Body mass index: Mean (SD)	39 (9.9)	42 (9.6)
Median (IQR)	39 (31-45)	41 (34-48)
Self-administered Comorbidity Questionnaire:		
Mean (SD)	9 (4.4)	9 (5.2)
Median (IQR)	9 (5-11)	9 (5-12)
Chronic oedema: Bilateral – no. (%)	31 (78)	35 (81)
Duration of oedema – no. (%)		
1-5yrs	17 (43)	13 (30)
>5yrs	23 (58)	30 (70)
Episodes of cellulitis per leg in 2-yrs before trial referral: Mean (SD)	2 (1.4)	2 (1.3)
Median (IQR)	2 (0-2)	2 (0-2)
Hospital admission for cellulitis in 2yrs before trial referral: Mean (SD)	1 (0.9)	1 (0.7)
Median (IQR)	1 (0-1)	1 (0.5-1)
Prophylactic antibiotics – no. (%)	2 (5)	2 (5)
Factors contributing to chronic oedema- no. (%)		
Obesity	26 (65)	30 (70)
Surgery/trauma	14 (35)	13 (30)
Venous Hypertension	11 (28)	14 (33)
Immobility	4 (10)	4 (9)
Primary Lymphoedema	3 (8)	3 (7)
Cancer	0 (0)	0 (0)
Other	6 (15)	5 (12)
Comorbidities- no. (%)		
Tinea pedis	14 (35)	15 (35)
Diabetes	10 (25)	14 (33)
Chronic venous insufficiency	10 (25)	13 (30)
Congestive heart failure	7 (18)	11 (26)

IQR, interquartile range; SD, standard deviation.

Cellulitis Group Costs

The resource use and costs associated with an episode of cellulitis are shown in Table 6. Of the 43 cellulitis group participants, 27 (63%) presented to the emergency department, 24 (56%) were admitted to hospital, 41 (95%) had one or more general practitioner appointments, 23 (53%) required non-prescription pain relief and 15 (35%) required prescription pain relief for their most recent episode of cellulitis. The total mean cost for a non-hospitalised episode of cellulitis was $1,826, whereas the mean cost for a hospitalised episode was 7.4 times higher, being $13,567.

Health Service Costs

The mean cost to health services for an episode of cellulitis was $5,287 ($4,289 USD). However, on average, cellulitis episodes requiring hospitalisation cost $9,071, which is almost 18 times higher than non-hospitalised episodes, which cost an average of $506. The highest cellulitis related costs were for hospital utilisation, with emergency department presentations costing a mean of $640 per participant and the average hospital admission costing $7,057 per hospitalised participant. General practitioner and other healthcare appointments were the next biggest contributor to cost, with antibiotics and pain-relief medications adding comparatively minimal expense. Resource use and costs were generally positively skewed (Table 10 in the Cost Analysis Supplementary Appendix), with a few participants with substantially higher resource utilisation increasing mean values. For example, 22 of 24 hospital admissions cost between $3,300 and $7,500, however two admissions costing over $24,000 resulted in the mean and median costs for hospitalisation being $7,057 and $5,831.

Patient Costs

The mean patient cost for an episode of cellulitis was $3,092 ($2,509 USD), with hospitalised patient costs being $4,496, compared to $1,320 for non-hospitalised patients. The highest costs were for patient and family time off work and assistance with ADLs, and general practitioner and other healthcare appointments were the next biggest contributor. Patient and family time off work, assistance with ADLs, and the overall combined resource costs were positively skewed (Table 10 in the Cost Analysis Supplementary Appendix). A total of 17 (40%) participants were employed, with 13 reporting they required time off work. Those who were employed took a mean of 15 days off work (range 0-45 days). Further, 26 (60%) participants needed assistance with ADLs or family to take time off work.

Table 6: Measured resource use and cost for recurrent cellulitis episodes

Measured Resources (per episode of cellulitis)	Cellulitis Episodes n=43			
	Number	**Health Service Costs ($)**	**Patient Costs ($)**	**Total Cost ($)**
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Hospital utilisation				
Emergency Department Presentations	1 (0.6)	640 (516)	-	640 (516)
Hospital LOS for cellulitis episodes requiring admission (days)[a]	8 (7.9)	7,057 (5,883)	-	7,057 (5,883)
Healthcare appointments				
General practitioner	3 (3.1)	105 (116)	106 (117)	211 (233)
Other	2 (4.9)	614 (1,208)	66 (144)	680 (1,296)
Antibiotics (prescriptions purchased)	2 (1.3)	11 (15)	34 (29)	46 (27)
Pain relief (days used)				
Prescription	5 (8.6)	8 (22)	20 (47)	28 (55)
Non-prescription	5 (8.4)	-	4 (7)	4 (7)
Travel for healthcare (number of trips)	7 (6.7)	-	43 (44)	43 (44)
Assistance with ADLs[b] (days)	8 (11.3)	-	644 (991)	644 (991)
Time off work (days)				
Patient	6 (11.2)	-	1,945 (3,715)	1,945 (3,715)
Family	1 (2.3)	-	238 (758)	238 (758)
Leisure time missed (days)				
Patient	14 (18.7)	-	-	-
Family	4 (8.9)	-	-	-
Combined resources per episode of cellulitis:				
All episodes (n=43)	-	5,287(6,344)	3,092 (4,483)	8,379 (8,442)
Hospitalised episodes (n= 24)	-	9,071(6,254)	4,496 (5,493)	13,567 (7,944)
Non-hospitalised episodes (n=19)	-	506 (842)	1,320 (1,551)	1,826 (2,106)

[a]Length of stay (LOS) calculations only included patients who were hospitalised (n=24).

[b]For ADL assistance calculations, reported family time away from work was subtracted from the reported number of days that ADL assistance was required to avoid doubling up on costs.

All costs are in 2017-2018 Australian dollars. The average exchange rate for the 2017-2018 financial year: $1 AUD= $0.8113 USD[162].

Compression Group Costs

The mean resource use and costs for compression therapy are shown in Table 7. Of the 40 compression group participants, 23 (58%) received compression bandaging to reduce their oedema before the provision of compression garments. These participants attended extra appointments, usually early on in their treatment course. The total mean cost for compression therapy over 18-months was $2,326 ($1,887 USD), with $1,229 attributed to the first 6-months and $1,117 to the following 12-months. These figures indicate compression therapy is more expensive during the initial intensive treatment phase, and after 6-months ongoing maintenance costs for compression therapy are reduced for both the health service and the patient.

Health Service Costs

Health service costs for compression therapy are greatest in the first 6-months of treatment, after which ongoing maintenance costs were 57% lower. The mean health service cost of compression therapy was $1,905 ($1,546 USD) per participant over 18-months, with $1,038 of that expenditure occurring within the first 6-months and $887 occurring in the following 12-months. The greatest expense was for lymphoedema service appointments, being $1045 over 18-months, however, appointment costs reduced substantially after the initial 6-month period. Compression garments were the second biggest expense, costing $795 per participant over 18-months. For the 65% of participants for whom compression garments were government-funded, the mean cost of compression garments was 1.5 times higher, being $1223 per participant. Participants with unilateral oedema cost 36% less than those with bilateral oedema.

Patient Costs

The mean patient cost for compression therapy was $421 ($342 USD) per participant over 18-months, with the first 6-months costing $191 and the following 12-months costing $230. Although only 35% of compression garments were patient-funded, they were still the greatest contributor to the overall cost for participants. The mean patient cost for compression garments was $242, with $118 being spent in the first 6-months and $124 in the following 12-months. The mean patient cost for compression garments was much higher among self-funding participants, being $691 over 18-months. Assistance with ADLs and time off work costs were positively skewed, with the mean sitting above the interquartile range (

Table 11 in the Cost Analysis Supplementary Appendix). Only four participants required up to one day off work, and two participants required assistance with ADLs for compression therapy. Of these two participants, one required 10-minutes of assistance per day over the 18-month period to apply and remove compression garments, which substantially positively skewed the total patient expenditure, particularly for those with unilateral oedema

Table 7: Measured resource use and cost for compression therapy over 18-months

Measured Resources (per participant)	Compression Therapy n=40			
	Number Mean (SD)	**Health Service Costs ($)** Mean (SD)	**Patient Costs ($)** Mean (SD)	**Total Cost ($)** Mean (SD)
Garment sets purchased				
0-6 months	2 (0.2)	292 (259)	118 (189)	410 (180)
7-18 months	3 (1.2)	503 (543)	124 (205)	627 (456)
Compression bandages applied				
0-6 months	3 (3.1)	59 (73)	-	59 (73)
7-18 months	0 (0.8)	6 (19)	-	6 (19)
Lymphedema service appointments				
0-6 months	4 (2.1)	686 (325)	-	686 (325)
7-18 months	2 (1.4)	378 (223)	-	378 (223)
Travel for healthcare (number of trips)				
0-6 months	4 (2.1)	-	29 (14)	29 (14)
7-18 months	2 (1.4)	-	16 (9)	16 (9)
Assistance with ADLs[a] (hours)				
0-6 months	1 (4.8)	-	37 (219)	37 (219)
7-18 months	2 (9.6)	-	74 (437)	74 (437)
Time off work (days)				
Patient	0 (0.2)	-	23 (78)	23 (78)
Family	0 (0)	-	0 (0)	0 (0)
Leisure time missed (days)				
Patient	0 (1.4)	-	-	-
Family	0 (0.1)	-	-	-
Combined resources per participant				
All participants (n=40)				
0-18 months	-	1,905 (1,097)	421 (825)	2,326 (1,169)
0-6 months	-	1,038 (539)	191 (320)	1,229 (582)
7-18 months	-	887 (708)	230 (515)	1,117 (737)
Participants with unilateral oedema (n=9)				
0-18 months	-	1,322 (592)	740 (1,548)	2,062 (1,566)
Participants with bilateral oedema (n=31)				
0-18 months	-	2,074 (1,158)	328 (455)	2,403 (1,046)

[a]For ADL assistance calculations, reported family time away from work was subtracted from the reported number of days that ADL assistance was required to avoid doubling up on costs

All costs are in 2017-2018 Australian dollars. The average exchange rate for the 2017-2018 financial year: $1 AUD= $0.8113 USD[162].

Sensitivity Analysis

After windsorising all identified outlier values, no mean total health service costs changed by more than 5%. For an episode of cellulitis, the average patient cost among hospitalised participants changed from $4,496 to $4,250 (5% change). For compression therapy, the patient cost over 18-months reduced from $421 to $317 (25% change). This change was particularly large for participants with unilateral oedema, where the average patient cost for compression therapy over 18-months reduced from $740 to $315 (57% change). This reduction in the cost of compression therapy for patients was related to one participant with unilateral oedema who required high levels of assistance with ADLs (daily assistance for garment application and removal).

RCT Outcomes and Costs

RCT Outcomes

During the RCT, 23 episodes of cellulitis occurred before the interim analysis and subsequent stopping of the trial for efficacy. Six episodes of cellulitis occurred in the experimental group, and 17 occurred in the control group, giving an incidence rate ratio of 0.21 (95% CI: 0.08 to 0.55, P=0.0005). Of those participants who experienced cellulitis, three and six required hospital admission in the experimental and control groups, respectively.

Measured Costs Applied to the RCT:

The mean annual costs per participant for both the experimental and control groups are shown in Table 8. The mean annual health service cost per person was $3,616 in the experimental group and $14,527 in the control group, giving a mean intergroup difference of $10,963 (95% CI, $1,000 to $24,590). The mean yearly patient costs were $1,356 and $11,856 per person in the experimental and control groups, respectively, providing a mean intergroup difference of $10,521 (95% CI, $1,806 to $24,933). The mean total (health service and patient) annual cost per person was $4,972 ($4,034 USD) for the experimental group and $26,382 ($21,404 USD) for the control group, giving an intergroup difference of $21,483 (95% CI, $3,136 to $48,176). Therefore, the mean total expenditure per participant was 81% lower in the experimental group. This reflects the higher incidence and costs related to cellulitis management in the control group (90% of total costs) versus the experimental group (48% of total costs).

Table 8: Measured costs applied to the RCT

Perspective	Mean annual cost per participant ($)		Mean intergroup difference ($) (95% CI)
	Experimental Group n=41	Control Group n=43	
Health Service	3,616	14,527	10,963 (1,000 to 24,590)
Patient	1,356	11,856	10,521 (1,806 to 24,933)
Total (Health + Patient)	4,972	26,382	21,483 (3,136 to 48,176)

The mean annual cost per participant, and the mean intergroup difference and 95% CI were calculated using non-parametric bootstrap sampling with 1000 samples.

All costs are in 2017-2018 Australian dollars. The average exchange rate for the 2017-2018 financial year: $1 AUD= $0.8113 USD[162].

DISCUSSION

This is the first analysis to demonstrate that compression therapy is a cost-saving treatment for preventing cellulitis in patients with recurrent cellulitis and co-morbid lower limb chronic oedema. While this trial assessed costs in Australian currency (AUD), the cost-savings presented may be proportionate in other countries with similar health systems. Daily costs incurred during the trial were 81% lower in the experimental group than in the control group. Compared to the control group, health service and patient specific costs in the experimental group were 75% and 89% lower, respectively. These results provide strong justification for healthcare systems to invest in compression therapy for these patients, as the benefits are clear from both health and economic perspectives.

During the RCT, total expenditure on cellulitis was calculated to be $147,648, of which 83% related to hospitalised participants. The reported mean LOS for cellulitis-related hospitalisations varies from 4.7 to 12.1[9,150]. The mean and median hospital LOS of 8 and 6.5 observed in the cellulitis group are on the higher end of reported Australian statistics[48,149], however, an above-average LOS in this population was expected as research has shown oedema is a risk factor for increased LOS for cellulitis-related admissions[49]. Additionally, hospital admissions have been observed to be longer for recurrent versus

primary episodes of cellulitis[35]. The increased LOS found in this population, and the high expenditure related to hospitalisation, highlights the importance of preventing cellulitis infections in this patient group.

Total expenditure on compression therapy during the RCT was $50,551 across 41 participants, with health services funding 84% and patients funding the remaining 16%. Government funding schemes differ between countries, and therefore the proportion of compression therapy expenditure funded by health services may also vary. Health service and patient costs for compression therapy were substantially higher in the first 6-months compared to the following 12-months. This was expected as initiating compression therapy involves multiple appointments for education, and for measurement and fitting of compression garments. Further, some patients also require a series of compression bandages to reduce limb volume before optimal measurement and fit of compression garments. Although these interventions may be required on an ongoing basis to manage chronic oedema, the frequency and consequently cost are usually much lower after the initial intensive treatment phase. After the initial 6-month period, the measured 12-month cost of compression therapy per patient, being $887 and $230 from health service and patient perspectives respectively, may be indicative of ongoing annual costs. Thus, provision of compression therapy has high upfront costs, but ongoing maintenance costs appear to be lower.

In addition to preventing cellulitis, compression therapy provides many other health benefits for patients with chronic oedema or venous disease. Compression therapy is a primary treatment modality for both chronic oedema[55] and chronic venous insufficiency[164], a common condition[165] and a known cause of chronic oedema[50]. Compression therapy has been found to increase the rate of healing for venous ulcers[139], reduce the rate the venous ulcer recurrence[146], reduce limb volume[151], improve skin condition[55], improve QOL for patients with chronic venous disease[166], and may prevent post-thrombotic syndrome[167]. Further, it is used to manage conditions which mimic cellulitis, such as lipodermatosclerosis[148]. Therefore, the health and financial benefits of compression therapy for patients with chronic oedema and cellulitis may be greater than that found in our trial. Thus, we believe our analysis presents a conservative perspective on the cost-savings of compression therapy in these patients.

A limitation of this trial was the early cessation for efficacy, as this limited the sample size and duration of the follow-up period. Although outliers were identified, they were accurate, and we believe they would occur in standard practice. Therefore, although we assessed their impact in the sensitivity analysis, their inclusion in the primary analysis is appropriate.

This cost-analysis indicates that compression therapy is cost-saving from both a patient and health service perspective for patients with chronic oedema and recurrent cellulitis. The health and economic benefits demonstrated by this research provide clinicians, health services and policy makers with strong justification to support the funding of compression therapy in the prevention of lower limb recurrent cellulitis. Further research with more participants and longer follow-up duration will allow for a robust analysis of its longer-term cost-effectiveness.

Table 9: Resources and their cost during the 2017-2018 financial year

Resource	Cost to Health	Cost to Patient	Source	Explanation
Emergency Department Presentation (per presentation)			Independent Hospital Pricing Authority[47]	
- Non-admitted patient	$561	NA		
- Admitted patient	$1030	NA		
Hospital Admission	Variable	NA	Independent Hospital Pricing Authority[149]	Health Information Services from both public ACT hospitals individually costed admissions based on the Australian Refined Diagnosis Related Groups (AR-DRGs). For three reported hospital admissions that occurred outside of the ACT, admission costs were calculated using an algorithm provided by Health Information Services that includes the 2017/2018 National Efficient Price, the average price weights for the two cellulitis AR-DRGs (J64A: Cellulitis, Major Complexity; and J64B: Cellulitis, Minor Complexity), and the hospital length of stay.
General Practitioner Appointments (per appointment)	$37.05	$37.39	Medicare Benefits Schedule[157,158]	The Medicare Benefits Schedule shows the cost of general practitioner appointments (Item 23: General Practitioner attendances to which no other item applies). Annual Medicare statistics provide the national average patient co-contribution for general practitioner appointments.
Outpatient Appointments (per appointment)			Independent Hospital Pricing Authority[149] and Medicare Benefits Schedule [158]	Independent Hospital Pricing Authorities' (IHPA) Tier 2 Non-Admitted Services Classification price[149] lists the costs for outpatient appointments. Annual Medicare statistics provide the national average patient co-contribution for appointments.
- Community nursing	$198	$4.43		
- Pathology	$210	$24.54		
- Rehabilitation	$255	$46.11		
- Allied Health	$162	$46.11		
- Hospital Outpatient (Infectious Diseases)	$699	$79.04		
- Hospital Outpatient (Obstetrics)	$251	$79.04		

Lymphedema Service Appointments (per appointment)	$156	NA	Independent Hospital Pricing Authority[149]	Independent Hospital Pricing Authorities' (IHPA) Tier 2 Non-Admitted Services Classification price for physiotherapy appointments.
Compression bandages (per bandage)	$23.6	NA	Hospital records	Company price paid by the hospital.
Compression Garments	Variable	Variable	Participant medical record and company price lists	The cost of compression garments was determined for each participant by auditing their medical record for quotes and invoices. Company price lists were used to ascertain costs if quotes or invoices were not retained. The cost of purchased garments, including the value of the sponsored garments, was assigned to the participant if they were self-funding, or to the health system if they were eligible for and received funding from government schemes (e.g. ENABLE for NSW residents or the ACT equipment scheme for ACT residents).
Time off work (per day)	NA	$330.6	Australian Bureau of Statistics[159]	Time off work for the participant or their family was priced on the average Australian weekly earnings reported by the Australian Bureau of Statistics.
Assistance with Activities of Daily Living (per hour)	NA	$45.54	National Disability Insurance Scheme[160]	The price is based on the hourly rate that the NDIS price guide recommends for provision of 'assistance with self-care activities during daytime weekdays' for people with 'standard needs'. For participants who reported requiring assistance with activities of daily living, it was assumed participants required 2hrs of assistance per day when related to a cellulitis infection, and 1hr per day when related to oedema management, unless the patient specified the precise time.
Travel for appointments (per trip)	NA	$6.60	Australian Taxation Office[161]	Travel for all appointments was assumed to be a 10km round trip with the price per km based on the Australian Tax Office's work-related car expenses.

Antibiotics (price per script) - Participants <66years - Participants ≥66years	 $23.96 $6.40	 NA $10.25	Pharmaceutical Benefits Scheme and Electronic Therapeutic Guidelines[153,154,168]	Medications were costed using the Pharmaceutical Benefit Schedule with the assumption that participants under the pension age (<66years) paid the general patient charge, while those meeting the pension age (≥66years) paid the concession price of $6.40 with the PBS funding the surplus. Antibiotic price was based on the average price for flucloxacillin, phenoxymethylpenicillin and cefalexin[20,168].
Non-prescription pain relief (per day)	$0.87		Pharmaceutical Benefits Scheme and Electronic Therapeutic Guidelines[153]	Average cost for ibuprofen (400mg 3x per day) and paracetamol (1000mg 4x per day).
Prescription pain relief	Variable	Variable	Pharmaceutical Benefits Scheme[153]	Medications were costed using the Pharmaceutical Benefit Schedule with the assumption that participants under the pension age (<66years) paid the general patient charge, while those meeting the pension age (≥66years) paid the concession price of $6.40 with the PBS funding the surplus. Prices were calculated per patient based on the number of days pain relief was used, with the dose estimated based on pharmacist advice. Participants who reported using prescription pain relief but did not specify the type were assumed to be using oxycodone as it was the most reported prescription medication.

Table 10: Measured resource use and cost for recurrent cellulitis episodes

Measured Resources (per episode of cellulitis)	Cellulitis Episodes n=43							
	Number		Health Service Costs ($)		Patient Costs ($)		Total Cost ($)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Hospital utilisation								
- Emergency Department Presentations	1 (0.6)	0 (0-1)	640 (516)	1,030 (0-1,030)	-	-	640 (516)	1,030 (0-1,030)
- Hospital LOS for cellulitis episodes requiring admission (days) [a]	8 (7.9)	6.5 (3.8-10.2)	7,057 (5,883)	5,831 (3,386-7,371)	-	-	7,057 (5,883)	5,831 (3,386-7,371)
Healthcare appointments								
-General practitioner	3 (3.1)	2 (1-3)	105 (116)	74 (37-111)	106 (117)	75 (37-112)	211 (233)	149 (74-223)
-Other	2 (4.9)	0 (0-2)	614 (1,208)	0 (0-544)	66 (144)	0 (0-79)	680 (1,296)	0 (0-609)
Antibiotics (prescriptions purchased)	2 (1.3)	2 (1-3)	11 (15)	0 (0-21)	34 (29)	24 (13-48)	46 (27)	48 (24-67)
Pain relief (days used)								
-Prescription	5 (8.6)	0 (0-4.5)	8 (22)	0 (0-0)	20 (47)	0 (0-20)	28 (55)	0 (0-33)
-Non-prescription	5 (8.4)	0 (0-8.5)	-	-	4 (7)	0 (0-7)	4 (7)	0 (0-7)
Travel for healthcare (number of trips)	7 (6.7)	5 (3-7)	-	-	43 (44)	33 (20-46)	43 (44)	33 (20-46)
Assistance with ADLs* (days)	8 (11.3)	1 (0-13)	-	-	644 (991)	91 (0-1,002)	644 (991)	91 (0-1,002)
Time off work (days)								
-Patient	6 (11.2)	0 (0-7)	-	-	1,945 (3,715)	0 (0-2,314)	1,945 (3,715)	0 (0-2,314)
-Family	1 (2.3)	0 (0-0)	-	-	238 (758)	0 (0-0)	238 (758)	0 (0-0)
Leisure time missed (days)								
-Patient	14 (18.7)	10 (0-20.5)	-	-	-	-	-	-
-Family	4 (8.9)	0 (0-2)	-	-	-	-	-	-
Combined resources per episode of cellulitis:								
-All episodes (n=43)	-	-	5,287(6,344)	4,439 (206-8,117)	3,092 (4,483)	1,087(151-3,603)	8,379 (8,442)	7,134 (1,434-11,897)
-Hospitalised episodes (n= 24)	-	-	9,071(6,254)	7,600 (5,601-8,574)	4,496 (5,493)	1,317 (263-7,998)	13,567 (7,944)	10,621 (8,428-17,905)
-Non-hospitalised episodes (n=19)	-	-	506 (842)	142 (74.1-533)	1,320 (1,551)	512 (136-2,696)	1,826 (2,106)	883 (210-2,887)

[a]Length of stay (LOS) calculations only included patients who were hospitalised (n=24).

[b]For ADL assistance calculations, reported family time away from work was subtracted from the reported number of days that ADL assistance was required to avoid doubling up on costs.

All costs are in 2017-2018 Australian dollars. The average exchange rate for the 2017-2018 financial year: $1 AUD= $0.8113 USD[162].

Table 11: Measured resource use and cost for compression therapy over 18-months

Measured Resources (per participant)	Compression Therapy n=40							
	Number		Health Service Costs ($)		Patient Costs ($)		Total Cost ($)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Garment sets purchased								
• 0-18 months	5 (1.2)	5 (4-6)	795 (767)	619 (0-1,560)	242 (383)	0 (0-459)	1,037 (584)	843 (552-1,560)
• 0-6 months	2 (0.2)	2 (2-2)	292 (259)	290 (0-586)	118 (189)	0 (0-205)	410 (180)	346 (290-593)
• 7-18 months	3 (1.2)	3 (2-4)	503 (543)	304 (0-1,013)	124 (205)	0 (0-251)	627 (456)	501 (301-1,013)
Compression bandages applied								
• 0-18 months	3 (3.5)	2 (0-4)	65 (83)	47 (0-94)	-	-	65 (83)	47 (0-94)
• 0-6 months	3 (3.1)	2 (0-4)	59 (73)	47 (0-94)	-	-	59 (73)	47 (0-94)
• 7-18 months	0 (0.8)	0 (0-0)	6 (19)	0 (0-0)	-	-	6 (19)	0 (0-0)
Lymphedema service appointments								
• 0-18 months	7 (2.8)	6 (5-8)	1,045 (432)	939 (780-1,248)	-	-	1,045 (432)	939 (780-1,248)
• 0-6 months	4 (2.1)	4 (3-6)	686 (325)	624 (468-936)	-	-	686 (325)	624 (468-936)
• 7-18 months	2 (1.4)	2 (2-3)	378 (223)	312 (312-468)	-	-	378 (223)	312 (312-468)
Travel for healthcare (number of trips)								
• 0-18 months	7 (2.8)	6 (5-8)	-	-	44 (18)	40 (33-53)	44 (18)	40 (33-53)
• 0-6 months	4 (2.1)	4 (3-6)	-	-	29 (14)	26 (20-40)	29 (14)	26 (20-40)
• 7-18 months	2 (1.4)	2 (2-3)	-	-	16 (9)	13 (13-20)	16 (9)	13 (13-20)
Assistance with ADLs[a] (hours)								
• 0-18 months	2 (14.4)	0 (0-0)	-	-	112 (656)	0 (0-0)	112 (656)	0 (0-0)
• 0-6 months	1 (4.8)	0 (0-0)	-	-	37 (219)	0 (0-0)	37 (219)	0 (0-0)
• 7-18 months	2 (9.6)	0 (0-0)	-	-	74 (437)	0 (0-0)	74 (437)	0 (0-0)
Time off work (days)								
• Patient	0 (0.2)	0 (0-0)	-	-	23 (78)	0 (0-0)	23 (78)	0 (0-0)
• Family	0 (0)	0 (0-0)	-	-	0.0	0 (0-0)	0.0	0 (0-0)
Leisure time missed (days)								
• Patient	0 (1.4)	0 (0-0)	-	-	-	-	-	-
• Family	0 (0.1)	0 (0-0)	-	-	-	-	-	-
Combined resource per participant								
All participants (n=40)								
• 0-18 months	-	-	1,905 (1,097)	1,682 (936-2,509)	421 (825)	69 (40-483)	2,326 (1,169)	2,190 (1,492-2,890)
• 0-6 months	-	-	1,038 (539)	954 (642-1,285)	191 (320)	46 (26-236)	1,229 (582)	1,094 (883-1,555)
• 7-18 months	-	-	887 (708)	616 (312-1,354)	230 (515)	23 (13-264)	1,117 (737)	923 (625-1,447)
Participants with unilateral oedema (n=9)								
• 0-18 months	-	-	1,322 (592)	1,452 (624-1,695)	740 (1,548)	53 (46-481)	2,062 (1,566)	1,561(1,294-1,810)
• 0-6 months	-	-	811 (405)	983 (312-1,114)	282 (554)	40 (33-165)	1,093 (689)	1,010 (638-1,173)
• 7-18 months	-	-	512 (227)	468 (312-624)	457 (995)	13 (13-316)	969 (918)	638 (628-761)

Participants with bilateral oedema (n=31)	-	-	2,074 (1,158)	2,176 (1,005-2,912)	328 (455)	73 (40-478)	2,403 (1,046)	2,332 (1,614-3,182)
• 0-18 months	-	-	1,103 (561)	934 (683-1,551)	165 (219)	46 (26-259)	1,269 (554)	1,100 (901-1,616)
• 0-6 months	-	-	996 (764)	872 (312-1,544)	164 (247)	26 (13 -233)	1,160 (688)	1,142 (623-1,557)
• 7-18 months								

[a]For ADL assistance calculations, reported family time away from work was subtracted from the reported number of days that ADL assistance was required to avoid doubling up on costs.

All costs are in 2017-2018 Australian dollars. The average exchange rate for the 2017-2018 financial year: $1 AUD= $0.8113 USD[162].

CHAPTER 5: Discussion

Research Findings and Conclusions:

The major finding of this project is that for patients with lower limb chronic oedema and a history of two or more episodes of cellulitis in the same leg within two years, compression therapy plus education on cellulitis prevention reduces the risk of cellulitis recurrence by 77% (95% CI, 0.0.09 to 0.59) compared to education alone[151]. Although factors such as obesity, or the presence of tinea or toe web intertrigo, or wounds have been reported to be associated with cellulitis recurrence[4,6], our data were unable to corroborate these findings. The 25% absolute difference in the event rates between the experimental and control groups (15% versus 40%) indicates four patients need to be treated to prevent one episode of cellulitis (number need to treat=4; 95% CI, 2 to 15). The trial showed compression therapy was safe and feasible in this patient population, with no adverse outcomes occurring and good adherence to treatment. During the trial, 73% of the participants in the experimental group reported wearing their garments five or more days per week, and 88% reported wearing them four or more days weekly. Although there are many barriers to compression therapy, adherence within our trial (73-88%) was comparable to adherence with daily penicillin/placebo use (78-79%)[23,83]. The lack of adverse outcomes and the high compliance with compression therapy may be a result of support from experienced clinicians whose expertise allowed appropriate prescription and education for participants based on individual requirements.

Prior to this research, prophylactic antibiotics were the only evidence-based treatment for cellulitis prevention[22]. However, this research has shown a substantial reduction in the risk of cellulitis recurrence (hazard ratio, 0.23%; 95% CI 0.0.09 to 0.59). This compares favourably with an older RCT which compared prophylactic penicillin to a placebo in patients with a history of two or more episodes of leg cellulitis (hazard ratio 0.55%; 95% CI, 0.35 to 0.86)[23]. Further, patients with preexisting oedema, multiple previous episodes of cellulitis (≥3), or a high BMI (≥33) have a decreased likelihood of responding to antibiotic prophylaxis[23]. As all participants in the current trial had one or more risk factors predictive of non-response to prophylactic antibiotics (all participants had chronic oedema, 79% had a BMI ≥33, and 26% had experienced ≥3 episodes of cellulitis), this research demonstrates that compression therapy is

effective at reducing cellulitis incidence in a population who are known to be at risk of prophylactic antibiotic failure.

Prevention of cellulitis using prophylactic antibiotics is problematic; the causative bacterial species is usually unknown[141], preventing targeted antibiotic prophylaxis; side effects are common[22]; the protective effect is lost after ceasing use[22,23]; and this practice may contribute to antibiotic resistance[169]. In contrast, compression therapy is: recommended long term[114]; has few side effects[151]; and its efficacy in preventing cellulitis is independent of the causative bacterial species. Further, for patients with chronic oedema, compression therapy has many additional benefits such as controlling oedema, improving skin integrity[89,147], reducing limb volume[151], and preventing and managing the progression of venous disease[145], including venous ulcers[139,146]. Compression therapy is also a primary treatment for many conditions which mimic cellulitis, such as lipdermatosclerosis[148] and venous stasis dermatitis[145], for which antibiotic prophylaxis is inappropriate. Therefore, compression therapy may be considered a superior alternative to prophylactic antibiotics for preventing cellulitis in patients with chronic oedema.

A second key finding was the positive impact of compression therapy on reducing and controlling leg volume. Over 12 months, leg volume of patients in the experimental group reduced by 181 ml (95% CI, -256 to -106), while it increased by 60 ml (95% CI, -38 to 159) in the control group, giving a between group difference of 241 ml (95% CI, -365 to -117). As this volume change occurred in only a small area of the leg between the ankle and knee, this significant finding is also clinically meaningful. This is the first RCT to demonstrate the beneficial effect of compression therapy on leg volume, as prior to this trial, only one low quality RCT has investigated the efficacy of compression therapy, with the trial only including patients with upper limb breast cancer related lymphoedema[102].

Other secondary research findings were the impact of compression therapy on QOL and cellulitis related hospital admissions. Over 12 months, the experimental group showed an improvement in the LYMQOL combined domain score compared to the control group (mean change, -0.3; 95% CI -0.6 to -0.1). However, whilst this result was statistically significant, the effect size was very small, making it clinically irrelevant. Over that same period, there were no measurable between group differences for the LYMQOL QOL score, or the EQ-5D visual analogue scale or descriptive system scores. Compared to the control group, the experimental group experienced fewer cellulitis related hospital admissions (3 versus 6). Further, those admissions that did occur tended to occur later in the experimental group compared

to the control group, with only one of three admissions occurring within the first 300 days for the experimental group, compared to five of six in the control group. Although there was no statistically significant difference between the two trial groups (hazard ratio, 0.38; 95% CI, 0.09 to 1.59), the finding is consistent with the protective effect of compression therapy. The absence of a significant between-group difference for cellulitis-related hospital admissions, and the small change in QOL, may be because the trial was not powered to detect a statistically significant effect for these outcomes and because it stopped early for efficacy.

A third major finding of this research is that compression therapy is cost saving in the prevention of recurrent cellulitis for adults with lower limb chronic oedema and recurrent cellulitis. During the RCT, compared to the control group, the mean annual cost per participant in the experimental group was 75% lower from a health service perspective (mean intergroup difference, $10,963; 95% CI, $1,000 to $24,590) and 89% lower from a patient perspective (mean intergroup difference, $10,521; 95% CI, $1,806 to $24,933). The lower costs in the experimental group were due to the lower incidence of cellulitis recurrence (6 versus 17 episodes) and cellulitis-related hospital admissions (3 versus 6 admissions).

Health services and patients incurred high costs for cellulitis infections. From a health service perspective, the average cost of a non-hospitalised episode of cellulitis was $506, whereas the cost for a hospitalised episode was almost 18 times higher, being $9,071. The highest health service costs for cellulitis were for hospital use, being emergency department visits and hospital admissions. From a patient perspective, the average cost of a non-hospitalised episode of cellulitis was $1320, whereas a hospitalised episode cost $4,496. From the patient perspective, the highest costs relating to cellulitis infections were for patient and family time off work and assistance with ADLs. The high costs for hospitalised cellulitis infections were similarly found by Goettsch et al., who observed that although only 7% of cellulitis cases require hospital admission, they account for 83% of total medical expenditure related to cellulitis[9].

Costs for compression therapy were highest in the initial 6 months, with ongoing maintenance costs reducing. From a health service perspective, the average cost of compression therapy over 18 months was $1,905, with over half of that expenditure occurring within the initial 6 months, and the highest expense being for lymphoedema service appointments. From a patient perspective, compression

therapy cost $421 over 18 months, with 45% of the total expenditure taking place in the first 6 months. Compression garments were the greatest expense for patients despite only 35% of garments being patient-funded, with the government funding garments for the remaining 65% of patients.

Context of this Research

This is the first RCT and linked costing analysis to assess the impact of compression therapy on cellulitis recurrence in patients with chronic oedema. As there is limited research on the topic in general, it is difficult to contextualise the current findings within the broader literature. This situation is unlikely to change soon as currently there is no evidence of active research on this topic listed in current clinical trials registries, including the Australian New Zealand Clinical Trials Registry, the European Union Clinical Trials Register, the World Health Organisation's International Clinical Trials Registry Platform, and the Clinical Trials Registry provided by the United States National Library of Medicine.

The project was conducted in an outpatient specialist lymphoedema service in Canberra, Australia. The research results are likely translatable to similar patient populations in other areas and countries with comparable socioeconomic demographics and health systems. However, the fact that all clinicians working within the service had completed specialist training to become accredited lymphoedema therapists limits the generalisability of these results to patients who can access similar services or therapists. To date, all trials assessing the benefit of oedema management on cellulitis incidence have utilised therapists with specialist training[63,91,92]. For compression therapy to be effective, it must be adequately compressive, fit well and be worn regularly, and to achieve this, specialist support is often required to overcome the barriers that hamper adherence to compression therapy. Thus, the efficacy of compression therapy in preventing cellulitis may be less if prescription is completed by clinicians without appropriate training or experience. Although our research was only conducted in patients with lower limb cellulitis, the results are likely to be translatable to patients with upper limb cellulitis on a background of chronic oedema due to the similar pathophysiology and ability to compress the area. This hypothesis is supported by one pre-post trial, which assessed the impact of complete decongestive therapy on both upper and lower limb cellulitis incidence[92]. Also, as the research was completed in a patient population at high risk of cellulitis recurrence[14,41], the reduction in cellulitis risk and associated cost savings are likely to be less pronounced in patients with a lower risk profile.

While there is little other research on this topic, existing publications support the findings of this project in largely similar contexts. Prior to the trial, Arsenault et al. (2011) and Ko et al. (1998) both found a reduction in lower and upper limb cellulitis incidence with the implementation of complete decongestive therapy by trained lymphoedema therapists[91,92]. However, to achieve the reduction in

cellulitis incidence, both trials used intensive complete decongestive therapy including manual lymphatic drainage, with one trial providing an average of 17 episodes of treatment per patient over a mean of 6 weeks[91], and the other providing one to two 90-minute treatment sessions daily for an average of 15.7 days[92]. By refining the treatment to provide education regarding skin care and exercise, and compression therapy, as supported by the evidence, our trial achieved a significant reduction in cellulitis and associated costs more efficiently, with an average of one 90-minute, and five 45-minute appointments per patient over 18 months.

While our RCT was in progress, Moffatt et al. completed a prospective cohort (pre-post implementation) trial in 2018 in the United Kingdom that also showed provision of compression therapy by specialist clinicians led to reduced lower limb cellulitis incidence, limb volume, and healthcare expenditure for patients with lower limb chronic oedema[63]. This trial found a similar effect size for limb volume reduction, being 155 ml per leg after 6-12 months, compared to 181 ml per leg at 12 months in our trial; and a proportionate decrease in health service expenditure, with a reduction by 65% at 12 months in their trial, and 75% in our trial[63]. This study implemented a shared care model, with specialised staff providing intensive treatment and compression therapy prescription, and generalist community staff then supporting patients to transition to long term care[63]. This trial likewise focussed on managing oedema through education, skin care, exercise and compression therapy[63], although the frequency of intervention was not specified[63]. Similar to our trial, Moffatt et al. found the overall reduction in healthcare expenditure resulted from reduced acute care expenditure, with costs shifting to the community for oedema management (compression bandaging and garments)[63].

Following the publication of our RCT, Burian et al. published the results of a cross-sectional study which included 7,477 patients with chronic oedema who were assessed between 2014-2017 across 40 sites in nine countries[79]. The study results showed that cellulitis risk increased with the stage of oedema, and controlled swelling was significantly associated with decreased cellulitis risk (OR 0·59, 95% CI 0.51 to 0.67)[79]. These results similarly align with our research findings.

Research Dissemination and Translation of Research into Practice

The results of this research have been disseminated broadly around the world, with translation into clinical practice being recommended[170]. Over 25 articles related to our clinical trial, aimed at both consumers and health professionals, have been published online and by peak organisation publications (Australasian Lymphology Association, the Canadian Lymphedema Framework and the British Lymphology Society) (Appendix A). The trial results have been discussed in international forums, webinars, journal clubs and conferences for a range of professions, including nurses, allied health, physicians, GPs and surgeons (Appendix A and pages v to viii of this thesis). Two infographics communicating the RCT results have been published (see Figure 16 and Figure 17), as well as two critical appraisals of the RCT by the Journal of Physiotherapy[171,172], and to date, the RCT has been viewed over 51,000 times and cited by 28 other publications.

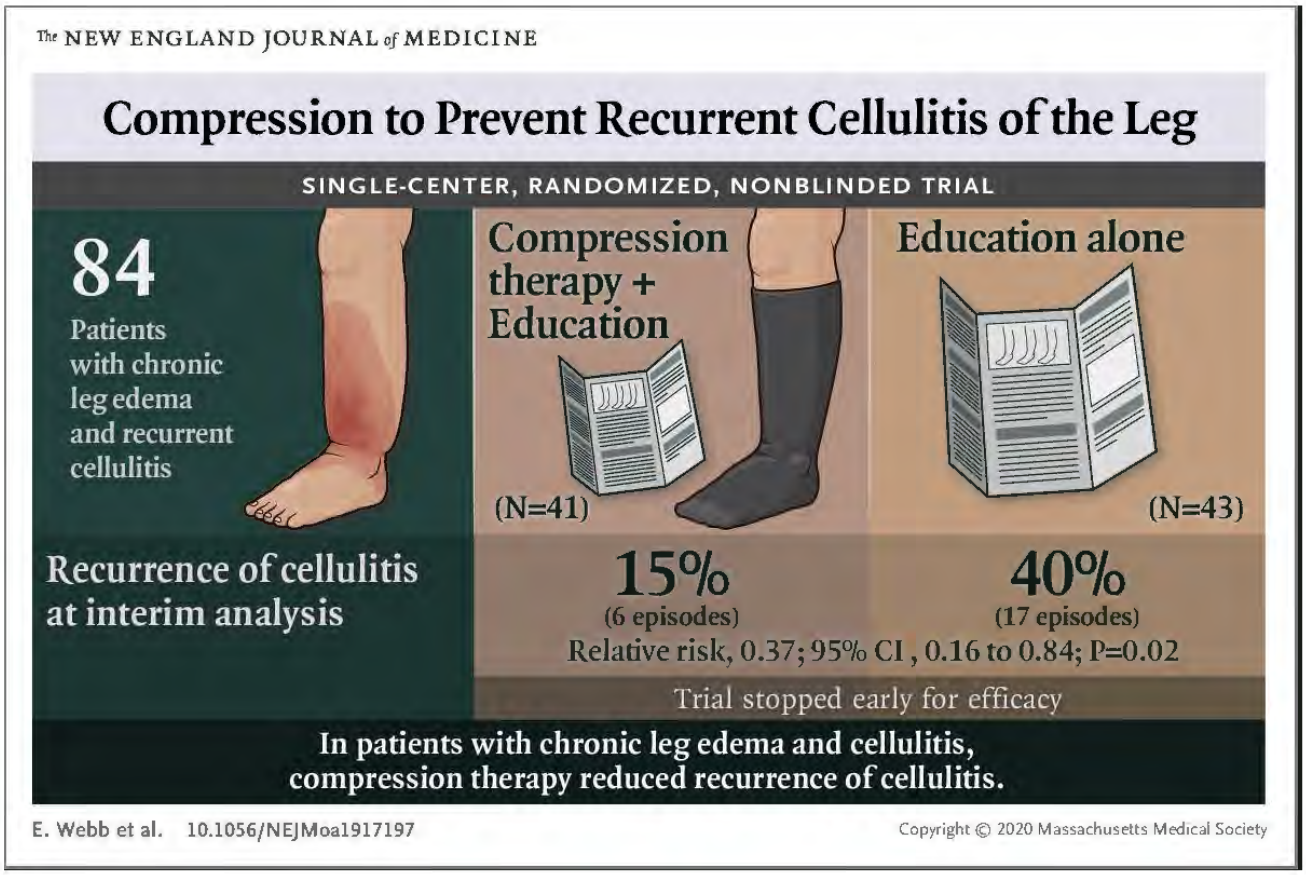

Figure 16: Compression to Prevent Recurrent Cellulitis of the Leg (published infographic)[151]

Figure 17: Compression therapy has global impact: A world first randomised trial (published infographic)[173]

The results from this research are being included in updated health resources and already appear to be translating into changed practice. The RCT results and the associated treatment recommendations have been published on the platform UpToDate[170], which is an online application designed to support health professionals to make evidence-based clinical decisions[174]. Medical professionals' reliance on UpToDate, being accessed over 1.6 million times daily by users across 190 countries, means the results of this research are likely being read and potentially implemented broadly around the world[174]. Additionally, the British Lymphology Society has advised they will be releasing their updated consensus statement on the management of cellulitis in lymphoedema at their conference in October 2022, and it is the author's understanding the RCT results will be reflected in their recommendations (*personal communication, July 2022*). The BLS's statement was used by the Australasian Lymphology Association to develop their consensus guideline on the topic, and as they have also recently announced their guideline is under review[175], it is expected the RCT results will also influence this document. Since the RCT results were published in 2020, further research has been designed and planned within Australia to implement and assess a multidisciplinary prevention program to reduce recurrent cellulitis through the management of risk factors, with the RCT and costing analysis results being used as the primary evidence to support the project and associated grant applications (*research plan shared via personal communication, June 2022*). Although there is currently anecdotal evidence to suggest the trial results are being translated into practice, further research to assess implementation is required to confirm this.

Strengths and Limitations of this Research

A strength of this research is that the protocol was designed to reflect current clinical practice within a usual outpatient setting, using standard public health resources. Participant interventions and follow-up time frames align with current practice, with participants being assessed and reviewed by a variety of accredited lymphoedema physiotherapists working within the unit. These factors maximised the ecological validity of the study and the likelihood of translation of findings into practice in similar settings. The robust research methodology also supports the trial's internal validity. Allocation was blinded, and randomisation was stratified based on prophylactic antibiotic use to prevent their use confounding results. Randomisation resulted in the participant demographics being well balanced at baseline, and further exploratory analysis confirmed that the presence of other common cellulitis risk factors did not influence the results. Intention to treat analysis was used, and outcome measures were chosen to prevent bias arising from lack of therapist and patient blinding: cellulitis was diagnosed independently to the trial, by the participant's treating physician or GP; limb volume was measured using a 3D scanning device called a perometer; and hospitalisation for cellulitis was confirmed using medical records. For the costing analysis, all patient records were audited to improve data accuracy. For the cost of compression therapy, apart from patient-reported time off work and assistance with ADLs, all the data were drawn purely from patient medical records, supporting the accuracy of this measurement. When assessing the cost of cellulitis episodes, participant hospital admissions were costed individually by Health Information Services based on current Australian guidelines for activity based funding, and other health service-related access was also checked where possible to support data accuracy.

Although the real-life setting and protocol of this research support its external validity in similar settings, it is also a limitation as the results are not generalisable to many areas and countries where patients do not have access to lymphoedema services or trained therapists. Also, because the trial population was at high risk of cellulitis recurrence due to having two or more episodes of cellulitis in the previous two years[14,41], the health and financial benefits may be different in patients with a lower risk profile due to fewer prior cellulitis episodes. Additionally, as up to 31% of cellulitis diagnoses are incorrect[31,32], it is possible that some of the measured episodes of cellulitis were misdiagnosed. However, as compression therapy is also a recommended treatment for many conditions that mimic cellulitis, such as lipodermatosclerosis[148] and venous stasis dermatitis[145], the fact that the intervention may have also

reduced the incidence of cellulitis mimics, for which antibiotics prescription is inappropriate, strengthens the case for using compression therapy within this patient population.

Other limitations of the trial are the small sample size and short duration of follow-up that resulted from the trial being stopped early for efficacy, meaning we only know the impact of compression therapy over a relatively short period of time (median follow up of 6 months). The RCT's cross-over design and the stopping rules were implemented to ensure participant safety; however, this design prevented ongoing monitoring of cellulitis incidence in the control group after an initial recurrence; and stopping the trial early may have resulted in overestimating the benefit of the intervention[176], and subsequently and financial benefits calculated in the costs analysis. Additionally, the trial was only powered for the primary outcome, and a larger sample size and longer duration of follow up may have given greater insight into the costs associated with cellulitis and chronic oedema, and the longer-term impact of compression therapy on the secondary outcomes of leg volume, QOL and hospitalisation for cellulitis.

The data collection for the cost analysis was completed retrospectively, which may have influenced the accuracy of the results, particularly in relation to cellulitis infections which relied more heavily on patient recall. However, as the greatest cellulitis-related costs arose from hospital presentations and those data were audited for accuracy, it is likely that the results are reasonably accurate. For future research in this area, use of patient diaries to collect these data prospectively may improve accuracy.

The trial was developed to replicate the participating service's standard care while minimising burden to participants, however, there was limited consumer input into the trial design as this was not standard practice during the planning phase in 2016. However, prior to designing the trial, patients from the participating clinical service were surveyed regarding the acceptability of the chosen model of care, with the results being reflected in the trial design. For example, time and cost were identified as potential burdens, which were addressed through minimising scheduled follow-up appointments and supporting access to government funding schemes for compression garments for eligible participants, and free compression garments for all participants through a sponsorship agreement. Going forwards, before further research is undertaken, engagement and consultation with consumers and clinicians is crucial to inform research design and execution.

Practical Implications and the Associated Challenges

The main practical implications of the research are clear. The RCT and cost analysis results indicate that for patients with lower limb chronic oedema and recurrent cellulitis, the provision of compression therapy by trained lymphoedema therapists has health and economic benefits for both patients and the health system, and therefore should be standard practice. Prophylactic antibiotics are the only other evidence-based treatment to prevent cellulitis recurrence but have been shown to be less effective in patients with oedema, obesity (BMI ≥33) or a history of 3 or more episodes of cellulitis[23]. Therefore, compression therapy should be the first line treatment for these patients, particularly as compression has many other potential health and functional benefits[55,139,146,166].

In addition to preventing cellulitis and reducing limb volume, compression therapy can have many other benefits for patients with chronic oedema. For chronic oedema, and chronic venous insufficiency, a common cause of chronic oedema[50], compression therapy is a primary treatment modality[55,145,177]. Compression therapy has been found to improve skin condition[55], improve QOL in patients with chronic venous disease[166], increase the rate of healing for venous ulcers[139], prevent recurrence of venous ulcers[146], and may prevent post-thrombotic syndrome[167]. Additionally, compression therapy is also a primary treatment for multiple conditions which are often misdiagnosed as cellulitis[145,148], for which antibiotic prescription is inappropriate. Thus, for patients with a misdiagnosis with cellulitis (i.e. 31% of all cellulitis diagnoses), compression therapy is likely to be beneficial, whist antibiotics may be ineffective with possible side effects[22]. When all the possible benefits of compression therapy are taken into consideration, the health and financial gains may be greater than that found in our trial.

For the patient group in our trial, the reduction in cellulitis incidence and limb volume was achieved using treatment comprising compression therapy plus education and skin care, which is dramatically less time and labour intensive than previously studied chronic oedema treatment models which include manual lymphatic drainage [91,92,96]. On this basis, and with the mounting evidence that manual lymphatic drainage is ineffective[96,97,99], manual lymphatic drainage should not be considered a fundamental component of treatment and should not be funded by public health systems. For patients with chronic oedema, it is still unknown if compression therapy is effective in reducing cellulitis incidence in other locations such as the arm, or in patients who have had no cellulitis, one episode, or less frequent infections compared to the trial cohort. However, until there is specific research to support clinical

decision making for these populations, it is appropriate to extrapolate these results to other patients, acknowledging the efficacy of the treatment is uncertain.

Although the clinical implications of the research are straightforward, there are some barriers to translating this knowledge into practice, with the primary barriers being appropriate referral of patients and access to lymphoedema therapists. As stated in the thesis introduction, cellulitis is referred to as 'a disease with no home'[26] due to being managed by a broad range of medical professionals in acute and community health settings. Thus, for effective translation into practice to occur, a broad range of health professionals need to not only be made aware of the benefits of compression, but also how to refer to a lymphoedema therapist, and no singular education or communication strategy is likely to achieve this. Focusing education on GPs may achieve the greatest benefit, with almost 80% of the Australian population having a regular GP[178] that could provide the appropriate referral. Ultimately, improved education regarding chronic oedema and its sequelae within medical degrees may enable more medical professionals to recognise chronic oedema, and to diagnose and refer these patients appropriately. The expense of services and consumables and poor access to lymphoedema therapists within Australia are also substantial barriers to patients accessing care, particularly if patients cannot afford private services[61]. Therefore, appropriate funding schemes and greater investment in education and services for chronic oedema are essential to support change and reduce cellulitis recurrence, particularly as the prevalence of chronic oedema is likely to increase with the expected changes in Australian population demographics[16,17].

Future Research

Research regarding the relationship between chronic oedema and cellulitis, and the efficacy of treatments targeting risk factors for cellulitis is very limited. Although there are many hypotheses, currently we are still unaware of why chronic oedema increases the risk of cellulitis, or the mechanism by which compression therapy reduces cellulitis recurrence. A greater understanding of the aetiology of cellulitis, and the pathophysiology of the relationship between cellulitis and oedema, could guide future treatment approaches. Further, an improved understanding of the pathophysiology of the relationship between cellulitis and other risk factors would also be useful. Management of risk factors such as poor skin integrity, tinea pedis or toe web intertrigo has long been thought to assist in reducing cellulitis incidence, however there is no research to confirm this.

Further research is required to demonstrate the efficacy of compression therapy for cellulitis prevention in a broader patient population. The results of our RCT applied to a specific patient population who were at high risk of lower limb cellulitis, with a history of two or more episodes of cellulitis in the past two years. To extrapolate these results further, it would be beneficial to investigate the effect of compression in patients with cellulitis in different locations (e.g. the arm) and in patients with different risk profiles (e.g. a history of no or one episode of cellulitis). Additionally, research into the timing of compression therapy may be useful. During our RCT, compression therapy was applied after cellulitis had resolved, however research on the impact of compression therapy on acute cellulitis has been identified as a research priority[25], including establishing whether or not it expediates recovery and prevents complications and recurrence.

A limitation of the RCT and cost analysis are the small sample size and short term follow up. Trials with larger populations and longer follow-up periods will allow us to gain a greater understanding of the long-term effects and costs of compression therapy. As compression therapy has many additional advantages for patients with chronic oedema, a broader range of outcome measures to quantify other benefits (e.g. change in skin integrity, use of other health services, prevalence of venous ulcers) may provide a more complete picture of the possible health and financial benefits for patients with chronic oedema and cellulitis. Another limitation of the trial was the possible misdiagnosis of cellulitis. Research to determine the best diagnostic criteria for cellulitis, and how to support health professionals to

accurately diagnose cellulitis, has also been identified as a research priority[25] which would support the accuracy and validity of future research.

Finally, while current guidelines are now recommending compression therapy be used to prevent cellulitis in patients with chronic oedema, further research is required to investigate how well it is being translated into practice. Translation research could be used to determine how broadly the research findings are being implemented and to identify the barriers to implementation. Further, research into different models of care can guide how compression therapy can be provided most efficiently and effectively. For example, while our RCT used specialist lymphoedema therapists, Moffatt et al. found a combination of specialist lymphoedema and non-specialist community resources was effective in reducing the incidence of cellulitis and health care expenditure[63]. Improved knowledge of best practice models of care for oedema management will support effective implementation in a wide variety of settings.

Closure

The findings of this research have been widely disseminated nationally and internationally, as noted in 'Research Dissemination and Translation of Research into Practice' in the discussion and appendix A, and on pages v to viii of this thesis. Forums presented at include the Australian Physiotherapy Association Conference (2019), the Australian Physiotherapy Association Virtual Webinar Series (2022), the Australian Physiotherapy Association Symposium (2018, 2019), the Australasian Lymphology Association Conference (2018, 2020, 2022), the International Lymphoedema Framework Conference (2021), the Wounds Australia Symposium (2019), the Asia-Pacific Three Minute Thesis (2019), the Canberra Health Research Meeting (2019) and two company run webinars directed at clinicians (2020). The results have also been provided to stakeholders via multiple lectures and grand rounds seminars to hospital staff, and to consumers during trial appointments (post interim analysis), a webinar to the ACT Lymphoedema Consumer Group (2021) and a local radio interview (2020).

The RCT protocol and results, and the cost analysis results have been published with open access in international journals[151,152,179,180], and the articles have been provided to funding bodies and ethics review committees for their records. The data have been de-identified, and all data and research paperwork has been stored electronically in a secure drive on the hospital server in accordance with ethical requirements. The Australian New Zealand Clinical Trials Registry has been updated to reflect the progress of the trial.

Summary

This is the first randomised trial to demonstrate that compression therapy prevents recurrent cellulitis in adults with lower limb chronic oedema, thus supporting current expert opinion regarding the value of compression therapy[2,10,13,55,90]. Further, compression therapy is effective in preventing cellulitis recurrence in patients who are at risk of antibiotic prophylaxis failure due to the presence of oedema, with or without obesity or a history of three or more episodes of cellulitis[23]. Additionally, compression therapy is effective in reducing limb volume. Lastly, for this patient population, compression therapy is cost-saving from both patient and health service perspectives. Therefore, for patients with chronic oedema, compression therapy should be the first-line treatment and standard practice to prevent recurrent cellulitis. With the proven health and economic benefits established in this trial, there is strong justification to better fund and enable access to compression therapy for these patients.

REFERENCES

1. Levell NJ, Wingfield CG, Garioch JJ. Severe lower limb cellulitis is best diagnosed by dermatologists and managed with shared care between primary and secondary care. *Br J Dermatol.* 2011;164(6):1326-1328.
2. Swartz MN. Clinical practice. Cellulitis. *N Engl J Med.* 2004;350(9):904-912.
3. Australian Institute of Health and Welfare. Prinicipal Diagnosis Data Cubes. 2021; https://www.aihw.gov.au/reports/hospitals/principal-diagnosis-data-cubes/contents/data-cubes. Accessed March 2022.
4. Pavlotsky F, Amrani S, Trau H. Recurrent erysipelas: risk factors. *J Dtsch Dermatol Ges.* 2004;2(2):89-95.
5. Karppelin M, Siljander T, Vuopio-Varkila J, et al. Factors predisposing to acute and recurrent bacterial non-necrotizing cellulitis in hospitalized patients: a prospective case-control study. *Clin Microbiol Infect.* 2010;16(6):729-734.
6. Inghammar M, Rasmussen M, Linder A. Recurrent erysipelas-risk factors and clinical presentation. *BMC Infect Dis.* 2014;14:270-270.
7. Australian Institute of Health and Welfare. Emergency department care 2017–18: Australian hospital statistics. Health services series no. 89. Cat. no. HSE 216. Canberra: AIHW. 2018; https://www.aihw.gov.au/getmedia/9ca4c770-3c3b-42fe-b071-3d758711c23a/aihw-hse-216.pdf.aspx?inline=true. Accessed September 2021.
8. Independent Hospital Pricing Authority. National Hospital Cost Data Collection Report Public Sector, Round 22 (Financial Year 2017-18). February 2020; https://www.ihpa.gov.au/publications/national-hospital-cost-data-collection-report-public-sector-round-22-financial-year. Accessed June 2021.
9. Goettsch WG, Bouwes Bavinck JN, Herings RM. Burden of illness of bacterial cellulitis and erysipelas of the leg in the Netherlands. *J Eur Acad Dermatol Venereol.* 2006;20(7):834-839.
10. Cox NH. Oedema as a risk factor for multiple episodes of cellulitis/erysipelas of the lower leg: a series with community follow-up. *Br J Dermatol.* 2006;155(5):947-950.
11. Moffatt CJ, Franks PJ, Doherty DC, et al. Lymphoedema: an underestimated health problem. *QJM.* 2003;96(10):731-738.

12. Dupuy A, Benchikhi H, Roujeau JC, et al. Risk factors for erysipelas of the leg (cellulitis): case-control study. *BMJ.* 1999;318(7198):1591-1594.
13. Chlebicki MP, Oh CC. Recurrent cellulitis: risk factors, etiology, pathogenesis and treatment. *Curr Infect Dis Rep.* 2014;16(9):422.
14. Bjornsdottir S, Gottfredsson M, Thorisdottir AS, et al. Risk factors for acute cellulitis of the lower limb: a prospective case-control study. *Clin Infect Dis.* 2005;41(10):1416-1422.
15. Keast DH, Despatis M, Allen JO, Brassard A. Chronic oedema/lymphoedema: under-recognised and under-treated. *Int Wound J.* 2015;12(3):328-333.
16. Australian institute of Health and Welfare. Older People. 2021; https://www.aihw.gov.au/reports-data/population-groups/older-people/overview. Accessed March 2022.
17. Cameron AJ, Welborn TA, Zimmet PZ, et al. Overweight and obesity in Australia: the 1999-2000 Australian Diabetes, Obesity and Lifestyle Study (AusDiab). *Med J Aust.* 2003;178(9):427-432.
18. Quere I, Palmier S, Noerregaard S, et al. LIMPRINT: Estimation of the Prevalence of Lymphoedema/Chronic Oedema in Acute Hospital in In-Patients. *Lymphat Res Biol.* 2019;17(2):135-140.
19. Moffatt CJ, Gaskin R, Sykorova M, et al. Prevalence and Risk Factors for Chronic Edema in U.K. Community Nursing Services. *Lymphat Res Biol.* 2019;17(2):147-154.
20. Australasian Lymphology Association. Consensus Guideline: Management of Cellulitis in Lymphoedema. 2008 [Reviewed 2015]; https://www.lymphoedema.org.au/public/7/files/Position%20Statements/ALA%20Consensus%20Guideline%20Cellulitis-Rebrand%202019(1).pdf. Accessed March 2022.
21. Therapeutic Goods Administration. Electronic Therapeutic Guidelines Complete [digital]: Preventing recurrent cellulitis. In. Melbourne: Therapuetic Guidelines Limited; 2021.
22. Dalal A, Eskin-Schwartz M, Mimouni D, et al. Interventions for the prevention of recurrent erysipelas and cellulitis. *Cochrane Database Syst Rev.* 2017(6).
23. Thomas KS, Crook AM, Nunn AJ, et al. Penicillin to prevent recurrent leg cellulitis. *N Engl J Med.* 2013;368(18):1695-1703.
24. Raff AB, Kroshinsky D. Cellulitis: A Review. *JAMA.* 2016;316(3):325-337.
25. Thomas KS, Brindle R, Chalmers JR, et al. Identifying priority areas for research into the diagnosis, treatment and prevention of cellulitis (erysipelas): results of a James Lind Alliance Priority Setting Partnership. *Br J Dermatol.* 2017;177(2):541-543.

26. Thomas KS. Studying a disease with no home--lessons in trial recruitment from the PATCH II study. *Trials.* 2010;11:22-22.
27. Koutkia P, Mylonakis E, Boyce J. Cellulitis: evaluation of possible predisposing factors in hospitalized patients. *Diagn Microbiol Infect Dis.* 1999;34(4):325-327.
28. Kulthanan K, Rongrungruang Y, Siriporn A, et al. Clinical and microbiologic findings in cellulitis in Thai patients. *J Med Assoc Thai.* 1999;82(6):587-592.
29. Baibergenova A, Drucker AM, Shear NH. Hospitalizations for cellulitis in Canada: a database study. *J Cutan Med Surg.* 2014;18(1):33-37.
30. Figtree M, Konecny P, Jennings Z, Goh C, Krilis SA, Miyakis S. Risk stratification and outcome of cellulitis admitted to hospital. *J Infect.* 2010;60(6):431-439.
31. Weng QY, Raff AB, Cohen JM, et al. Costs and Consequences Associated With Misdiagnosed Lower Extremity Cellulitis. *JAMA Dermatol.* 2017;153(2):141-146.
32. Ko LN, Garza-Mayers AC, St John J, et al. Effect of Dermatology Consultation on Outcomes for Patients With Presumed Cellulitis: A Randomized Clinical Trial. *JAMA Dermatol.* 2018;154(5):529-536.
33. Australian Commission on Safety and Quality in Health Care and Australian Institute of Health and Welfare. *Australian Atlas of Healthcare Variation 2021.* Sydney. 2021.
34. Jorup-Ronstrom C, Britton S. Recurrent erysipelas: predisposing factors and costs of prophylaxis. *Infection.* 1987;15(2):105-106.
35. Cannon J, Dyer J, Carapetis J, Manning L. Epidemiology and risk factors for recurrent severe lower limb cellulitis: a longitudinal cohort study. *Clin Microbiol Infect.* 2018;24(10):1084-1088.
36. Australian Institute of Health and Welfare 2020. *Disparities in potentially preventable hospitalisations across Australia, 2012–13 to 2017–18.* Canberra: AIHW, Australian Government; 2020.
37. Australian Institute of Health and Welfare. Potentially preventable hospitalisations in Australia by age groups and small geographic areas, 2017–18. In. Canberra: AIHW, Australian Government; 2021.
38. Falster M, Jorm, L. A guide to the potentially preventable hospitalisations indicator in Australia. Centre for Big Data Research in Health, University of New South Wales in consultation with Australian Commission on Safety and Quality in Health Care and Australian Institute of Health and Welfare. In. Sydney. 2017.

39. Simonsen S, Orman E, Hatch B, et al. Cellulitis incidence in a defined population. *Epidemiol Infect.* 2006;134:293-299.
40. Cranendonk DR, Lavrijsen APM, Prins JM, Wiersinga WJ. Cellulitis: current insights into pathophysiology and clinical management. *Neth J Med.* 2017;75(9):366-378.
41. Quirke M, Ayoub F, McCabe A, et al. Risk factors for nonpurulent leg cellulitis: a systematic review and meta-analysis. *Br J Dermatol.* 2017;177(2):382-394.
42. Olafsdottir LB, Erlendsdóttir H, Melo-Cristino J, et al. Invasive infections due to Streptococcus pyogenes: seasonal variation of severity and clinical characteristics, Iceland, 1975 to 2012. *Euro Surveill* 2014;19(17):5-14.
43. Manning L, Cannon J, Dyer J, Carapetis J. Seasonal and regional patterns of lower leg cellulitis in Western Australia. *Intern Med J.* 2019;49(2):212-216.
44. Mason JM, Thomas KS, Crook AM, et al. Prophylactic antibiotics to prevent cellulitis of the leg: economic analysis of the PATCH I & II trials. *Plos One.* 2014;9(2):e82694-e82694.
45. Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. *Cochrane Database Syst Rev.* 2010(6):CD004299.
46. Carter K, Kilburn S, Featherstone P. Cellulitis and treatment: a qualitative study of experiences. *Br J Nurs.* 2007;16(6):S22-24, S26-28.
47. Independent Hospital Pricing Authority. National Hospital Cost Data Collection: What is the cost of Australia's emergency care patients? 2020; https://www.ihpa.gov.au/sites/default/files/publications/round_22_nhcdc_infographics_emergency.pdf. Accessed June 2021.
48. Kameshwar K, Karahalios A, Janus E, Karunajeewa H. False economies in home-based parenteral antibiotic treatment: a health-economic case study of management of lower-limb cellulitis in Australia. *J Antimicrob Chemother.* 2016;71(3):830-835.
49. Morpeth SC, Chambers ST, Gallagher K, Frampton C, Pithie AD. Lower limb cellulitis: features associated with length of hospital stay. *J Infect.* 2006;52(1):23-29.
50. Moffatt C, Keeley V, Quere I. The Concept of Chronic Edema-A Neglected Public Health Issue and an International Response: The LIMPRINT Study. *Lymphat Res Biol.* 2019;17(2):121-126.
51. Levick JR, Michel CC. Microvascular fluid exchange and the revised Starling principle. *Cardiovasc Res.* 2010;87(2):198-210.
52. Mortimer PS, Levick JR. Chronic peripheral oedema: the critical role of the lymphatic system. *Clini Med (Lond).* 2004;4(5):448-453.

53. National Lymphoedema Partnership. Consensus Statement on the Chronic Oedema – Lymphoedema Interface. 2015; https://www.lympho.org/wp-content/uploads/2021/09/Chronic-Oedema-definition-NLP-June-15.pdf. Accessed March 2022.
54. International Society of Lymphology. The Diagnosis and Treatment of Peripheral Lymphedema: 2016 Consensus Document of the International Society of Lymphology. *Lymphology.* 2016;49(4):170-184.
55. Lymphoedema Framework. *Best Practice for the Management of Lymphoedema. International consensus.* London: MEP Ltd; 2006.
56. Moffatt CJ, Keeley V, Franks PJ, Rich A, Pinnington LL. Chronic oedema: a prevalent health care problem for UK health services. *Int Wound J.* 2017;14(5):772-781.
57. Eklof B, Rutherford RB, Bergan JJ, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg.* 2004;40(6):1248-1252.
58. O'Malley E, Ahern T, Dunlevy C, Lehane C, Kirby B, O'Shea D. Obesity-related chronic lymphoedema-like swelling and physical function. *QJM.* 2015;108(3):183-187.
59. Shallwani SM, Hodgson P, Towers A. Comparisons Between Cancer-Related and Noncancer-Related Lymphedema: An Overview of New Patients Referred to a Specialized Hospital-Based Center in Canada. *Lymphat Res Biol.* 2017;15(1):64-69.
60. The National Lymphoedema Partnership. Commissioning Guidance for Lymphoedema Services for Adults in the United Kingdom. 2019; https://www.lymphoedema.org/wp-content/uploads/2020/01/nlp_commissioning_guidance_march_2019.pdf. Accessed April 2022.
61. Sierla R, Black, D, Sze Mun Lee, T, Kilbreath, S. Access to treatment for breast cancer-related lymphoedema in Australia. *Aust Fam Physician.* 2013;42:892-895.
62. Gordon SJ, Murray SG, Sutton T, et al. LIMPRINT in Australia. *Lymphat Res Biol.* 2019;17(2):173-177.
63. Moffatt CJ, Doherty DC, Franks PJ, Mortimer PS. Community-Based Treatment for Chronic Edema: An Effective Service Model. *Lymphat Res Biol.* 2018;16(1):92-99.
64. World Health Organization. Lymphatic Filariasis. 2022; https://www.who.int/news-room/fact-sheets/detail/lymphatic-filariasis. Accessed March 2022.
65. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *Lancet Oncol.* 2013;14(6):500-515.

66. Toyserkani NM, Jørgensen MG, Haugaard K, Sørensen JA. Seroma indicates increased risk of lymphedema following breast cancer treatment: A retrospective cohort study. *Breast.* 2017;32:102-104.
67. Warren LE, Miller CL, Horick N, et al. The impact of radiation therapy on the risk of lymphedema after treatment for breast cancer: a prospective cohort study. *Int J Radiat Oncol Biol Phys.* 2014;88(3):565-571.
68. Woods M. Risk factors for the development of oedema and lymphoedema. *Br J Nurs.* 2019;28(4):219-222.
69. Simmons J, Keeley V, Frisby J, et al. *Position Document: The Management of Lymphoedema in Advanced Cancer and Oedema at the End of Life.* International Lymphoedema Framework and Canadian Lymphedema Framework; 2010.
70. Keeley V. Drugs that may exacerbate and those used to treat lymphoedema. *J Lymphoedema.* 2008;3(1).
71. Australian Institute of Health and Welfare. Older Australians: Demographic profile. 2021; https://www.aihw.gov.au/reports/older-people/older-australians/contents/demographic-profile#Australia%E2%80%99s%20older%20population. Accessed 25 March 2022, 2022.
72. AIHW: Bennett S, Magnus P, Gibson D. Obesity trends in older Australians. AIHW bulletin no. 12. Cat. no. AUS 42. In. Canberra: AIHW, Australian Government; 2004.
73. Fu MR, Ridner SH, Hu SH, Stewart BR, Cormier JN, Armer JM. Psychosocial impact of lymphedema: a systematic review of literature from 2004 to 2011. *Psychooncology.* 2013;22(7):1466-1484.
74. Morgan PA, Franks PJ, Moffatt CJ. Health-related quality of life with lymphoedema: a review of the literature. *Int Wound J.* 2005;2(1):47-62.
75. Greene A, Meskell P. The impact of lower limb chronic oedema on patients' quality of life. *Int Wound J.* 2016;14.
76. Mercier G, Pastor J, Moffatt C, Franks P, Quere I. LIMPRINT: Health-Related Quality of Life in Adult Patients with Chronic Edema. *Lymphat Res Biol.* 2019;17(2):163-167.
77. Klernas P, Johnsson A, Horstmann V, Johansson K. Health-related quality of life in patients with lymphoedema - a cross-sectional study. *Scand J Caring Sci.* 2018;32(2):634-644.
78. Humphreys I, Thomas MJ. Evaluation of the economic impact of a national lymphoedema service in Wales. *Br J Nurs.* 2017;26(20):1093-1100.

79. Burian EA, Karlsmark T, Franks PJ, Keeley V, Quere I, Moffatt CJ. Cellulitis in chronic oedema of the lower leg: an international cross-sectional study. *Br J Dermatol.* 2021;185(1):110-118.
80. Tay EY, Fook-Chong S, Oh CC, Thirumoorthy T, Pang SM, Lee HY. Cellulitis Recurrence Score: a tool for predicting recurrence of lower limb cellulitis. *J Am Acad Dermatol.* 2015;72(1):140-145.
81. Mallon E, Powell S, Mortimer P, Ryan TJ. Evidence for altered cell-mediated immunity in postmastectomy lymphoedema. *Br J Dermatol.* 1997;137(6):928-933.
82. Damstra RJ, van Steensel MA, Boomsma JH, Nelemans P, Veraart JC. Erysipelas as a sign of subclinical primary lymphoedema: a prospective quantitative scintigraphic study of 40 patients with unilateral erysipelas of the leg. *Br J Dermatol.* 2008;158(6):1210-1215.
83. Thomas K, Crook A, Foster K, et al. Prophylactic antibiotics for the prevention of cellulitis (erysipelas) of the leg: results of the UK Dermatology Clinical Trials Network's PATCH II trial. *Br J Dermatol.* 2012;166(1):169-178.
84. Soo JK, Bicanic TA, Heenan S, Mortimer PS. Lymphatic abnormalities demonstrated by lymphoscintigraphy after lower limb cellulitis. *Br J Dermatol.* 2008;158(6):1350-1353.
85. Stephens M, Liao S. Neutrophil-lymphatic interactions during acute and chronic disease. *Cell Tissue Res.* 2018;371.
86. Liao S, Cheng G, Conner DA, et al. Impaired lymphatic contraction associated with immunosuppression. *Proc Natl Acad Sci U S A.* 2011;108(46):18784-18789.
87. Al-Niaimi F, Cox N. Cellulitis and lymphoedema. *J Lymphoedema.* 2009;4:38-42.
88. Liao S, Padera TP. Lymphatic function and immune regulation in health and disease. *Lymphat Res Biol.* 2013;11(3):136-143.
89. Rich A. How to care for uncomplicated skin and keep it free of complications. *Br J Community Nurs.* 2007;12(4):S6-S9.
90. Cox NH, Colver GB, Paterson WD. Management and morbidity of cellulitis of the leg. *J R Soc Med.* 1998;91(12):634-637.
91. Arsenault K, Rielly L, Wise H. Effects of Complete Decongestive Therapy on the Incidence Rate of Hospitalization for the Management of Recurrent Cellulitis in Adults with Lymphedema. *Rehabil Oncol.* 2011;29(3):14-20.
92. Ko DS, Lerner R, Klose G, Cosimi AB. Effective treatment of lymphedema of the extremities. *Arch Surg.* 1998;133(4):452-458.
93. Moffatt C, Partsch H, Schuren J, et al. Compression Therapy: A position document on compression bandaging. *The International Lymphoedema Framework.* 2012:1-75.

94. Lawenda BD, Mondry TE, Johnstone PA. Lymphedema: a primer on the identification and management of a chronic condition in oncologic treatment. *CA Cancer J Clin.* 2009;59(1):8-24.
95. Badger C, Preston N, Seers K, Mortimer P. Physical therapies for reducing and controlling lymphoedema of the limbs. *Cochrane Database Syst Rev.* 2004(4):Cd003141.
96. Thompson B, Gaitatzis K, Janse de Jonge X, Blackwell R, Koelmeyer LA. Manual lymphatic drainage treatment for lymphedema: a systematic review of the literature. *J Cancer Surviv.* 2021;15(2):244-258.
97. Huang TW, Tseng SH, Lin CC, et al. Effects of manual lymphatic drainage on breast cancer-related lymphedema: a systematic review and meta-analysis of randomized controlled trials. *World J Surg Oncol.* 2013;11:15.
98. Ezzo J, Manheimer E, McNeely ML, et al. Manual lymphatic drainage for lymphedema following breast cancer treatment. *Cochrane Database Syst Rev.* 2015(5):CD003475.
99. De Vrieze T, Gebruers N, Nevelsteen I, et al. Manual lymphatic drainage with or without fluoroscopy guidance did not substantially improve the effect of decongestive lymphatic therapy in people with breast cancer-related lymphoedema (EFforT-BCRL trial): a multicentre randomised trial. *J Physiother.* 2022;68(2):110-122.
100. Tambour M, Holt M, Speyer A, Christensen R, Gram B. Manual lymphatic drainage adds no further volume reduction to Complete Decongestive Therapy on breast cancer-related lymphoedema: a multicentre, randomised, single-blind trial. *Br J Cancer.* 2018;119(10):1215-1222.
101. Hayes SC, Singh B, Reul-Hirche H, et al. The Effect of Exercise for the Prevention and Treatment of Cancer-related Lymphedema: A Systematic Review with Meta-analysis. *Med Sci Sports Exerc.* 2022;54(8):1389-1399.
102. Hornsby R. The use of compression to treat lymphoedema. *Prof Nurse.* 1995;11(2):127-128.
103. McNeely ML, Magee DJ, Lees AW, Bagnall KM, Haykowsky M, Hanson J. The addition of manual lymph drainage to compression therapy for breast cancer related lymphedema: a randomized controlled trial. *Breast Cancer Res Treat.* 2004;86(2):95-106.
104. Bergmann A, da Costa Leite Ferreira MG, de Aguiar SS, et al. Physiotherapy in upper limb lymphedema after breast cancer treatment: a randomized study. *Lymphology.* 2014;47(2):82-91.
105. Gradalski T, Ochalek K, Kurpiewska J. Complex Decongestive Lymphatic Therapy With or Without Vodder II Manual Lymph Drainage in More Severe Chronic Postmastectomy Upper Limb

Lymphedema: A Randomized Noninferiority Prospective Study. *J Pain Symptom Manage.* 2015;50(6):750-757.

106. Andersen L, Højris I, Erlandsen M, Andersen J. Treatment of breast-cancer-related lymphedema with or without manual lymphatic drainage--a randomized study. *Acta Oncol.* 2000;39(3):399-405.

107. Badger CM, Peacock JL, Mortimer PS. A randomized, controlled, parallel-group clinical trial comparing multilayer bandaging followed by hosiery versus hosiery alone in the treatment of patients with lymphedema of the limb. *Cancer.* 2000;88(12):2832-2837.

108. Tsai H-J, Hung H-C, Yang J-L, Huang C-S, Tsauo J-Y. Could Kinesio tape replace the bandage in decongestive lymphatic therapy for breast-cancer-related lymphedema? A pilot study. *Support Care Cancer.* 2009;17(11):1353.

109. Didem K, Ufuk YS, Serdar S, Zumre A. The comparison of two different physiotherapy methods in treatment of lymphedema after breast surgery. *Breast Cancer Res Treat.* 2005;93(1):49-54.

110. 3M. 3M Compression Therapy Bandages. 2022; https://www.3m.com.au/3M/en_AU/p/c/medical/bandages-dressings/compression-therapy/. Accessed 29 March 2022.

111. Moffatt CJ, Franks PJ, Hardy D, Lewis M, Parker V, Feldman JL. A preliminary randomized controlled study to determine the application frequency of a new lymphoedema bandaging system. *Br J Dermatol.* 2012;166(3):624-632.

112. Paramanandam VS, Dylke E, Clark GM, et al. Prophylactic Use of Compression Sleeves Reduces the Incidence of Arm Swelling in Women at High Risk of Breast Cancer-Related Lymphedema: A Randomized Controlled Trial. *J Clin Oncol.* 2022;40(18):2004-2012.

113. Ridner SH, Dietrich MS, Boyages J, et al. A Comparison of Bioimpedance Spectroscopy or Tape Measure Triggered Compression Intervention in Chronic Breast Cancer Lymphedema Prevention. *Lymphat Res Biol.* 2022.

114. Lymphoedema Framework. Template for Practice: compression hosiery in lymphoedema. In. London: MEP Ltd; 2006.

115. Partsch H. Improving the venous pumping function in chronic venous insufficiency by compression as dependent on pressure and material. *Vasa.* 1984;13(1):58-64.

116. European Wound Management Association (EWMA). Position Document: Understanding compression therapy. In. London: MEP Ltd; 2003.

117. Franks PJ, Moffatt CJ, Doherty DC, Williams AF, Jeffs E, Mortimer PS. Assessment of health-related quality of life in patients with lymphedema of the lower limb. *Wound Repair Regen.* 2006;14(2):110-118.
118. Chitambira F. Patient perspectives: Explaining low rates of compliance to compression therapy. *Wound Practice and Research.* 2019;27(4):168–174.
119. Anderson I. Optimising concordance with compression hosiery in the community setting. *Br J Community Nurs* 2015;20(2):67-72.
120. Dylke ES, Kilbreath S. Current rehabilitation processes do not prevent long-term impairments after treatment for breast cancer in Australia. *Aust Fam Physician.* 2015;44(6):405-409.
121. NSW Agency for Clinical Innovation. Lymphoedema: A guide for clinical services. In. Sydney: ACI; 2018.
122. Eriksson B, Jorup-Rönström C, Karkkonen K, Sjöblom AC, Holm SE. Erysipelas: clinical and bacteriologic spectrum and serological aspects. *Clin Infect Dis.* 1996;23(5):1091-1098.
123. The Australian Commission on Safety and Quality in Healthcare. Australian Atlas of Healthcare Variation 2017. In. Sydney. 2017:81-90.
124. National Health Performance Authority. Healthy Communities: Potentially preventable hospitalisations in 2013–14. In. Canberra: AIHW, Australian Government; 2015.
125. National Health Performance Authority. Hospital Performance: Costs of acute admitted patients in public hospitals in 2011–12. In. Canberra: AIHW, Australian Government; 2016.
126. Todd M. Chronic oedema: impact and management. *Br J Nurs.* 2013;22(11):623-627.
127. Sullivan T, de Barra E. Diagnosis and management of cellulitis. *Clin Med (Lond).* 2018;18(2):160-163.
128. Australasian Lymphology Association. About the National Lymphoedema Practitioners Register. [Website]. 2018; http://www.lymphoedema.org.au/the-register-updated/. Accessed September 2018.
129. Carratala J, Roson B, Fernandez-Sabe N, et al. Factors associated with complications and mortality in adult patients hospitalized for infectious cellulitis. *Eur J Clin Microbiol Infect Dis.* 2003;22(3):151-157.
130. Nassaji M, Ghorbani R, Ghashghaee S. Risk factors of acute cellulitis in adult patients: A case-control study. *EJM.* 2016;21(1):26-30.
131. Man IO, Markland KL, Morrissey MC. The validity and reliability of the Perometer in evaluating human knee volume. *Clin Physiol Funct Imaging.* 2004;24(6):352-358.

132. Czerniec S, Ward L, Lee M-J, Refshauge K, Beith J, L Kilbreath S. Segmental measurement of breast cancer-related arm lymphoedema using perometry and bioimpedance spectroscopy. *Support Care Cancer.* 2010;19:703-710.
133. Czerniec SA, Ward LC, Refshauge KM, et al. Assessment of breast cancer-related arm lymphedema-comparison of physical measurement methods and self-report. *Cancer Invest.* 2010;28(1):54-62.
134. Bulley C, Coutts F, Tan C-W. Perometry limb volume measurement: Protocol development and reliability. *Eur J Physiother.* 2013;15(4).
135. Devoogdt N, Lemkens H, Geraerts I, et al. A new device to measure upper limb circumferences: validity and reliability. *Int Angiol.* 2010;29(5):401-407.
136. Keeley V, Crooks S, Locke J, Veigas D, Riches K, Hilliam R. A quality of life measure for limb lymphoedema (LYMQOL). *J lymphoedema.* 2010;5:26-37.
137. Yang Y, Brazier J, Longworth L. EQ-5D in skin conditions: an assessment of validity and responsiveness. *Eur J Health Econ.* 2015;16(9):927-939.
138. R Core Team. R: A language and environment for statistical computing. 2018. https://www.R-project.org/.
139. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. *Cochrane Database Syst Rev.* 2012;11(11).
140. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med.* 2001;33(5):337-343.
141. Chira S, Miller LG. Staphylococcus aureus is the most common identified cause of cellulitis: a systematic review. *Epidemiol Infect.* 2010;138(3):313-317.
142. Australian Commission on Safety and Quality in Health Care. Antimicrobial Stewardship in Australian Health Care 2018. In. Sydney: ACSQHC; 2018.
143. Yasuhara H, Shigematsu H, Muto T. A study of the advantages of elastic stockings for leg lymphedema. *Int Angiol.* 1996;15(3):272-277.
144. Pappas CJ, O'Donnell TF, Jr. Long-term results of compression treatment for lymphedema. *J Vasc Surg.* 1992;16(4):555-562.
145. Rathbun SW, Kirkpatrick AC. Treatment of chronic venous insufficiency. *Curr Treat Options Cardiovasc Med.* 2007;9(2):115-126.
146. Nelson EA, Bell-Syer SEM. Compression for preventing recurrence of venous ulcers. *Cochrane Database Syst Rev.* 2014(9).

147. Elwell R. The management and treatment of hyperkeratosis. *Br J Nurs.* 2017;26(8):468-470.
148. Miteva M, Romanelli P, Kirsner RS. Lipodermatosclerosis. *Dermatol Ther.* 2010;23(4):375-388.
149. Independent Hospital Pricing Authority. National Hospital Cost Data Collection Report, Public Sector, Round 22 (Financial year 2017-18). February 2021; https://www.ihpa.gov.au/publications/national-hospital-cost-data-collection-report-public-sector-round-22-financial-year. Accessed June 2021.
150. Challener D, Marcelin J, Visscher S, Baddour L. Hospital costs for patients with lower extremity cellulitis: a retrospective population-based study. *Hosp Pract (1995).* 2017;45(5):196-200.
151. Webb E, Neeman T, Bowden FJ, Gaida J, Mumford V, Bissett B. Compression Therapy to Prevent Recurrent Cellulitis of the Leg. *N Engl J Med.* 2020;383(7):630-639.
152. Webb E, Neeman T, Gaida J, Bowden FJ, Mumford V, Bissett B. Impact of Compression Therapy on Cellulitis (ICTOC) in adults with chronic oedema: a randomised controlled trial protocol. *BMJ Open.* 2019;9(8):e029225.
153. Australian Government Department of Health. Schedule of Pharmaceutical Benefits. January 2018; https://www.pbs.gov.au/info/publication/schedule/archive. Accessed July 2021.
154. Australian Government Department of Health. Pharmaceutical Benefits: Fees, Patient Contributions and Safety Net Thresholds. 2021; https://www.pbs.gov.au/info/healthpro/explanatory-notes/front/fee. Accessed 13 July 2021.
155. Australian Government Department of Social Services. Age Pension. 2019; https://www.dss.gov.au/seniors/benefits-payments/age-pension. Accessed July 2021.
156. Independent Hospital Pricing Authority. Australian Refined Diagnosis Related Groups Version 10.0 Final Report. 2019; https://www.ihpa.gov.au/what-we-do/admitted-acute-care/ar-drg-version-10. Accessed July 2021.
157. Australian Government Department of Health. Medicare Benefits Schedule Book: Operating from 1 January 2018. 2017; http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/90CB91EE0B6FB8A9CA2586140082584E/$File/201801-MBS.pdf. Accessed July 2021.
158. Australian Government Department of Health. Annual Medicare statistics. 2020; https://www1.health.gov.au/internet/main/publishing.nsf/Content/Medicare%20Statistics-1. Accessed July 2021.

159. Australian Bureau of Statstics. Average Weekly Earnings, Australia, May 2018. August 2018; https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/6302.0Main+Features1May%202018. Accessed July 2021.

160. National Disability Insurance Agency. NDIS Price Guide: Australian Capital Territory, Northern Territory, South Australia, Western Australia. 2017; file:///C:/Users/lizzi/Downloads/PB%20Price%20Guide%20201718%20ACT%20NT%20SA%20WA%20PDF_1.pdf. Accessed 23 July 2021.

161. Australian Government Australia Taxation Office. Car Expenses. May 2021; https://www.ato.gov.au/Individuals/Income-and-deductions/Deductions-you-can-claim/Transport-and-travel-expenses/Car-expenses/. Accessed July 2021.

162. Australian Tax Office. Rates for financial year ending 30 June 2018. 2018; https://www.ato.gov.au/Tax-professionals/TP/Financial-year-ending-30-June-2018/. Accessed 01 February 2022.

163. Mowbray FI, Fox-Wasylyshyn SM, El-Masri MM. Univariate Outliers: A Conceptual Overview for the Nurse Researcher. *Can J Nurs Res.* 2019;51(1):31-37.

164. Nicolaides A, Kakkos S, Baekgaard N, et al. Management of chronic venous disorders of the lower limbs. Guidelines According to Scientific Evidence. Part I. *Int Angiol.* 2018;37(3):181-254.

165. SAGE GROUP. Chronic venous disease (CVD): epidemiology, costs and consequences. http://thesagegroup.us/pages/reports/CVD-report.php. Accessed 23 November 2021.

166. Demczyszak I, Sutkowska E, Jasiak M, Fortuna M, Mazurek J. The impact of compression garments on the quality of life in patients with chronic venous disease. *Fizjoterapia.* 2017;24 (2):19–22.

167. Appelen D, van Loo E, Prins MH, Neumann MH, Kolbach DN. Compression therapy for prevention of post-thrombotic syndrome. *Cochrane Database Syst Rev.* 2017;9:CD004174.

168. Electronic Therapeutic Guidelines Complete [digital]. Antibiotics: Cellulitis and Erysipelas. In. Melbourne: Therapuetic Guidelines Limited; 2021.

169. Michael CA, Dominey-Howes D, Labbate M. The antimicrobial resistance crisis: causes, consequences, and management. *Front Public Health.* 2014;2:145.

170. UpToDate. Cellulitis and skin abscess in adults: Treatment. 2020; https://www.uptodate.com/contents/cellulitis-and-skin-abscess-in-adults-treatment. Accessed 2020.

171. Cavalheri V. Critically appraised paper: In people with chronic oedema of the leg and cellulitis, compression therapy is more effective at reducing recurrence of cellulitis than conservative treatment [synopsis]. *J Physiother.* 2021;67(1):62.
172. Paramanandam VS. Critically appraised paper: In people with chronic oedema of the leg and cellulitis, compression therapy is more effective at reducing recurrence of cellulitis than conservative treatment [commentary]. *J Physiother.* 2021;67(1):62.
173. Australian Physiotherapy Association. Compression therapy to prevent recurrent cellulitis of the leg. 2020; https://australian.physio/research/prf/translation/compression-therapy-prevent-recurrent-cellulitis-leg. Accessed 30 Nov 2020, 2020.
174. UpToDate. About Us. 2020; https://www.uptodate.com/home/about-us, 2020.
175. Australasian Lymphology Association. ALA Position Statements, Papers and Guidelines. 2022; https://www.lymphoedema.org.au/about-lymphoedema/position-statements/. Accessed July 2022.
176. Montori VM, Devereaux PJ, Adhikari NKJ, et al. Randomized Trials Stopped Early for Benefit: A Systematic Review. *JAMA.* 2005;294(17):2203-2209.
177. Nicolaides AN, Allegra C, Bergan J, et al. Management of chronic venous disorders of the lower limbs: guidelines according to scientific evidence. *Int Angiol.* 2008;27(1):1-59.
178. The Royal Australian College of General Practitioners. General practice: Health of the nation 2017. In. East Melbourne: The Royal Australian College of General Practitioners; 2017.
179. Webb E, Bissett B, Neeman T, Bowden F, Preston E, Mumford V. Compression Therapy Is Cost-Saving in the Prevention of Lower Limb Recurrent Cellulitis in Patients with Chronic Edema. *Lymphat Res Biol.* 2022.
180. Webb E, Bowden FJ, Bissett B. Letter to the editor: Compression Therapy to Prevent Recurrent Cellulitis of the Leg. *N Engl J Med.* 2020;383(19):1891-1892.

APPENDIX A: Evidence of dissemination of research

Title	Format	Author/Publisher, Date published	Intended Audience	Website Link or Reference
1. Tools for practice: Under Pressure: Compression stockings for recurrent cellulitis?	Tool for practice	Jamie Grunwald, Dr Christina Korownyk and Betsy Thomas (The Patients, Experience, Evidence, Research (PEER) team), the College of Family Physicians of Canada, Nov 2021	Health professionals	https://gomainpro.ca/wp-content/uploads/tools-for-practice/1635783832_tfp301_compstockings.pdf
2. Journal Club: Compression Therapy to Prevent Recurrent Cellulitis of the Leg	Presentation/lecture	Dr Olivia Seecof, Department of Family and Community Presentations and ground rounds, Thomas Jefferson University, Nov 2020	Health professionals, students	Seecof, Olivia. Journal Club: Compression Therapy to Prevent Recurrent Cellulitis of the Leg. *Department of Family & Community Medicine Presentations and Grand Rounds.* 2020; Paper 456: https://jdc.jefferson.edu/fmlectures/456.
3. Compression Reduces Recurrent Cellulitis in Patients with Chronic Leg Edema	Journal Article	Professor Mark Ebell, American Family Physician, February 2021	Health professionals	Ebell MH. Compression Reduces Recurrent Cellulitis in Patients with Chronic Leg Edema. *American family physician.* 2021;103(4):247.
4. Compression stockings for recurrent cellulitis	Journal Article	Jamie Grunwald, Christina Korownyk and Betsy Thomas, Canadian Family Physician, 2022	Health professionals	Grunwald J, Korownyk CS, Thomas B. Compression stockings for recurrent cellulitis. *Canadian Family Physician.* 2022;68(3):194-194.

Title	Format	Author/Publisher, Date published	Intended Audience	Website Link or Reference
5. Cellulitis in Chronic oedema	Webinar	Dr Tonny Karlsmark and Dr Ewa Anna Burian, The International Lymphoedema Framework, April 2021	Health professionals	https://lymphoedemaeducation.com.au/2021/09/cellulitis-update/
6. Top 10 papers in clinical infectious diseases	Conference Presentation	Professor Joshua Davis, Australasian Society for Infectious Diseases Annual Scientific Meeting, 26 March 2021	Infectious Diseases Physicians	Davis, J. Top 10 papers in clinical infectious diseases. Presented at the Australasian Society for Infectious Diseases Annual Scientific Meeting; 26 March 2021. https://asid.eventsair.com/asid-annual-scientific-meeting-2021/speakers. Accessed 30 June 2021.
7. Compression Counters Cellulitis	Quarterly Publication 'Lymph Exchange'	Elizabeth Webb, Australasian Lymphology Association, Feb 2021	Lymphoedema clinicians	Webb E. Compression Counters Cellulitis. Lymph Exchange. Australasian Lymphology Association; February 2021.
8. Spotlight on Research: What's new in cellulitis	Quarterly Publication 'News and Views'	Professor Vaughan Keeley, British Lymphology Society, 2021	Health Professionals	Keeley, V. Spotlight on Research: What's new in cellulitis. News & Views. British Lymphology Society; 2021.
9. Compression Counters Cellulitis: How compression therapy substantially reduces the recurrence of cellulitis	Quarterly Publication 'News and Views'	Elizabeth Webb, British Lymphology Society, 2021	Lymphoedema clinicians	Webb, E. Compression Counters Cellulitis: How compression therapy substantially reduces the recurrence of cellulitis. News & Views. British Lymphology Society; 2021.

Title	Format	Author/Publisher, Date published	Intended Audience	Website Link or Reference
10. Compression Counters Cellulitis	Quarterly Publication 'Pathways'	Elizabeth Webb, Canadian Lymphoedema Framework, March 2021	Lymphoedema clinicians and consumers	Webb E. Compression Counters Cellulitis (feature article). Pathways: Canada's Lymphedema Magazine. Canadian Lymphedema Framework; March 2021.
11. Compression garments reduced risk of recurrent cellulitis in adults with chronic edema	Online	American College of Physicians, August 2020	Health professionals	http://www.acpinternist.org/weekly/archives/2020/08/18/6.htm
12. Compression Therapy Cuts Cellulitis Risk in Chronic Leg Edema	Online	Medscape, August 2020	Health professionals	https://www.medscape.com/viewarticle/935845
13. Compression therapy prevents recurrence of cellulitis	Online	The Hospitalist, Dec 2021	Health professionals	https://www.the-hospitalist.org/hospitalist/article/249557/infectious-diseases/compression-therapy-prevents-recurrence-cellulitis
14. Compression therapy lowers odds of cellulitis in people with chronic leg edema	Online	Reuters Health, Dec 2020	Health professionals	https://www.mdalert.com/news/article/compression-therapy-lowers-odds-of-cellulitis-in-people-with-chronic-leg-edema
15. NEJM: Compression Therapy Prevention of Recurrent Cellulitis Without Antibiotics	Online	MedicalResearch.com, August 2020	Health professional, researchers, consumers	https://medicalresearch.com/author-interviews/nejm-compression-therapy-prevention-of-recurrent-cellulitis-without-antibiotics/55093/
16. Compression Therapy to Prevent Recurrent Cellulitis	Online	Physician's Weekly Online, Sept 2020	Health professionals	https://www.physiciansweekly.com/compression-therapy-to-prevent-recurrent-cellulitis/

Title	Format	Author/Publisher, Date published	Intended Audience	Website Link or Reference
17. Compression therapy may lower recurrent cellulitis in patients with chronic leg edema	Online	2 Minute Medicine, August 2022	Health professionals	https://www.2minutemedicine.com/compression-therapy-may-lower-recurrent-cellulitis-in-patients-with-chronic-leg-edema/
18. Compression therapy thwarts recurring cellulitis in small trial - Clinical Daily News	Online	McKnight's Long Term Care News, August 2020	Health professionals	https://www.mcknights.com/news/clinical-news/compression-therapy-thwarts-recurring-cellulitis-in-small-trial/
19. Compression therapy may help prevent cellulitis in chronic leg edema	Online	Healio, August 2020	Health professionals	https://www.healio.com/news/dermatology/20200818/compression-therapy-may-help-prevent-cellulitis-in-chronic-leg-edema
20. UC research hits the world stage	Online	University of Canberra Newsroom, August 2020	Students and academics	https://www.canberra.edu.au/about-uc/media/newsroom/2020/august/uc-research-hits-the-world-stage
21. Compression Therapy to Prevent Recurrent Leg Cellulitis	Online	NEJM Journal Watch, August 2020	Health professionals, academics	https://www.jwatch.org/na52157/2020/08/12/compression-therapy-prevent-recurrent-leg-cellulitis
22. Compression Therapy Reduces Recurrent Leg Cellulitis, Finds NEJM Study	Online	Medical dialogues, August 2020	Health professionals	https://medicaldialogues.in/medicine/news/compression-therapy-reduces-recurrent-leg-cellulitis-finds-study-68555
23. Compression Therapy Shows Promising Results in Reducing Incidents of Cellulitis	Online	Health Units, August 2020	Health professional, consumers	https://healthunits.com/news/compression-therapy-shows-promising-results-in-reducing-incidents-of-cellulitis/

Title	Format	Author/Publisher, Date published	Intended Audience	Website Link or Reference
24. Compression Therapy Lowers Recurrence of Cellulitis of Leg	Online	Physicians Briefing, August 2020	Health Professionals	https://www.physiciansbriefing.com/dermatology-3/misc-skin-disorders-news-620/compression-therapy-lowers-recurrence-of-cellulitis-of-leg-760348.html
25. UC student research hits the global stage	Online	Canberra Weekly, August 2020	Consumers, public	https://canberraweekly.com.au/uc-student-research-hits-the-global-stage/
26. Compression therapy study has global implications	Online	Australian Physiotherapy Association, October 2020	Health professionals	https://australian.physio/inmotion/compression-therapy-study-has-global-implications
27. Prevention of recurrent cellulitis	Online	The University of British Columbia: This changes my practice, June 2022	Health professionals	https://thischangedmypractice.com/prevention-of-recurrent-cellulitis/
28. Compression Therapy to Prevent Recurrent Cellulitis of the Leg	Online	Metabolic Health Digest, Nov 2020	Health professionals and consumers	https://www.metabolichealthdigest.com/compression-therapy-to-prevent-recurrent-cellulitis-of-the-leg/
29. Compression Therapy To Prevent Recurrent Cellulitis Of The Leg… Way To Go Bruce!	Online	Doctors Writing, March 2021	Health professionals	https://www.doctorswriting.com/news/compression-therapy-to-prevent-recurrent-cellulitis-of-the-leg-way-to-go-bruce
30. Compression therapy helps prevent recurrence of cellulitis	Online	Univadis, 2020	Health professionals and consumers	https://www.univadis.es/viewarticle/compression-therapy-helps-prevent-recurrence-of-cellulitis-727358

APPENDIX B: Evidence of ethical approvals

Ethical approvals were gained from:

- Australian Capital Territory Health: ETH.4.17.092
- Calvary Public Hospital Bruce: 53-2016
- University of Canberra: cross-institutional approval.

ACT Government
Health

ACT Health
Research Ethics and Governance Office
Human Research Ethics Committee

Ms Elizabeth Webb
Physiotherapy Department
Calvary Public Hospital
Haydon Dr
Bruce ACT 2617

Dear Ms Webb

ETH.4.17.092

The ACT Health Human Research Ethics Committee considered the proposed:

A randomised controlled trial to assess the impact of compression therapy to manage chronic oedema on recurrence of cellulitis at its meeting of 1 May 2017.

I am pleased to inform you that, following further correspondence, the committee agreed the proposal satisfied the requirements for ethically acceptable research as per the National Statement on Ethical Conduct in Human Research and as such the application has been approved.

Approval includes the following documents:

- NEAF
- Research Proposal
- Participant Information Sheet, revised 16 May 2017
- Consent Form, revised 16 May 2017
- Referral Form
- Core Tool
- Cellulitis Tool
- Assessment Post Initial Intervention
- LYMQOL – Lower Limb

I confirm that the ACT Health Human Research Ethics Committee is constituted according to the National Statement on Ethical Conduct in Human Research 2007 and is certified for single review of multi-centre clinical trials. ACT Health HREC operates in compliance with applicable regulatory requirements and the International Conference on Harmonization Guidelines on Good Clinical Practice.

I attach for your records an Outcome of Consideration of Protocol form.

Please note: this letter gives approval for ACT Health sites only. Please ensure appropriate approvals are in place at non-ACT Health sites.

Yours sincerely

Louise Morauta PSM PhD
Chair
ACT Health Human Research Ethics Committee

18 May 2017

PO Box 11 Woden ACT 2606 | Phone: 6174 7968 or 6174 5659 | E ethics@act.gov.au

Calvary | Public Hospital Bruce

Hospitality
Healing
Stewardship
Respect

17/01/17

Elizabeth Webb

Senior Clinician, Calvary Public Hospital Bruce
Physiotherapy Department

Cnr Belconnen Way & Haydon drive, Bruce, ACT

Dear Elizabeth

Re: 53-2016 "A randomised controlled trial to assess the impact of compression therapy to manage chronic oedema on recurrence of cellulitis"

I am pleased to advise that the Calvary Public Hospital Bruce Human Research Ethics Committee has approved your study titled "A randomised controlled trial to assess the impact of compression therapy to manage chronic oedema on recurrence of cellulitis" out of session.

Approval is granted from your anticipated commencement date 01/01/17 as stated in the application.

If your research continues past the anticipated completion date 01/06/22 stated in the application, it is expected that you will notify and seek continued approval from the HREC. Please note that approval is for a maximum three year period. If your research continues past a three year period it is a requirement that you **reapply** to the Human Research Ethics Committee for continued approval. Your date for renewal is 01/01/20

Following documents were tabled and approved as a part of the assessment process:-

- NEAF Cellulitis Study
- Research Proposal Cellulitis 21.11.16
- Literature Review
- Letter of Intent for Haddenham Healthcare Sponsorship
- Referral Form
- Participant Information Sheet
- Participant Consent Form
- Core Tool
- Cellulitis Tool
- LYMQOL Tool
- Estimate of Costs Form

- Elizabeth Webb CV
- Marie Coulombe CV
- Cover Letter to Calvary HREC

Please note that the Committee requires annual reports on the progress of your research. Reports should include:

- Progress to date (or outcome in the case of completed research)
- Maintenance and security of records
- Compliance with the approved protocol
- Compliance with any conditions of approval

The Committee also requires an immediate report in any of the following events:

- Any serious or unexpected adverse effect on participants
- Any proposed changes to the protocol
- Any unforeseen events that might affect continued ethical acceptability of the project
- Discontinuation of the project before the expected date of completion
- Any change in status of the researcher (e.g. change in employment)

An electronic reporting template is available on our website. Failure to submit reports will result in your approval being suspended or cancelled.

Should you wish to publish your project and Calvary Public Hospital Bruce/Calvary John James Hospital/Clare Holland House/Calvary Retirement Community is in any way identified, the Committee requires that you submit your paper for HREC approval prior to publication.

Yours sincerely,

Dr John Vinen

Chair, Human Research Ethics Committee

Calvary Public Hospital Bruce

ACT 2617

UNIVERSITY OF CANBERRA
AUSTRALIA'S CAPITAL UNIVERSITY

19 June 2017

APPROVED – ETH.4.17.092

Dr Bernie Bissett
Faculty of Health
University of Canberra
Canberra ACT 2601

Dear Bernie,

The Human Research Ethics Committee has considered your application to conduct research with human subjects for the project **A randomised controlled trial to assess the impact of compression therapy to manage chronic oedema on recurrence of cellulitis.**

The Committee made the following evaluation: Cross-institutional approval granted

The following general conditions apply to your approval.

These requirements are determined by University policy and the ***National Statement on Ethical Conduct in Human Research*** (National Health and Medical Research Council, 2007).

Monitoring:	You must provide the Committee with annual reports as well as a final report upon completion of the study. Please note: all amendments and any reviews must also be submitted to the Committee that granted original approval.
Reporting Adverse Events	You must report any unexpected adverse events or complications that occur anytime during the conduct of the research study or during the follow up period after the research. Please refer these matters promptly to the HREC. Failure to do so may result in the withdrawal of the Ethics approval.
Discontinuation of research:	You must inform the Committee, giving reasons, if the research is not conducted or is discontinued.
Extension of approval:	If your project will not be complete by the anticipated completion date, you must apply in writing for extension of approval. Application should be made before current approval expires; should specify a new completion date; should include reasons for your request.
Contact details and notification of changes:	You should advise the Committee of any change of address during or soon after the approval period including, if appropriate, email address(es).

Yours sincerely
Human Research Ethics Committee

Hendryk Flaegel
Research Ethics & Integrity
Research Services
T (02) 6201 5220
E hendryk.flaegel@canberra.edu.au

www.canberra.edu.au
Postal Address:
University of Canberra ACT 2601 Australia
Location:
University Drive Bruce ACT
Australian Government Higher Education Registered Provider Number (CRICOS): 00212K

APPENDIX C: Study tool and publication permissions

Permission/entitlement to include published articles in thesis:

a) BMJ Open

b) New England Journal of Medicine

c) Lymphatic Research and Biology

Permission to use the following study tools:

a) LYMQOL

b) EQ-5D-3L

BMJ Open

The below email from BMJ Open confirms authors can reuse their published articles within a thesis.

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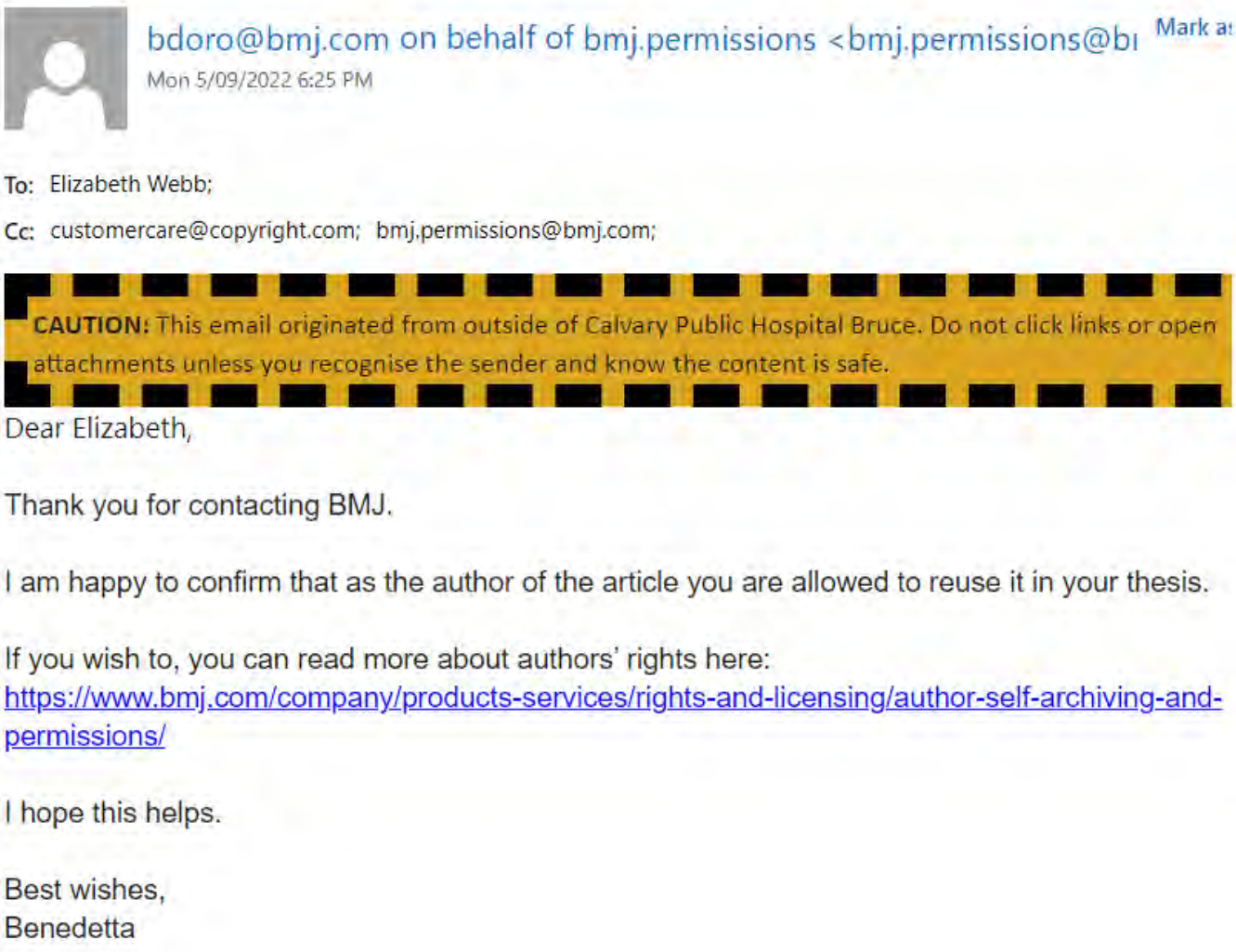

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Benedetta

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Lymphatic Research and Biology

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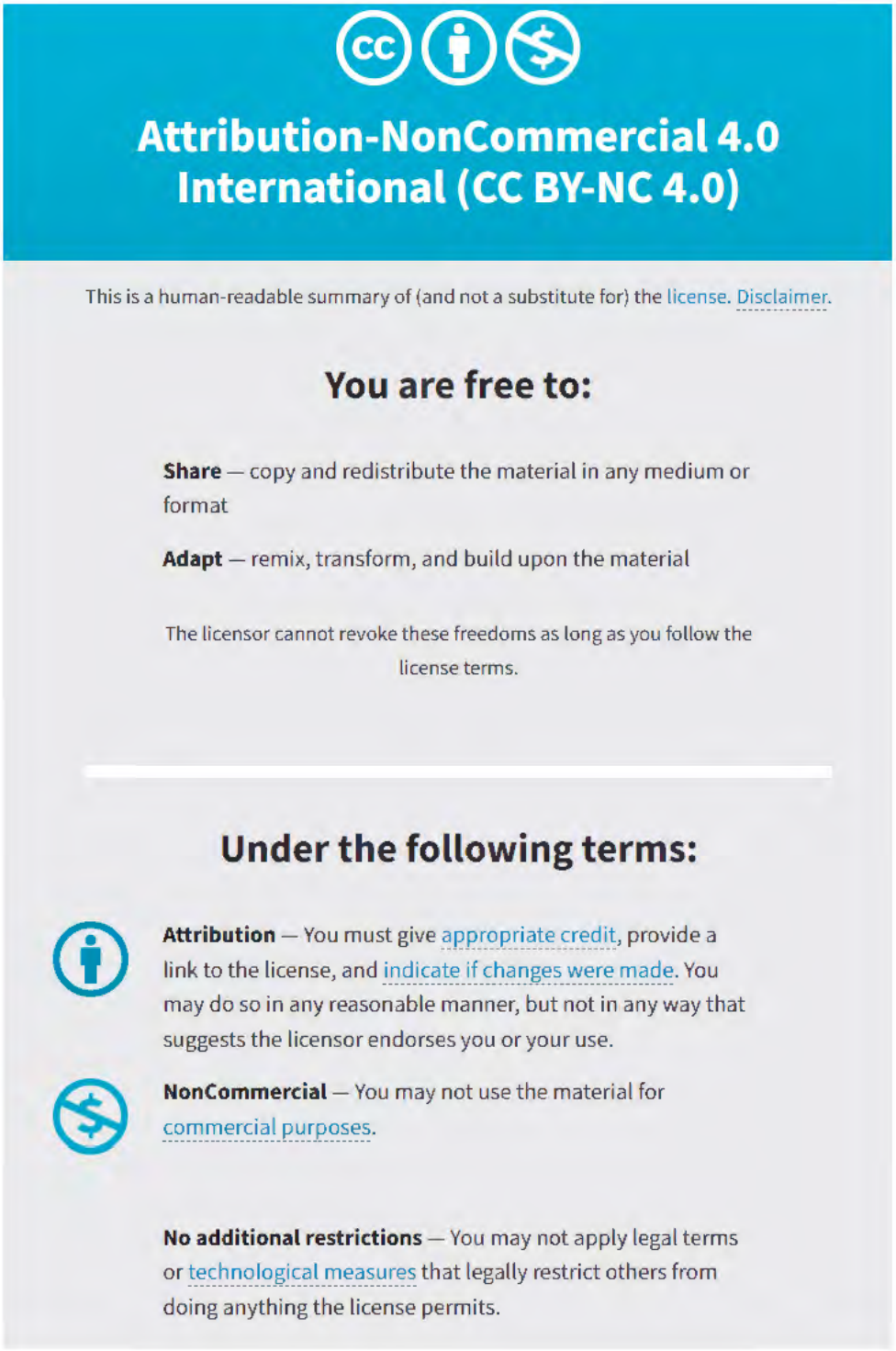

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LYMQOL Registration of Intended Use:

Name: Elizabeth Webb **Title:** Physiotherapist

Work Address: Calvary Public Hospital Bruce, Haydon drive, Bruce ACT 2617, Australia

Contact Number +612 6201 6190

Email Address elizabeth.webb@calvary-act.com.au

Intended use: Research Project / Clinical Audit / Clinical Application / Other

Details: (Please include information about the patient group (age, diagnosis), numbers of patients, number of times LYMQOL will be completed by each patient etc.)

RCT to assess the impact of compression therapy to manage chronic oedema on recurrence of cellulitis. Plan to recruit 152 participants c chronic oedema & Hx of ≥2 episodes leg cellulitis in past 2 years - all participants ≥18 yrs.

Please send me revised versions of LYMQOL: Yes ☑ No ☐

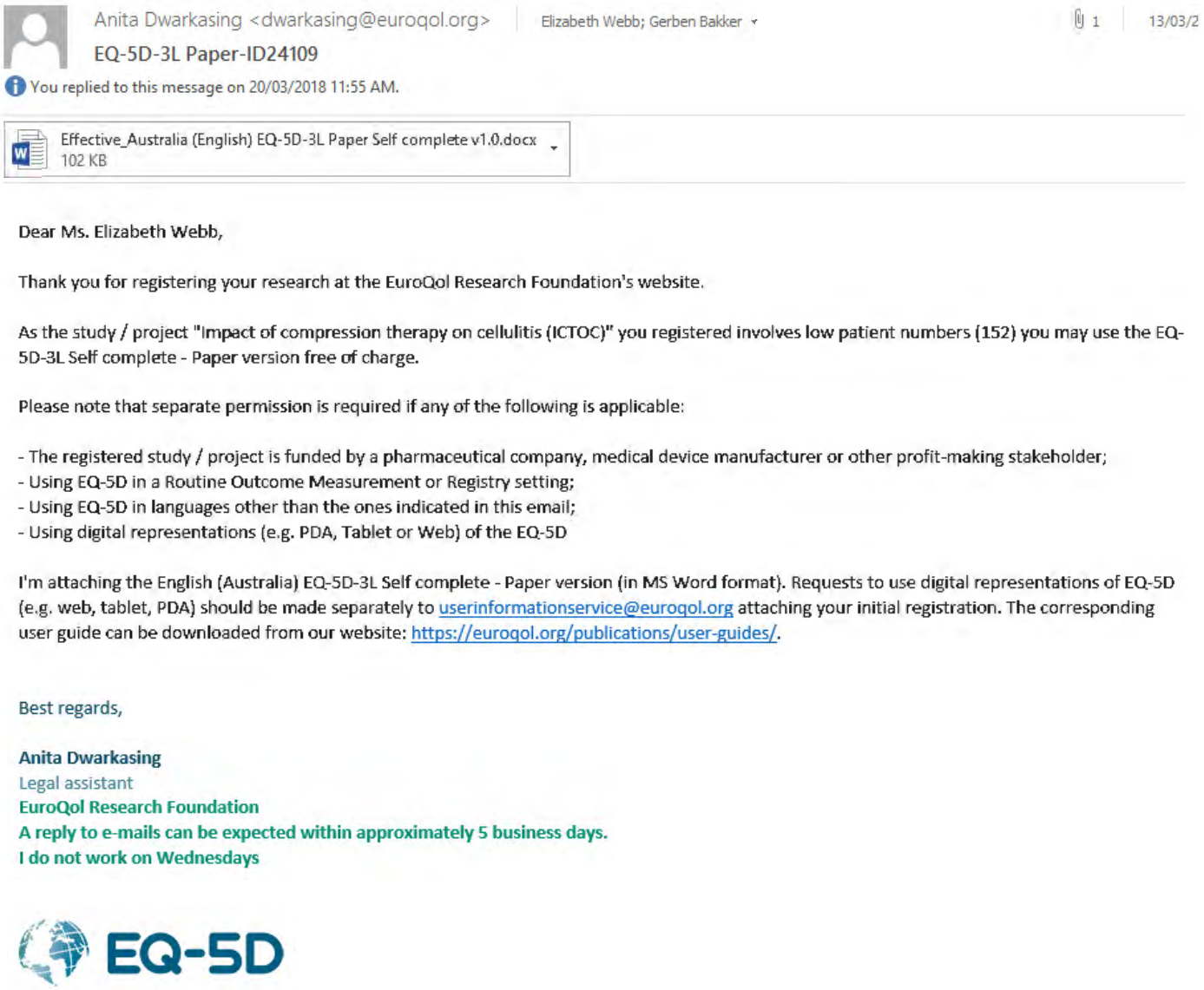
Please send me the references of future publications: Yes ☑ No ☐

Thank you for taking the time to complete this form.

Please return completed forms to
Katie Riches (Research Nurse),
Nightingale Macmillan Unit,
Royal Derby Hospital, Uttoxeter Rd.
Derby. DE22 3NE.

Lymqol to be completed 5x over 3yrs

EQ-5D-3L Registration



Anita Dwarkasing <dwarkasing@euroqol.org> | Elizabeth Webb; Gerben Bakker | 1 | 13/03/2

EQ-5D-3L Paper-ID24109

You replied to this message on 20/03/2018 11:55 AM.

Effective_Australia (English) EQ-5D-3L Paper Self complete v1.0.docx
102 KB

Dear Ms. Elizabeth Webb,

Thank you for registering your research at the EuroQol Research Foundation's website.

As the study / project "Impact of compression therapy on cellulitis (ICTOC)" you registered involves low patient numbers (152) you may use the EQ-5D-3L Self complete - Paper version free of charge.

Please note that separate permission is required if any of the following is applicable:

- The registered study / project is funded by a pharmaceutical company, medical device manufacturer or other profit-making stakeholder;
- Using EQ-5D in a Routine Outcome Measurement or Registry setting;
- Using EQ-5D in languages other than the ones indicated in this email;
- Using digital representations (e.g. PDA, Tablet or Web) of the EQ-5D

I'm attaching the English (Australia) EQ-5D-3L Self complete - Paper version (in MS Word format). Requests to use digital representations of EQ-5D (e.g. web, tablet, PDA) should be made separately to userinformationservice@euroqol.org attaching your initial registration. The corresponding user guide can be downloaded from our website: https://euroqol.org/publications/user-guides/.

Best regards,

Anita Dwarkasing
Legal assistant
EuroQol Research Foundation
A reply to e-mails can be expected within approximately 5 business days.
I do not work on Wednesdays

EQ-5D

APPENDIX D: Published copy of paper one

Impact of Compression Therapy on Cellulitis (ICTOC) in adults with chronic oedema: a randomised controlled trial protocol

BMJ Open

Impact of Compression Therapy on Cellulitis (ICTOC) in adults with chronic oedema: a randomised controlled trial protocol

Elizabeth Webb,[1,2] Teresa Neeman,[3] Jamie Gaida,[4] Francis J Bowden,[5,6] Virginia Mumford,[7] Bernie Bissett[2]

To cite: Webb E, Neeman T, Gaida J, *et al*. Impact of Compression Therapy on Cellulitis (ICTOC) in adults with chronic oedema: a randomised controlled trial protocol. *BMJ Open* 2019;**9**:e029225. doi:10.1136/bmjopen-2019-029225

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-029225).

Received 17 January 2019
Revised 30 June 2019
Accepted 3 July 2019

For numbered affiliations see end of article.

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Elizabeth Webb;
elizabeth.webb@calvary-act.com.au

ABSTRACT

Introduction Cellulitis represents a significant burden to patients' quality of life (QOL) and cost to the healthcare system, especially due to its recurrent nature. Chronic oedema is a strong risk factor for both an initial episode of cellulitis and cellulitis recurrence. Expert consensus advises compression therapy to prevent cellulitis recurrence in individuals with chronic oedema, however, there is little supporting evidence. This research aims to determine if the management of chronic oedema using compression therapy effectively delays the recurrence of lower limb cellulitis.

Methods and analysis A randomised controlled trial with cross-over will be used to assess the impact of compression therapy on clinical outcomes (time to next episode of cellulitis, rate of cellulitis-related hospital presentations, QOL and leg volume). Using concealed allocation, 162 participants will be randomised into the intervention (compression) or control (no compression) group. Randomisation will be stratified by prophylactic antibiotic use. Participants will be followed up at 6 monthly intervals for up to 3 years or until 45 episodes of cellulitis occur across the cohort. Following an episode of recurrent cellulitis, control group participants will cross-over to the intervention group. Survival analysis will be undertaken to assess the primary outcome measure of time to cellulitis recurrence. The hypotheses are that compression therapy to control lower limb chronic oedema will delay recurrent lower limb cellulitis, reduce the rate of associated hospitalisations, minimise affected limb volume and improve the QOL of this population.

Ethics and dissemination Ethics approval has been obtained from the ethics committees of all relevant institutions. Results will be disseminated through relevant peer-reviewed journal articles and conference presentations.

Trial registration number ACTRN12617000412336; Pre-results. The ICTOC trial is currently in progress. Participant recruitment started in May 2017 and is expected to continue until December 2019.

Strengths and limitations of this study

- Randomisation of participants will be stratified by prophylactic antibiotic use to ensure antibiotic use does not confound treatment outcome.
- Due to the nature of the intervention, blinding is not feasible for participants or assessors.
- Assessment tools and methods (perometer, diagnosis of cellulitis by medical practitioners external to the trial, verification of data using the medical record or general practitioner) have been selected to minimise potential measurement bias.
- The use of broad inclusion criteria will allow for trial results to be generalised to adults across a range of settings nationally and internationally.

BACKGROUND AND RATIONALE

Cellulitis is a common acute bacterial infection of the skin and subcutaneous tissue.[1] The majority of cellulitis episodes (69%–81%) occur in the lower limbs.[2–4] In Australia, lower limb cellulitis is associated with significant health costs due to frequent hospital admissions and high levels of morbidity. In 2014–2015, there were 59 466 hospitalisations for cellulitis,[5] with the average admission lasting 4.3 days.[6] In 2013–2014, cellulitis was the third leading cause of potentially preventable hospital admissions, with over half of all admissions for cellulitis being considered potentially preventable.[6 7] Erysipelas is an infection similar to cellulitis, which typically affects more superficial tissues. As the terms erysipelas and cellulitis are often used interchangeably and most clinical studies do not differentiate between them, this paper will consider them as one entity.

Recurrence of cellulitis is common and represents a significant proportion of the disease burden. In a 3-year time frame cellulitis has been reported to recur in 29%–47% of patients,[8 9] with a case series in Sweden finding that 13% of patients admitted for cellulitis developed two or more recurrences within 3 years.[9] In light of the significant recurrence rates, effective interventions

which reduce recurrence could limit the disease burden and improve patient outcomes.

Oedema occurs when capillary filtration overwhelms the available lymphatic drainage.[10] Lymphoedema specifically refers to persistent oedema resulting from lymphatic drainage failure.[11] Chronic oedema is an umbrella term that refers to oedema resulting from insufficient lymphatic drainage, where the principal cause of oedema may be increased capillary filtration and/or lymphatic drainage failure.[11] As such, the term chronic oedema encompasses oedema of various aetiologies, including lymphoedema. For the purpose of this trial, we will use the term chronic oedema.

Lymphoedema and chronic oedema are potent risk factors for developing lower limb cellulitis and for its recurrence.[4 8 12 13] It is broadly accepted that the relationship between cellulitis and chronic oedema is a vicious cycle.[8 14] Chronic oedema predisposes individuals to cellulitis and with each episode of cellulitis, the lymphatic system is further impaired, increasing residual oedema and heightening risk of future cellulitis infections.[14] Thus, chronic oedema is not only a result of cellulitis but also increases the risk of recurrence.[14]

The standard treatment for chronic oedema includes compression therapy and skin care.[15] Compression bandaging can be used to reduce oedema in a limb, and daily wear of compression garments is used to control oedema. There is general consensus that in addition to antibiotic prescription, compression to manage oedema should be an adjuvant treatment for patients with chronic oedema who are experiencing cellulitis recurrence.[1 8 14 16] Despite this common recommendation and the strong evidence supporting the relationship between oedema and cellulitis, there is a paucity of evidence to support the use of compression to manage chronic oedema to prevent cellulitis recurrence.

The time-intensive nature of compression therapy and the fact that measuring meaningful outcomes requires lengthy assessment periods probably contribute to the lack of research in this field. Only one study has been conducted on the impact of oedema management on cellulitis recurrence,[17] with a second study incidentally observing a reduction in 'infection' among patients receiving oedema management, although this was not a research objective.[18] While both studies support the hypothesis that oedema management decreases cellulitis recurrence, their conclusions are hampered by methodological limitations, including pre-post intervention methods, small sample sizes and change in infection rate not being specified a research objective.[17 18] While research regarding compression therapy to prevent cellulitis recurrence is scarce, there is high-quality evidence to support the use of prophylactic antibiotics. A multicentre, double-blind, randomised controlled trial (RCT) found that the use of prophylactic antibiotics in patients experiencing recurrent cellulitis is effective in preventing subsequent attacks, although the effect diminishes following prophylaxis cessation.[19] A 2017 Cochrane systematic review of interventions to prevent cellulitis identified six studies investigating prophylactic antibiotics, but no other randomised trials investigating other prophylactic measures such as oedema management or skin care.[20] Thus further research into the efficacy of prophylactic measures other than antibiotic is warranted.[20]

The following protocol describes a RCT with cross-over to determine if the use of compression therapy for adults experiencing lower limb recurrent cellulitis and chronic oedema will delay cellulitis recurrence.

RESEARCH HYPOTHESES

The hypotheses are that compression therapy to control lower limb chronic oedema will delay recurrent lower limb cellulitis, reduce the rate of associated hospitalisations, minimise affected limb volume and improve the quality of life (QOL) of this population.

RESEARCH OBJECTIVES

Primary objective

The primary objective was to determine if compression therapy delays the recurrence of lower limb cellulitis in adults with lower limb chronic oedema and recurrent cellulitis.

Secondary objectives

The secondary objectives were to determine if, in adults with lower limb chronic oedema and recurrent cellulitis, compression therapy: (1) reduces the rate of cellulitis-related hospital presentations; (2) reduces affected leg volume; and (3) improves QOL.

TRIAL DESIGN

A RCT with cross-over will be used to assess the impact of compression therapy on clinical outcomes (time to next episode of cellulitis, rate of cellulitis-related hospital presentations, QOL and leg volume). Participants will be randomised to the intervention or control group by block randomisation using sealed opaque envelopes. As prophylactic antibiotics have been shown to influence cellulitis recurrence,[19–21] randomisation of participants will be stratified by prophylactic antibiotic use. Following an episode of cellulitis, participants in the control group will cross-over into the intervention group, whereas intervention group participants will remain in their original group and continue to receive compression therapy. Figure 1 shows the proposed participant allocation process.

The absence of high-quality evidence regarding the impact of compression therapy on recurrence of cellulitis means there is uncertainty as to whether it is an effective intervention, justifying the use of an RCT. Although there is no high-quality evidence to support the use of the compression therapy to prevent cellulitis in this patient population, it reflects the accepted expert opinion and the standard clinical practice of the institution conducting the trial.

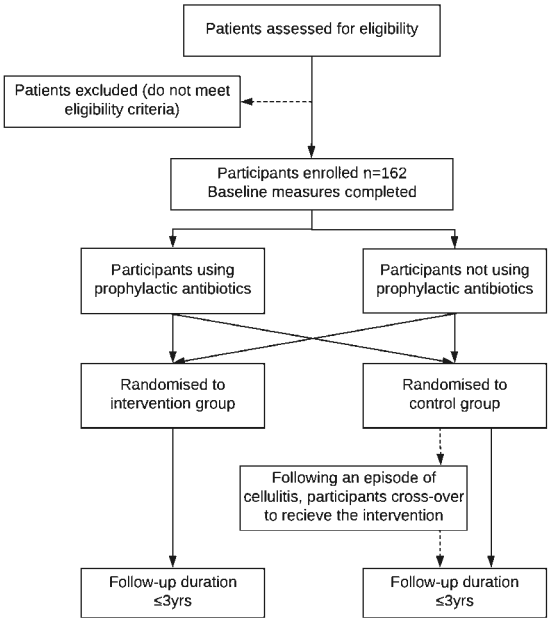

Figure 1 Anticipated participant flow through trial.

Therefore, the trial design crosses the control group participants over into the intervention group following the first episode of cellulitis to ensure no participant continues to experience recurrent cellulitis episodes without receiving the institution's standard intervention.

METHODS

Study setting and population

The trial will be conducted at the Calvary Public Hospital Bruce (CPHB) outpatient lymphoedema clinic. Adults with lower limb chronic oedema and a history of recurrent cellulitis who meet the eligibility criteria will be recruited from the two major ACT public hospitals (CPHB and Canberra Hospital) and general practitioners servicing the ACT and nearby NSW residents.

Eligibility criteria

Inclusion criteria

- ≥ 18 years of age.
- Two or more episodes of cellulitis diagnosed in the same leg in the past 2 years (at the time of referral). Clinical diagnosis of cellulitis ideally will have been based on the presence of acute erythema, oedema, warmth and pain, with spreading involvement of the skin and subcutaneous tissues, malaise and possibly fever.[1 22 23]
- Chronic oedema (oedema persisting ≥3 months) in the leg(s) that have had recurrent cellulitis diagnosed (presence of oedema confirmed by an accredited lymphoedema therapist through interview and physical examination, including a thorough medical history combined with limb palpation and visual assessment).
- Understanding of involvement in the study as per the participant information sheet.
- Provision of informed consent.
- Able to attend regularly scheduled appointments for the duration of the study.
- Has a valid Medicare number.

Exclusion criteria

- Currently wearing effective compression garments (≥compression class 2, or compression class 1 if considered effective by a lymphoedema therapist) regularly (≥5 days per week).
- Declines to participate or is unable to participate for whatever reason.
- Receiving end of life care.
- Medically unstable.
- Chronic wound/ulcer, or a wound/ulcer requiring specialist treatment or treatment that prevents the use of compression garments.
- Unable to wear compression (unable to don/doff garments or has a medical condition that contraindicates the use of compression).

Interventions

All assessments, interventions and outcome measures will be conducted by a physiotherapist or occupational therapist who meets the registration requirements for category one of the Australian National Lymphoedema Practitioners Register.[24]

At the initial appointment, eligibility will be formally checked, and those who consent to participate will undergo stratified randomisation using sealed, opaque and identical envelopes that are sequentially numbered. Prior to randomisation, baseline measures including number of episodes of cellulitis in the 2 years prior to referral, duration of chronic oedema, referral source and demographics will be captured. The presence of identified potential risk factors for cellulitis will also be recorded, including history of tinea or other fungal infections between toes, diabetes mellitus, obesity and chronic venous insufficiency.[3 4 12 25 26]

At the initial appointment, participants in both the control and intervention groups will receive education (verbal and written) regarding cellulitis and how to decrease the risk of recurrence. Education will include the benefits of skin care, prevention of tinea or other fungal infections between toes, maintaining healthy body weight and regular exercise.

For the intervention group, the initial appointment will also be used to plan appropriate compression therapy which will be provided at subsequent appointments. Compression therapy will involve the application of compression garments (compression stockings or wraps) and may or may not involve compression bandaging to minimise oedema prior to the fitting of compression garments. The number of appointments necessary for the provision of compression therapy will be individualised to meet participant requirements.

Participants in both groups will be followed for up to 3 years at 6 monthly intervals (table 1) to complete outcome measures and to continue to receive the allocated treatment (education with or without compression therapy). At each appointment, the therapist will inform each participant of changes in their limb volume, providing tangible feedback to support ongoing participant attendance. Throughout the trial, participants in the intervention group may require additional appointments for compression therapy (compression bandaging, and measure for and provision of compression garments). Intervention compliance (number of days per week garments are worn) and adverse effects will be captured by self-report.

Cross-over of control group participants will be triggered on clinician identification of cellulitis. The recurrence of cellulitis will be checked at scheduled appointments, however, if a participant reports a recurrence between scheduled assessments, they will be reviewed at an additional appointment to record outcome measures (table 1), and to commence cross-over for control group participants. Date of cross-over will be defined as the day compression garments are initially fitted.

Outcome measures

Table 1 shows the timeline for completion of trial activities and outcome measures.

The primary outcome is 'observed time to the first episode of cellulitis recurrence'. Cellulitis recurrence will only be assessed in a leg that has been assessed as having chronic oedema, thus if cellulitis occurs in a leg that was not previously identified as having chronic oedema, the infection will not be considered a recurrence. Cellulitis will be diagnosed by medical practitioners external to the study. Date of cellulitis recurrence (and associated hospitalisation) will be gained by participant self-report and may be verified using medical records from the hospitals and/or general practitioners.

Secondary outcomes include: (1) rate of cellulitis-related hospital admissions; (2) percent change in leg volume from baseline, measured using the perometer; (3) QOL, assessed using the LYMQOL and EuroQol Five Dimension Scale (ED-5D-3L). The occurrence of cellulitis-related hospital admissions will be measured in the same manner as cellulitis recurrence.

Percent change in leg volume will be measured using a perometer, an optoelectronic imaging device designed to measure limb volume.[27] The perometer has excellent intra-rater reliability (ICC=1.0; 95% CI: 0.99 to 1.00) and inter-rater reliability (ICC=1.0; 95% CI: 0.97 to 1.00), is sensitive to changes in limb volume[28–30] and is a valid measure of knee volume.[27] Leg volume will be measured between 53 and 400 mm height from the ground using the perometer. Monthly calibration of the perometer will be conducted using a standardised object of known volume (875 mL) to minimise instrument error, ensuring consistency of this measurement device across the duration of the trial. Use of this device will also prevent potential differential measurement bias arising from lack of therapist blinding.

Where limb volume cannot be measured using the perometer, due to impaired mobility of a participant or equipment failure, summated circumferential leg measurements will be used following expert clinical guidelines. Circumferential leg measures will be taken at the mid foot, oblique ankle and at 10, 20, 30 and 40 cm intervals up the leg using a measurement board. Circumferential limb measurement also has excellent intra-rater reliability (ICC=0.977–0.996; 95% CI: 0.960 to 0.998) and inter-rater reliability (ICC=0.942–0.994; 95% CI: 0.936 to 0.997).[31]

QOL will be measured using LYMQOL, a validated, condition-specific QOL tool for people with lower limb lymphoedema,[32] and the EQ-5D-3L, a generic preference-based measure of health-related QOL that comprises five dimensions of health.[33] The EQ-5D can be used to calculate quality-adjusted life years for the purpose of economic evaluation.[33] A systematic review has found the EQ-5D has good validity and responsiveness for people with skin diseases, although the tool has not been specifically validated within a population suffering cellulitis.[33]

Exploratory analysis will be conducted to test the robustness of the trial hypotheses and may include assessment of cellulitis recurrence post cross-over, intervention compliance, participant demographics, risk factors and per protocol analysis.

Sample size and duration of follow-up

The sample size has been calculated for the primary objective of detecting a difference in time to cellulitis recurrence between the control and intervention groups. The sample size estimation is based on the assumptions that the 3-year cellulitis recurrence rate in control participants is approximately 47%[8] and compression therapy will reduce the 3-year incidence of recurrent cellulitis by 50%.[17 18] Assuming that events occur at a constant rate, these assumptions correspond to a hazard ratio (HR) of 0.42. The eligibility criteria of two or more episodes of cellulitis in the same leg in the past 2 years has been used so that the trial cohort have an increased likelihood of cellulitis reoccurring during the follow-up period.

It is assumed that patients will be recruited over a 2.5 year period, and the total study duration will be 3.5 years. Length of participant follow-up will vary based on time of enrolment. Using a sequential design software package gsDesign in R,[34] in order to detect a HR of 0.42 with 80% power and 2.5% (one-sided) type 1 error, a total of 45 cellulitis recurrences are needed. Under the present recruitment and recurrence assumptions, we plan to recruit 162 participants (81 per arm).

An interim analysis will be performed by a Data Monitoring Committee after 23 episodes of cellulitis. A log-rank test will be used to assess group differences. If a nominal (one sided) significance level of p=0.003 is detected, indicating a strong clinical effect, the study will be ceased. If the Data Monitoring Committee recommends that the study continue to 45 episodes of cellulitis,

Table 1 Timeline per patient for RCT outcome measures

Time point	Enrolment	Assessment post initial intervention	Assessment post cellulitis recurrence	Cross -over	6	12	18	24	30	36
Body mass index	X		X	X	X	X	X	X	X	X
Perometer (limb volume)	X	X	X	X	X	X	X	X	X	X
Summated limb circumferences	X	X	X	X	X	X	X	X	X	X
ED-5D-3L	X					X		X		X
LYMQOL	X				X	X		X		X
Cellulitis recurrence date/s			X		X	X	X	X	X	X
Hospitalisation due to cellulitis (date, length of stay)			X		X	X	X	X	X	X
Verification of cellulitis recurrence and associated hospitalisation using medical record/general practitioner report			X		X	X	X	X	X	X
Intervention provided (type of garment, application of compression bandages)		X	X	X	X	X	X	X	X	X
Presence of fungal infections/tinea/maceration or cracking of skin between toes			X		X	X	X	X	X	X
Adverse events			X		X	X	X	X	X	X
Intervention compliance			X		X	X	X	X	X	X
Occurrence of wounds/ulcers (acute/chronic)					X	X	X	X	X	X

Primary and secondary outcome measures have been underlined. Identified potential risk factors have been italicised.[3 12]
ED-5D-3L, RCT, randomised controlled trial.

the final analysis will use a log-rank test with (one-sided) significance level p=0.0238. These efficacy bounds were derived using a Hwang-Shih-DeCani spending function with gamma = −4 to preserve an overall type 1 error rate of 5%.

Recruitment and enrolment of participants

Recruitment will be conducted over a 2.5-year period. A multifaceted recruitment strategy will be used. In order to capture acute patients (seen in CPHB and Canberra Hospital emergency departments and wards), all patients diagnosed with lower limb cellulitis during their hospital presentation will be sent information regarding the trial and how to contact the CPHB lymphoedema service if they would like to learn more information or self-refer. To recruit from the community, the study will be advertised via posters, radio and articles in various magazines and newspapers, providing information about the trial and encouraging self-referral. Education (in-services, faxes, newsletters and posters) and referral forms will be provided to recruitment sites (Canberra Hospital, CPHB, General Practices within the surrounding region) to encourage health professionals to refer patients. Patients from these sites must consent to a referral to the CPHB lymphoedema service for the study, but do not need to consent to participate in the trial at the time of referral.

After self-referral, a screening phone call will be conducted to check inclusion/exclusion criteria, and for those who appear to be eligible, an appointment at the service will be made with a lymphoedema therapist. At this appointment, candidates will be provided with participant information and consent forms, a verbal explanation of the study and an opportunity to ask questions, prior to choosing to consent or decline to participate.

To promote participation in the study, a free set of compression garments will be offered by a secondary sponsor. Compression garments are expensive, which can provide a barrier to treatment compliance. Participants in the intervention group will receive the free garments at intervention commencement. Participants in the control group will receive the free garments following their first cellulitis recurrence (cross-over) or on study completion for those who do not experience recurrence.

Patient and public involvement

A patient-centred approach was used to design this study. The trial design replicates the institution's standard clinical practice as closely as possible, while aiming to minimise any additional burden to participants. Patients from the participating clinical service were surveyed to assess acceptability of the model of care undertaken by the trial. As the time required to attend appointments was identified as a potential burden, the trial was designed to minimise scheduled follow-up appointments. Cost of compression therapy was identified as a likely financial burden which is minimised through the provision of two sets of free compression garments and use of accessible funding schemes. Referral processes were developed to enable patients to self-refer to the trial. The cross-over design feature was chosen to ensure participants do not continue to experience episodes of recurrent cellulitis without receiving the institution's standard intervention.

Assignment of interventions and blinding

Participants will be assigned to the intervention or control group in a 1:1 allocation ratio using block randomisation, with a block size of 10. Sealed sequentially numbered opaque envelopes will be used to ensure concealed allocation. A computer-generated allocation sequence will be created and supplied by a consultant statistician and saved in a folder only accessible by administration staff. Administration staff will prepare the sealed sequentially numbered opaque envelopes, ensuring therapists involved in participant allocation have no premature access to the letters.

Therapists will not be blinded due to the practicalities of providing the intervention within a small team of four specialised clinicians. Further, the visible nature of the treatment and lack of feasible sham interventions prevent effective blinding of both assessors and participants. Additionally, for ethical reasons, participants will be fully informed of both the potential interventions, prior to consenting to participate.

Data management and quality assurance

Prior to any involvement in the trial, therapists will receive training regarding trial implementation and completion of outcome measures. Refresher training will be provided to therapists annually and the trial protocol will be kept readily available.

For the duration of the study, data will be stored in identifiable form in both a locked office and on a secure access hard drive, accessible only by designated research staff. Data will be entered by a research officer or members of the research team. For quality assurance, data completeness will be reviewed annually, and all entered data will be cross-checked against written records at least once after initial entry. Following trial conclusion and prior to data analysis, all data will be de-identified. Data will be stored for a minimum of 7 years as per CPHB policy, however data may be retained for longer for identified new, ethically approved ancillary studies. A contract with the secondary sponsor ensures that they will have no involvement in the study design, in the collection, analysis, or interpretation of data, in the writing of the manuscript or in the decision to submit the manuscript for publication.

Participant retention

Once a participant is enrolled in the study, every effort will be made to ensure they are followed up as per the protocol. Where participants cannot attend a scheduled appointment, a phone call assessment may be completed to gain the primary outcome measure. Phone call assessment will not allow for completion of limb volume or QOL measures but will capture the date of cellulitis recurrence and cellulitis-related hospitalisation.

Participants can withdraw from the study at any point. For participants who withdraw, the medical record and/or general practitioner report may be checked according to the schedule for cellulitis recurrence and cellulitis-related hospitalisation.

Termination criteria

Participants will be withdrawn from the study in the case of death, withdrawal of consent or if they develop a wound or lymphorrhoea requiring compression for effective management.[35]

Proposed methods for data analysis

For the main outcome measure of 'time to the first episode of recurrent cellulitis', survival analysis will be undertaken. Kaplan-Meier plots will be used to visualise patterns of time to first cellulitis recurrence between the groups, with a log-rank test being used to determine if there is a statistically significant difference between the groups. Cox proportional hazards regression may also be used to adjust for important risk factors. Right censoring will be used for participants who are lost to follow-up. Intention to treat analysis will be used, with all enrolled participants being assessed according to their randomisation, regardless of protocol adherence.

For the secondary outcomes of percent change in limb volume and QOL, measures will be taken at multiple time points. Therefore, groups will be compared using a linear-mixed model or using a repeated measures analysis. A generalised linear model will be used to assess the rate of cellulitis-related hospital admissions.

MINIMISING BIAS

Selection and attrition bias

Use of randomisation will minimise selection bias and confounding. Stratification will ensure that the use of prophylactic antibiotics is not confounded with treatment assignment. The presence and distribution of other known potential confounding factors will be measured and reported. Intention to treat analysis will be used to prevent attrition bias that may occur through loss to follow-up of participants.

Internal validity

Use of an RCT and validated measurement tools support the internal validity of this research. The lack of blinding of therapists and participants has the potential to induce surveillance and recall bias and lead to differential measurement error in the reporting of cellulitis recurrence. To minimise this, the accuracy of self-report of recurrence may be cross-checked with the participant's general practitioner or medical record (from CPHB and Canberra Hospital). Diagnosis of cellulitis by doctors external to the study and use of perometry to measure limb volume will reduce the risk of measurement bias and thus differential measurement error. Calibration of the perometer will be performed to prevent non-differential measurement error that could result from machine error.

Control and intervention group participants have the same appointment schedule throughout the duration of the trial, however participants in the intervention group may attend more appointments than the control group. This systematic difference in clinician contact could influence the participant's perceived benefit, allowing potential bias in self-reported measures (LYMQOL, EQ-5D).

Participants enrolled in the trial have a history of two or more episodes of cellulitis diagnosed by medical practitioners independent to the trial. As misdiagnosis of lower limb cellulitis is not uncommon,[36] the trial may include incorrectly diagnosed participants leading to non-differential misclassification.

ANALYSIS OF COSTS

A within-trial cost-analysis assessment will be conducted. Data obtained from the trial and participant medical records will be used to assess the cost of oedema management and the cost of an episode of cellulitis from both an individual and a health systems perspective. On completion of the RCT, the cost-effectiveness and cost-utility of chronic oedema management to prevent recurrent cellulitis may be assessed.

ETHICS AND DISSEMINATION

Ethics approval has been granted for these studies by three institutional committees:

1. Calvary Public Hospital Bruce Human Research Ethics Committee (53-2016).
2. Australian Capital Territory Health Human Research Ethics Committee (ETH.4.17.092).
3. University of Canberra Human Research Ethics Committee (cross-institutional approval).

Regardless of the outcome of the trial, the findings are planned to be submitted for publication in relevant peer-reviewed journals and for presentations at national and international conferences. Key findings will be disseminated to identified stakeholders, including primary contact clinicians for patients experiencing cellulitis (doctors and health professionals in acute and community settings), clinicians who manage chronic oedema and professionals who may be involved in developing relevant policy and practice. On request, participants will be provided with a copy of the trial results.

DISCUSSION

Although current expert consensus recommends compression therapy to prevent the recurrence of cellulitis in patients with lower limb chronic oedema, the evidence supporting this recommendation is lacking. This study aims to review the efficacy of compression therapy to allow for better-informed practice and policy. Given the high incidence of cellulitis within Australia and around the world, reducing cellulitis recurrence will significantly

decrease the cost to the healthcare system and reduce the financial and personal burden of sufferers. Further, should compression therapy reduce the recurrence of cellulitis, this may limit the dependence and widespread prescription of prophylactic antibiotics. This trial will be performed on adults receiving healthcare services in the Australian Capital Territory, however, the results will be relevant to cellulitis management throughout Australia and internationally.

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Acknowledgements The authors acknowledge the Calvary Public Hospital Bruce Lymphoedema Team, specifically Gemma Arnold, Marie-Michelle Coulombe, Ingrid Thé, Abby Benton, Emma May, Sarah Squires, Caitlin Norris, Nievelle Chand, Sarah Toohey, Ashlee Cashion and Bhavleen Singh.

Contributors EW: trial design and implementation, contribution of original material, editing and approval of final manuscript. BB: trial implementation support and contribution of original material. TN: trial design input and statistical support. VM: economic analysis support. BB, TN, JG, FB and VM: provided supervision, contributed to refinement of the protocol and approved the final manuscript.

Funding Calvary Public Hospital Bruce is the primary sponsor, funding clinician time to initiate and manage the trial. Haddenham Healthcare is a secondary sponsor, providing two sets of free compression garments for each trial participant. Haddenham Healthcare had no role in designing this study and will not be involved in the trial implementation, analyses, data interpretation, or publication or dissemination of results. Haddenham Healthcare will not have access to trial data.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The Human Research Ethics Committees of Calvary Public Hospital Bruce, Australian Capital Territory Health and University of Canberra all approved this trial.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Swartz MN. Clinical practice. Cellulitis. *N Engl J Med* 2004;350:904–12.
2. Eriksson B, Jorup-Rönström C, Karkkonen K, *et al*. Erysipelas: clinical and bacteriologic spectrum and serological aspects. *Clin Infect Dis* 1996;23:1091–8.
3. Pavlotsky F, Amrani S, Trau H. Recurrent erysipelas: risk factors. *J Dtsch Dermatol Ges* 2004;2:89–95.
4. Inghammar M, Rasmussen M, Linder A. Recurrent erysipelas--risk factors and clinical presentation. *BMC Infect Dis* 2014;14:270–70.
5. The Australian Commission on Safety and Quality in Healthcare. Australian Atlas of Healthcare Variation 2017. 2017:81–90.
6. National Health Performance Authority. Healthy communities: potentially preventable hospitalisations in 2013–14. 2015.
7. National Health Performance Authority. Hospital Performance: costs of acute admitted patients in public hospitals in 2011–12. 2015.
8. Cox NH. Oedema as a risk factor for multiple episodes of cellulitis/erysipelas of the lower leg: a series with community follow-up. *Br J Dermatol* 2006;155:947–50.
9. Jorup-Rönström C, Britton S. Recurrent erysipelas: predisposing factors and costs of prophylaxis. *Infection* 1987;15:105–6.
10. Mortimer PS, Levick JR. Chronic peripheral oedema: the critical role of the lymphatic system. *Clin Med* 2004;4:448–53.
11. Moffatt C, Keeley V, Quere I. The concept of chronic Edema-A neglected public health issue and an international response: the LIMPRINT study. *Lymphat Res Biol* 2019;17:121–6.
12. Dupuy A, Benchikhi H, Roujeau JC, *et al*. Risk factors for erysipelas of the leg (cellulitis): case-control study. *BMJ* 1999;318:1591–4.
13. Karppelin M, Siljander T, Vuopio-Varkila J, *et al*. Factors predisposing to acute and recurrent bacterial non-necrotizing cellulitis in hospitalized patients: a prospective case-control study. *Clin Microbiol Infect* 2010;16:729–34.
14. Chlebicki MP, Oh CC, Cc O. Recurrent cellulitis: risk factors, etiology, pathogenesis and treatment. *Curr Infect Dis Rep* 2014;16:422.
15. Todd M. Chronic oedema: impact and management. *Br J Nurs* 2013;22:623–7.
16. Cox NH, Colver GB, Paterson WD. Management and morbidity of cellulitis of the leg. *J R Soc Med* 1998;91:634–7.
17. Arsenault K, Rielly L, Wise H. Effects of complete decongestive therapy on the incidence rate of hospitalization for the management of recurrent cellulitis in adults with lymphedema. *Rehabil Oncol* 2011;29:14–20.
18. Ko DS, Lerner R, Klose G, *et al*. Effective treatment of lymphedema of the extremities. *Arch Surg* 1998;133:452–8.
19. Thomas KS, Crook AM, Nunn AJ, *et al*. Penicillin to prevent recurrent leg cellulitis. *N Engl J Med* 2013;368:1695–703.
20. Dalal A, Eskin-Schwartz M, Mimouni D, *et al*. Interventions for the prevention of recurrent erysipelas and cellulitis. *Cochrane Database Syst Rev* 2017;6:CD009758.
21. Thomas K, Crook A, Foster K, *et al*. Prophylactic antibiotics for the prevention of cellulitis (erysipelas) of the leg: results of the UK Dermatology clinical trials network's PATCH II trial. *Br J Dermatol* 2012;166:169–78.
22. Sullivan T, de Barra E. Diagnosis and management of cellulitis. *Clin Med* 2018;18:160–3.
23. Raff AB, Kroshinsky D. Cellulitis: a review. *JAMA* 2016;316:325–37.
24. Australasian Lymphology Association. About the National Lymphoedema Practitioners Register. 2018 http://www.lymphoedema.org.au/the-register-updated (Accessed Sep 2018).
25. Carratalà J, Rosón B, Fernández-Sabé N, *et al*. Factors associated with complications and mortality in adult patients hospitalized for infectious cellulitis. *Eur J Clin Microbiol Infect Dis* 2003;22:151–7.
26. Nassaji M, Ghorbani R, Ghashghaee S. Risk factors of acute cellulitis in adult patients: a case-control study. *EJM* 2016;21:26–30.
27. Man IO, Markland KL, Morrissey MC. The validity and reliability of the perometer in evaluating human knee volume. *Clin Physiol Funct Imaging* 2004;24:352–8.
28. Czerniec SA, Ward LC, Lee MJ, *et al*. Segmental measurement of breast cancer-related arm lymphoedema using perometry and bioimpedance spectroscopy. *Support Care Cancer* 2011;19:703–10.
29. Czerniec SA, Ward LC, Refshauge KM, *et al*. Assessment of breast cancer-related arm lymphedema--comparison of physical measurement methods and self-report. *Cancer Invest* 2010;28:54–62.
30. Bulley C, Coutts F, Tan CW. Perometry limb volume measurement: protocol development and reliability. *Eur J Physiother* 2013;15:193–200.
31. Devoogdt N, Lemkens H, Geraerts I, *et al*. A new device to measure upper limb circumferences: validity and reliability. *Int Angiol* 2010;29:401–7.
32. Keeley V, Crooks S, Locke J, *et al*. A quality of life measure for limb lymphoedema (LYMQOL). *J lymphoedema* 2010;5:26–37.
33. Yang Y, Brazier J, Longworth L. EQ-5D in skin conditions: an assessment of validity and responsiveness. *Eur J Health Econ* 2015;16:927–39.
34. R Core Team. R: A language and environment for statistical computing: R Foundation for Statistical Computing, Vienna, Austria. 2018 https://www.R-project.org (Accessed Dec 2018).
35. O'Meara S, Cullum N, Nelson EA, *et al*. Compression for venous leg ulcers. *Cochrane Database Syst Rev* 2012;11:CD000265.
36. Weng QY, Raff AB, Cohen JM, *et al*. Costs and consequences associated with misdiagnosed lower extremity cellulitis. *JAMA Dermatol* 2017;153:141–6.

APPENDIX E: Published copy of paper two and letter of response to the editor

Compression Therapy to Prevent Recurrent Cellulitis of the Leg

Letter to the editor: Compression Therapy to Prevent Recurrent Cellulitis of the Leg

ORIGINAL ARTICLE

Compression Therapy to Prevent Recurrent Cellulitis of the Leg

Elizabeth Webb, M.P.H., Teresa Neeman, Ph.D., Francis J. Bowden, M.D., Jamie Gaida, Ph.D., Virginia Mumford, Ph.D., and Bernie Bissett, Ph.D.

ABSTRACT

BACKGROUND

Chronic edema of the leg is a risk factor for cellulitis. Daily use of compression garments on the leg has been recommended to prevent the recurrence of cellulitis, but there is limited evidence from trials regarding its effectiveness.

METHODS

In this single-center, randomized, nonblinded trial, we assigned participants with chronic edema of the leg and recurrent cellulitis, in a 1:1 ratio, to receive leg compression therapy plus education on cellulitis prevention (compression group) or education alone (control group). Follow-up occurred every 6 months for up to 3 years or until 45 episodes of cellulitis had occurred in the trial. The primary outcome was the recurrence of cellulitis. Participants in the control group who had an episode of cellulitis crossed over to the compression group. Secondary outcomes included cellulitis-related hospital admission and quality-of-life assessments.

RESULTS

A total of 183 patients were screened, and 84 were enrolled; 41 participants were assigned to the compression group, and 43 to the control group. At the time of a planned interim analysis, when 23 episodes of cellulitis had occurred, 6 participants (15%) in the compression group and 17 (40%) in the control group had had an episode of cellulitis (hazard ratio, 0.23; 95% confidence interval [CI], 0.09 to 0.59; P=0.002; relative risk [post hoc analysis], 0.37; 95% CI, 0.16 to 0.84; P=0.02), and the trial was stopped for efficacy. A total of 3 participants (7%) in the compression group and 6 (14%) in the control group were hospitalized for cellulitis (hazard ratio, 0.38; 95% CI, 0.09 to 1.59). Most quality-of-life outcomes did not differ between the two groups. No adverse events occurred during the trial.

CONCLUSIONS

In this small, single-center, nonblinded trial involving patients with chronic edema of the leg and cellulitis, compression therapy resulted in a lower incidence of recurrence of cellulitis than conservative treatment. (Funded by Calvary Public Hospital Bruce; Australian and New Zealand Clinical Trials Registry number, ACTRN12617000412336.)

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N Engl J Med 2020;383:630-9.
DOI: 10.1056/NEJMoa1917197

Cellulitis is a common bacterial infection of the skin and subcutaneous tissue that occurs mostly in the legs and is associated with health care costs[1] and adverse health outcomes.[2] Recurrence of cellulitis is common: up to 47% of patients have a recurrent episode within 3 years.[3] Penicillin prophylaxis is effective in preventing recurrence of cellulitis, although a trial published in the *Journal* in 2013 showed that the protective effect diminishes progressively once the antibiotic agent is discontinued.[4] A Cochrane review of interventions to prevent cellulitis identified six studies investigating prophylactic antibiotics, but no randomized trials of other interventions such as edema management were identified.[5] The efficacy of nonantibiotic treatments to prevent cellulitis has not been well studied.[5,6]

Chronic edema refers to swelling that persists for 3 months or longer and has various and often mixed causes. The principal cause of edema may be increased capillary filtration or failure of lymphatic drainage,[7,8] which results from conditions such as lymphedema, venous hypertension, immobility, obesity, and heart failure. Chronic edema is a risk factor for cellulitis of the leg and for recurrent cellulitis.[3,9-11]

Compression therapy has been used to reduce and control chronic edema. This treatment involves the daily wearing of compression garments such as stockings, with or without a short period of compression bandaging to reduce swelling before compression garments are fitted. Compression garments and bandages exert the greatest degree of compression at the ankle and gradually apply less pressure proximally along the limb. By exerting this type of graduated pressure on the leg, compression therapy reduces the formation and accumulation of interstitial fluid and shifts fluid proximally, away from the lower leg.[12] Guidelines have suggested the use of compression therapy to prevent recurrent cellulitis in patients with chronic edema of the leg, and compression therapy is widely used by clinicians[2,3,13,14]; however, there are limited data from trials to support this practice. We conducted a randomized, controlled, single-center trial to determine whether compression therapy would prevent the recurrence of cellulitis of the leg in adults with chronic edema of the leg.

METHODS

TRIAL DESIGN AND OVERSIGHT

Participants were randomly assigned in a 1:1 ratio to receive either compression therapy plus education regarding prevention of cellulitis (compression group) or education alone (control group). Randomization was stratified according to prophylactic antibiotic use (yes or no), with a planned maximum follow-up of 3 years. Participants in the control group crossed over to the compression group when they had an episode of cellulitis. Assessors and participants were aware of the trial-group assignments.

The trial was conducted at Calvary Public Hospital Bruce (Canberra, Australia). The protocol (available with the full text of this article at NEJM.org) was approved by three institutional human research ethics committees. Participants provided written informed consent before the trial. The authors designed and implemented the trial and collected and analyzed the data. The first author wrote the first draft of the manuscript, and all authors contributed to subsequent drafts. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. Haddenham Healthcare manufactured and provided the compression garments but had no involvement in the design, conduct, analysis, or reporting of the trial and did not have access to the trial data.

PARTICIPANTS

Participants were recruited at one of two primary public hospitals or were referred by general practitioners servicing the local region. Patients were eligible to participate if they had a history of two or more episodes of cellulitis in the same leg in the 2 years before referral to the trial and had edema lasting longer than 3 months in one or both legs, with recurrent cellulitis. Full inclusion and exclusion criteria are provided in the protocol. The presence of edema was confirmed by means of interview and physical examination by specialist lymphedema physiotherapists. Patients were excluded from the trial if they were younger than 18 years of age, were already wearing effective compression garments 5 or more days per week, were receiving end-of-life care, had a clinically unstable condition, or had a chronic

wound or a wound requiring specialist treatment, or if compression therapy was contraindicated.

Compression garments are categorized by manufacturers into four numbered classes according to the pressure they exert at the ankle.[15] If patients were already wearing garments of compression class 2 or higher (providing 23 to 32 mm Hg of pressure), the garments were considered to be effective and the patients were excluded from the trial. Patients who were wearing class 1 garments (providing 18 to 21 mm Hg of pressure) were excluded if a lymphedema therapist determined that this lower amount of pressure was effective for the patient.

INTERVENTIONS AND ASSESSMENTS

All assessments and interventions were performed in the outpatient department of the hospital by specialist lymphedema physiotherapists who were aware of the trial-group assignments. Baseline measures, including demographic characteristics, leg volume, and quality of life, were recorded before randomization. Cellulitis was diagnosed by general medical practitioners or by hospital physicians who were not otherwise involved in the trial; the diagnosis was confirmed by trial assessors. Trial assessors verified the dates of recurrence and hospitalization with the use of medical records. Participants were encouraged to report episodes of cellulitis at the time that they occurred. In addition, participants were interviewed at the 6-month follow-up appointments to determine whether there had been unreported recurrences of cellulitis. If a recurrence was reported between scheduled follow-up appointments, participants were seen for an additional appointment with a lymphedema therapist to record outcome measures (date of cellulitis diagnosis and associated hospitalization); participants in the control group commenced crossover to the compression group at this time. An episode of cellulitis was recorded only if it occurred in a leg in which chronic edema had been identified at baseline; in the case of edema in both legs, recurrence of cellulitis was recorded as a single event if it occurred in either leg. Quality-of-life measures, leg volume, adherence to wearing garments in the compression group, and adverse events were assessed at the 6-month appointments. If participants could not attend their scheduled appointments, assessment was performed by means of telephone to check for cellulitis recurrence and associated hospital admission; quality-of-life assessments were obtained by means of mailed surveys.

Education about cellulitis prevention was provided to participants in the two trial groups at the initial appointment and at follow-up appointments and included information on the benefits of skin care, prevention of interdigital fungal infections, healthy body weight, and regular exercise. Participants assigned to the compression group were instructed to wear compression garments throughout the day and were provided information on use, safety, cleanliness, and application and removal of the garments. Two free sets of compression garments were provided to participants in the compression group at the beginning of the trial and to participants in the control group when they crossed over to the compression group.

When appropriate, a short period (typically 3 to 5 days) of therapist-applied compression bandaging to minimize edema was provided immediately before the compression garments were fitted (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The majority of prescribed compression garments were knee-high compression stockings that included the foot, with or without the toes (Fig. S2); less often, leg-and-foot compression wraps were prescribed (Fig. S3). The number of appointments required to provide compression therapy was not prespecified and varied according to the individual needs of the participants.

The prescribed garment type and compression class were determined on the basis of edema severity, leg shape, skin condition, and the ease of application and removal by the participants or their caregivers. If chronic edema was present in both legs, compression therapy was provided for both legs. Replacement of compression garments was recommended after 6 to 12 months of wear, with no restrictions on the brand used.

Participants in the control group who had an episode of cellulitis crossed over to the compression group to receive compression therapy. The date of crossover was defined as the day that compression garments were initially fitted. Participation in the trial was terminated in the case of death, withdrawal of consent, or development of a wound or lymphorrhea for which management with compression therapy was advised and was supported by evidence.[16] No further outcome

measures were obtained for participants who were withdrawn from the trial.

OUTCOMES

The primary outcome was the recurrence of cellulitis. Secondary outcomes were cellulitis-related hospital admission, change in leg volume, and quality-of-life measures. Leg volume was measured with the use of a perometer (an optoelectronic imaging device). Scanning was performed on the leg starting at a height of 5.3 cm from the bottom of the foot and extending up the leg to a height of 40.0 cm (Fig. S4). The perometer was calibrated to a standardized object every 2 weeks throughout the trial to ensure reliability.

Quality of life was assessed with the use of the quality-of-life measure for limb lymphedema (LYMQOL)[17] and the EuroQol Group 5–Dimensions 3-Level scale (EQ-5D-3L).[18] The LYMQOL consists of two components that are assessed separately: a quality-of-life score (scores range from 0 to 10, with higher scores indicating better quality of life) and a combined score that encompasses four domains (symptoms, appearance, function, and mood), each scored at four levels (not at all, a little, quite a bit, or a lot; combined scores range from 4 to 16, with lower scores indicating better quality of life).[17] The EQ-5D-3L also consists of two components that are assessed separately: a visual analogue scale that assesses the overall health state (scores range from 0 [worst imaginable health state] to 100 [best imaginable health state]) and a descriptive system that assesses five dimensions of quality of life (mobility, personal care, usual activities, pain and discomfort, and anxiety and depression) at three levels (no problems, some problems, or extreme problems; total scores for the descriptive system range from 5 to 15, with lower scores indicating better quality of life).[18]

Adherence to the intervention in the compression group was determined on the basis of the number of days per week that garments were worn. Adverse effects were reported by participants during the 6-month assessments with therapists.

STATISTICAL ANALYSIS

Assuming that recurrence of cellulitis at 3 years would occur in 47% of participants in the control group (on the basis of previous reports[3,4]) and that there would be a 50% lower incidence of cellulitis in the compression group than in the control group,[19,20] we calculated that 45 events of cellulitis would be needed to give the trial 80% power to detect a hazard ratio for recurrence of cellulitis of 0.42, at a one-sided type I error rate of 2.5%. On the basis of these assumptions, we planned to recruit 162 participants (see the Supplementary Appendix). Randomization was stratified according to prophylactic antibiotic use, with the use of block sizes of 10. To prevent bias in assignment of participants to a particular group, sealed, opaque, sequentially numbered, identical envelopes were used to ensure concealment of trial-group assignments.

The statistical analysis plan prespecified that after 23 episodes of cellulitis had occurred, an independent data monitoring committee would review the results of the interim analysis and recommend whether the trial should stop early. A post hoc stopping rule for the time-to-event analysis was determined on the basis of a one-sided significance level of 0.003 with the use of a log-rank test. If the trial continued until 45 episodes of cellulitis occurred, the final analysis would use a log-rank test with a one-sided significance level of 0.0238 to preserve an overall type I error rate of 5%.

Only data collected on or before the first interim analysis were used in the intention-to-treat analysis of the primary outcome and the secondary outcome of cellulitis-related hospital admission. Therefore, no data on outcomes for participants who crossed over to the compression group were included in the primary analysis. For the secondary outcomes of leg volume and quality of life, data for each participant in the control group were collected until crossover occurred, and data for participants in the compression group were collected until the last participant in the control group crossed over to the compression group.

Kaplan–Meier plots were used for the analysis of the primary outcome and for the analysis of the secondary outcome of cellulitis-related hospital admission. The log-rank test was used to test for between-group differences. Cox proportional-hazards regression was used to estimate the hazard ratios and to assess the contribution of other risk factors for cellulitis. The proportional-hazards assumption was assessed with the use of correlation of scaled Schoenfeld residuals and transformed survival time (cox.zph in the survival package of R software [R Project

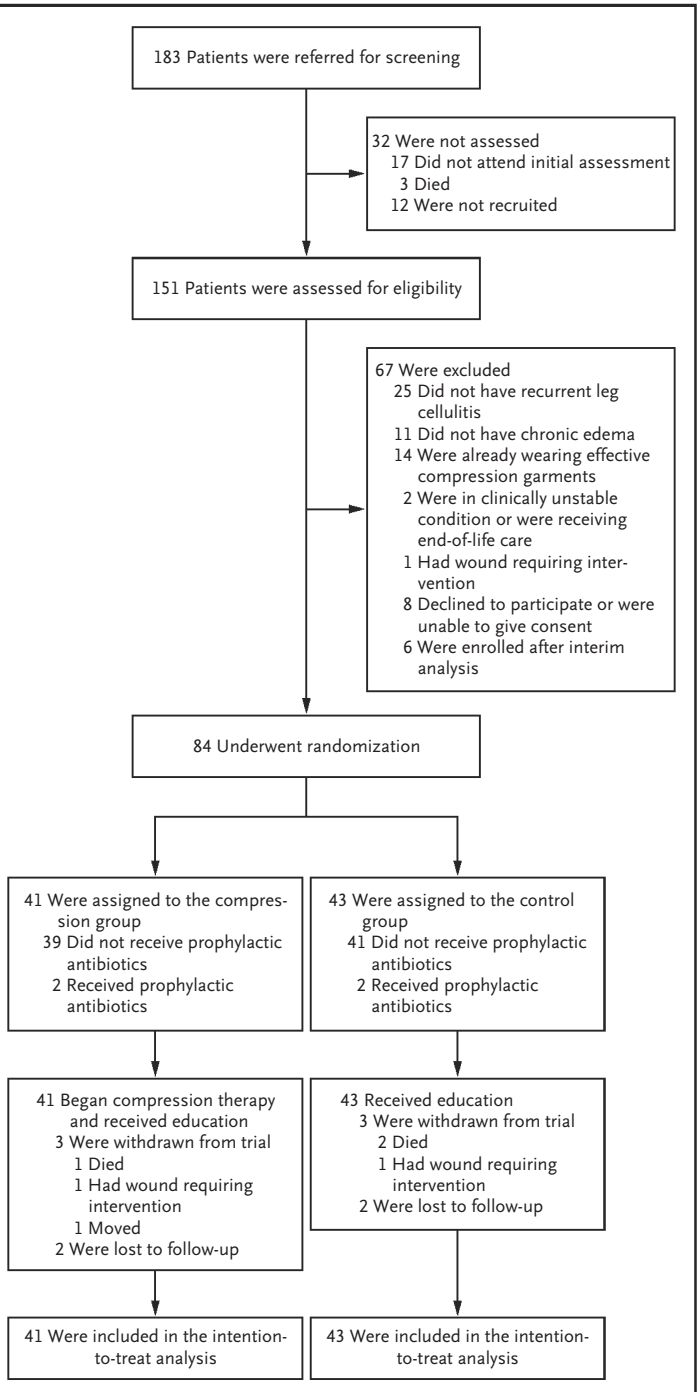


Figure 1. Eligibility, Randomization, and Follow-up.

for Statistical Computing]). Because the proportional-hazards assumption was not met, a post hoc analysis of relative risk was performed. Data for participants who were lost to follow-up were censored at the time of the last contact.

Mixed-effects linear models were used to assess between-group differences in the change in leg volume and quality of life over time, with group and time as fixed effects and participant identification number as the random effect. The two components of each quality-of-life scale were analyzed separately. Missing data were assumed to be missing at random. There was no plan for adjustment for multiple comparisons in the analyses of secondary outcomes, and the widths of confidence intervals were not adjusted for multiplicity; therefore, no clinical conclusions can be made from these data. The statistical analysis plan is available with the protocol. All analyses were performed with the use of R software, version 3.6.0.[21]

RESULTS

PARTICIPANTS

A total of 183 patients were screened and 84 were enrolled from June 2017 through February 2019 (Fig. 1). In September 2018, after nine events of cellulitis had occurred in 67 participants, lymphedema therapists who were aware of the trial-group assignments noted that there may have been a large between-group difference in recurrence. This potential difference between groups was brought to the attention of the human research ethics committees overseeing the trial. Therefore, in September 2018, the committees advised the introduction of stopping rules to ensure that the trial population was not exposed to risk, and an interim analysis plan with formal stopping rules was prepared and added as an amendment to the protocol. On March 26, 2019, the data monitoring committee advised, on the basis of the post hoc stopping rule, that the trial should be stopped for efficacy and recruitment should cease; the committee also recommended that crossover should commence to provide participants in the control group with compression therapy.

At the time that the trial was stopped, 41 participants had been assigned to the compression group, and 43 to the control group. During the trial, 2 participants (5%) in each group were lost to follow-up. Data for 3 participants (7%) in the compression group were censored because of death (1 [2%]), occurrence of a wound (1 [2%]), and relocation to a different state (1 [2%]). In the control group, 3 participants (7%) were with-

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Compression (N=41)	Control (N=43)	Total (N=84)
Age			
Mean	65.0±15.1	64.0±12.9	64.0±13.9
Median (interquartile range)	68 (52–75)	66 (57–72)	66 (55–74)
Female sex — no. (%)	19 (46)	22 (51)	41 (49)
Body-mass index†			
Mean	39.0±10.0	42.0±9.8	41.0±9.9
Median (interquartile range)	39 (31–47)	41 (34–47)	40 (33–47)
Chronic edema in both legs — no. (%)	32 (78)	34 (79)	66 (79)
Duration of edema — no. (%)			
1–5 yr	14 (34)	17 (40)	31 (37)
>5 yr	27 (66)	26 (60)	53 (63)
Episodes of cellulitis per leg in the 2 yr before trial referral‡			
Mean	2.0±1.5	2.0±1.4	2.0±1.5
Median (interquartile range)	2 (0–2)	2 (1–2)	2 (0–2)
Hospital admissions for cellulitis in the 2 yr before trial referral			
Mean	1.0±0.9	1.0±1.5	1.0±1.2
Median (interquartile range)	1 (0–2)	1 (0–1.5)	1 (0–2)
Prophylactic antibiotic use — no. (%)	2 (5)	2 (5)	4 (5)
Factors contributing to chronic edema — no. (%)			
Obesity	26 (63)	27 (63)	53 (63)
Surgery or trauma	14 (34)	13 (30)	27 (32)
Venous hypertension	15 (37)	11 (26)	26 (31)
Immobility	3 (7)	7 (16)	10 (12)
Primary lymphedema	3 (7)	2 (5)	5 (6)
Cancer	0	1 (2)	1 (1)
Other	6 (15)	3 (7)	9 (11)
Coexisting conditions — no. (%)			
Tinea pedis	13 (32)	17 (40)	30 (36)
Diabetes	10 (24)	14 (33)	24 (29)
Chronic venous insufficiency	12 (29)	11 (26)	23 (27)
Congestive heart failure	10 (24)	7 (16)	17 (20)

* Plus–minus values are means ±SD. It is assumed that all participants had some degree of edema related to previous episodes of cellulitis.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Both legs were assessed for previous episodes of cellulitis.

drawn because of death (2 [5%]) and occurrence of a wound (1 [2%]) (Fig. 1).

Baseline demographic characteristics were similar in the two groups (Table 1). Two participants in each group were using prophylactic antibiotics at the time of enrollment and continued using them throughout the course of the trial. No other participants used prophylactic antibiotics before an episode of cellulitis during the trial. Before provision of compression garments, 24 participants in the compression group received therapist-applied compression bandaging

to minimize leg edema. Compression stockings were prescribed for all participants in the compression group, and a combination of compression stockings and compression wraps were prescribed for 3 participants.

At the time of the interim analysis, the follow-up time ranged from 0 to 511 days, with a median of 186 days. Participants who had not had an event of cellulitis or a follow-up appointment at the time of the interim analysis were recorded as having had 0 days of follow-up. The median follow-up was 209 days in the compression group and 77 days in the control group. The median follow-up was short in the control group because of the participants whose data were censored after they had had an episode of cellulitis. Because data collection for leg volume and quality-of-life outcomes continued for participants in the control group until they crossed over to the compression group and continued for participants in the compression group until the last participant in the control group crossed over, the median follow-up in the two groups was 336 days for those outcomes.

Before the interim analysis was performed, 88% of the participants in the compression group reported during a follow-up interview that they wore the garments 4 or more days per week, and 73% reported that they wore the garments 5 or more days per week. No adverse outcomes were reported in participants who wore compression stockings or compression wraps.

OUTCOMES

At the time the trial was stopped, recurrence of cellulitis (the primary outcome) had occurred in 6 of 41 participants (15%) in the compression group and in 17 of 43 (40%) in the control group (hazard ratio, 0.23; 95% confidence interval [CI], 0.09 to 0.59; P=0.002) (Table 2 and Fig. 2). Because the proportional-hazards assumption was not met, relative risk was calculated post hoc. The relative risk was 0.37 (95% CI, 0.16 to 0.84; P=0.02), favoring the compression group. Table S1 shows the results of the exploratory analysis of the influence of factors that are typically associated with recurrent cellulitis (body-mass index [BMI, the weight in kilograms divided by the square of the height in meters] ≥40, tinea pedis or toe-web intertrigo, ≥3 episodes of cellulitis in either leg in the 2 years before enrollment, or development of a wound during the trial).[4,10,22]

Hospital admission for cellulitis (a secondary outcome) occurred in 3 participants (7%) in the compression group and in 6 (14%) in the control group (hazard ratio, 0.38; 95% CI, 0.09 to 1.59) at the time of the interim analysis (Table 2). After 6 months, 1 participant (2%) in the compression group and 5 (12%) in the control group had been hospitalized for cellulitis (Fig. S5). After 12 months, the mean leg volume among participants in the compression group was 181 ml less than that at baseline; among participants in the control group, the mean leg volume had increased by 60 ml (between-group difference in change, −241 ml; 95% CI, −365 to −117) (Table 2 and Fig. S6).

At 12 months, the mean LYMQOL combined score had decreased (reflecting a better quality of life) by 0.5 points in the compression group and by 0.2 points in the control group (between-group difference in change, −0.3 points; 95% CI, −0.6 to −0.1) (Table 2). There were no substantial between-group differences in the LYMQOL quality-of-life score (between-group difference in change, 0.8 points; 95% CI, −0.1 to 1.7), the EQ-5D-3L visual analogue scale (between-group difference in change, 8 points; 95% CI, −5 to 16), or the score on the descriptive system of the EQ-5D-3L (between-group difference in change, 0.8 points; 95% CI, −0.4 to 2.1) (Table 2).

DISCUSSION

This single-center, nonblinded, randomized trial, which was stopped early for efficacy, showed that compression therapy resulted in a lower incidence of recurrent cellulitis than conservative treatment in adults with chronic edema of the leg. This result supports expert opinion, but data from trials are limited.[2,3,13,14] The results of the analyses of hospitalization for cellulitis and of the change in leg volume from baseline were in the same direction as those of the primary outcome, but the lack of a prespecified plan for adjustment for multiple comparisons of secondary outcomes precludes clinical conclusions from these data. However, most quality-of-life measures did not differ substantially between the trial groups. Because the trial was stopped after the interim analysis, we were not able to report data on the 3-year effect of compression therapy on leg volume, as we had intended.

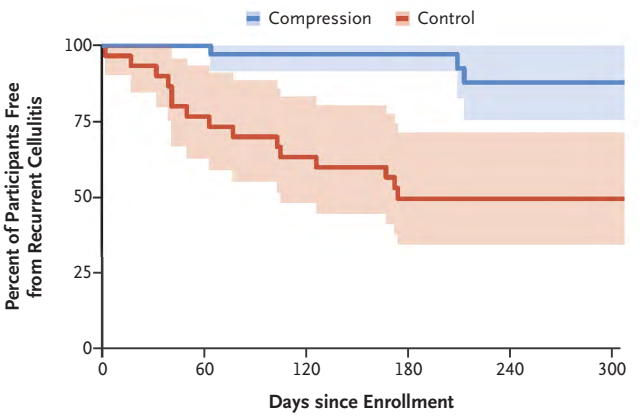
A Cochrane review showed that antibiotics

Table 2. Primary and Secondary Outcomes.

Outcome	Compression (N=41)	Control (N=43)	Between-Group Difference	Hazard Ratio or Relative Risk (95% CI)
Primary outcome: recurrence of cellulitis*				
No. (%)	6 (15)	17 (40)	11 (25)†	0.23 (0.09 to 0.59)‡
Relative risk (95% CI)				0.37 (0.16 to 0.84)§
Secondary outcomes¶				
Hospitalization for cellulitis — no. (%)*	3 (7)	6 (14)	3 (7)†	0.38 (0.09 to 1.59)
Mean change in leg volume at 12 mo‖**				
Change in volume (95% CI) — ml	−181 (−256 to −106)	60 (−38 to 159)	−241 (−365 to −117)	
Percent change (95% CI)	−4.3 (−5.8 to −2.9)	1.3 (−0.6 to 3.3)	−5.7 (−8.1 to −3.2)††	
Mean change in LYMQOL score at 12 mo (95% CI)‖‡‡				
Combined score	−0.5 (−0.6 to −0.4)	−0.2 (−0.3 to 0.02)	−0.3 (−0.6 to −0.1)	
Quality-of-life assessment	0.5 (−0.1 to 1.1)	−0.3 (−1.1 to 0.4)	0.8 (−0.1 to 1.7)	
Mean change in EQ-5D-3L score at 12 mo (95% CI)‖§§				
Visual analogue scale	−1 (−9 to 7)	−9 (−20 to 2)	8 (−5 to 16)	
Descriptive system	−0.3 (−0.9 to 0.4)	−1.1 (−2.2 to 0.01)	0.8 (−0.4 to 2.1)	

* Only data collected before the interim analysis were included in the analysis of recurrence of cellulitis and of hospitalization for recurrence of cellulitis.
† Shown is the difference between the control group and the compression group in the number of participants and the difference in percentage points.
‡ P=0.002.
§ P=0.02. The post hoc analysis of relative risk was performed because the proportional-hazards assumption was not met.
¶ Confidence intervals for secondary outcomes have not been corrected for multiple comparisons, and no clinical inferences can be made from these data.
‖ For this outcome, data were collected for participants in the control group until they crossed over to the compression group; data were collected for participants in the compression group until the last participant in the control group had crossed over. The mean change (slope) was estimated with the use of mixed-effects linear models that included baseline data and all available follow-up data.
** Change in leg volume was calculated on the basis of the change from the original volume measure of the same leg at the initial assessment. The contralateral leg was not used as a comparison for ipsilateral edema.
†† The value is the difference in percentage points.
‡‡ The quality-of-life measure for limb lymphedema (LYMQOL) has two components that are assessed separately: a quality-of-life score (scores range from 0 to 10, with higher scores indicating better quality of life) and a combined score that encompasses four domains (symptoms, appearance, function, and mood), each scored at four levels (not at all, a little, quite a bit, or a lot; combined scores range from 4 to 16, with lower scores indicating better quality of life).
§§ The EuroQol Group 5–Dimensions 3-Level scale (EQ-5D-3L) has two components that are assessed separately: a visual analogue scale that assesses the overall health state (scores range from 0 [worst imaginable health state] to 100 [best imaginable health state]) and a descriptive system that assesses five dimensions of quality of life (mobility, personal care, usual activities, pain and discomfort, and anxiety and depression) at three levels (no problems, some problems, or extreme problems); total scores for the descriptive system range from 5 to 15, with lower scores indicating better quality of life.

were the only prophylactic treatments for cellulitis of the leg that have been supported by randomized trials.[5] However, patients with preexisting edema, multiple previous episodes of cellulitis (≥3 episodes), or a high BMI (≥33) were less likely to benefit from antibiotic prophylaxis than other patients with cellulitis.[4] All participants in our trial had one or more risk factors that are predictive of antibiotic prophylaxis failure: all had preexisting edema, 79% had a BMI of 33 or greater, and 26% had had three or more episodes of cellulitis in the 2 years before the trial. We found that compression therapy reduced cellulitis recurrence in the participants in our trial, who were at risk for failure of antibiotic prophylaxis.



No. of Participants						
Compression	41	36	30	26	18	13
Control	43	23	19	13	8	6

Figure 2. Freedom from Recurrence of Cellulitis over Time.

Shown are the Kaplan–Meier estimates of the freedom from recurrence of cellulitis in the compression group and the control group. The shaded areas indicate 95% confidence intervals. The median follow-up was 186 days.

Prevention of cellulitis by means of prophylactic antibiotics can cause side effects,[5] and the bacterial species precipitating cellulitis is usually unidentifiable,[23] which hinders targeted antibiotic prophylaxis.[24] In comparison, long-term use of compression therapy has been recommended[15] and has shown benefits in controlling edema in patients with chronic edema of the leg[20,25,26]; in addition, its efficacy is not related to the causative bacterial species. Long-term use of compression therapy has the additional potential advantages of managing chronic venous insufficiency,[27] venous ulcers,[16,28] and skin conditions (e.g., hyperkeratosis),[29,30] which are all common in patients with chronic edema. Furthermore, compression therapy is the primary treatment for lipodermatosclerosis, a condition that is often misdiagnosed as cellulitis[31] and for which antibiotic treatment is ineffective.

The mechanism by which compression therapy prevents recurrent cellulitis is not known. The relationship between chronic edema and cellulitis is considered to be multifactorial[32]: chronic edema provides a medium for bacterial growth,[32] altered lymphatic function and decreased lymphatic drainage can impair the immune response to pathogens,[33,34] and chronic edema can impair skin integrity,[30] increasing susceptibility to entry of bacteria through the skin.[32] Compression therapy could potentially decrease the risk of cellulitis by lessening edema, improving immune response and skin integrity, and providing physical protection for the skin. Future studies could explore the role of these mechanisms in cellulitis associated with chronic edema of the leg.

A potential source of bias in this trial is the fact that assessors and participants were aware of the trial-group assignments. Although the trial assessors, who were lymphedema therapists, had no influence on making the diagnosis of cellulitis, medical practitioners external to the trial who diagnosed cellulitis could have been influenced by the participants, who were aware of their trial-group assignments. The trial assessors also requested an early review of trial results because they anecdotally reported outcomes that favored the compression group, and this could also have introduced bias. With respect to measurement of leg volume, the calibrated perometer was used to mitigate the risk of bias because assessors were aware of the trial-group assignments. Difficulty in applying and removing compression garments is often a barrier to adherence to compression therapy; however, in our trial, 88% of the participants wore their garments 4 or more days per week. This high adherence may have been the result of support from experienced clinicians and may limit generalizability of our findings to other settings in which access to specialist lymphedema physiotherapists is not available.

Other trial limitations include the short duration of follow-up and possible misdiagnosis of cellulitis by medical practitioners. Although misdiagnosis of cellulitis is common,[35] this trial aimed to reflect standard clinical practice, and we accepted the diagnosis of cellulitis as determined by medical practitioners. The point estimates of differences in effect sizes between trial groups are imprecise because of the small size of the trial and because the trial was stopped early with post hoc stopping rules. The time to recurrence of cellulitis was reported by the participants; therefore, the precise time to recurrence may have varied by a few days or longer because the participants' recollection may not have been accurate.

This small, single-center, unblinded trial showed that compression therapy prevented the recurrence of cellulitis in patients with chronic

edema and a history of two or more previous episodes of cellulitis. Larger and longer trials are necessary in order to determine the effect of compression therapy on the recurrence of cellulitis, especially in settings without access to specialized lymphedema services.

Supported by Calvary Public Hospital Bruce, which funded the clinician time to initiate and manage the trial.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Robert Fleet for conducting the statistical analysis for the interim analysis and for participating as a member of the independent data monitoring committee; Angie Fearon and Jeremy Witchalls for participating as members of the independent data monitoring committee; Ming Ling for assistance with obtaining and refining the recruitment data; and the Calvary Public Hospital Bruce Lymphedema Team and Administration Team (especially Gemma Arnold, Marie-Michelle Coulombe, Emma May, Abby Benton, Caitlin Norris, Joshua Pogson, Alicia Palmer, Nievelle Chand, Sarah Toohey, Ashlee Cashion, and Bhavleen Singh) for assisting with data collection and trial administration.

REFERENCES

1. Levell NJ, Wingfield CG, Garioch JJ. Severe lower limb cellulitis is best diagnosed by dermatologists and managed with shared care between primary and secondary care. Br J Dermatol 2011;164:1326-8.
2. Cox NH, Colver GB, Paterson WD. Management and morbidity of cellulitis of the leg. J R Soc Med 1998;91:634-7.
3. Cox NH. Oedema as a risk factor for multiple episodes of cellulitis/erysipelas of the lower leg: a series with community follow-up. Br J Dermatol 2006;155:947-50.
4. Thomas KS, Crook AM, Nunn AJ, et al. Penicillin to prevent recurrent leg cellulitis. N Engl J Med 2013;368:1695-703.
5. Dalal A, Eskin-Schwartz M, Mimouni D, et al. Interventions for the prevention of recurrent erysipelas and cellulitis. Cochrane Database Syst Rev 2017;6:CD009758.
6. Thomas KS, Brindle R, Chalmers JR, et al. Identifying priority areas for research into the diagnosis, treatment and prevention of cellulitis (erysipelas): results of a James Lind Alliance Priority Setting Partnership. Br J Dermatol 2017;177:541-3.
7. Mortimer PS, Levick JR. Chronic peripheral oedema: the critical role of the lymphatic system. Clin Med (Lond) 2004;4:448-53.
8. Moffatt C, Keeley V, Quere I. The concept of chronic edema — a neglected public health issue and an international response: the LIMPRINT study. Lymphat Res Biol 2019;17:121-6.
9. Inghammar M, Rasmussen M, Linder A. Recurrent erysipelas — risk factors and clinical presentation. BMC Infect Dis 2014;14:270.
10. Dupuy A, Benchikhi H, Roujeau JC, et al. Risk factors for erysipelas of the leg (cellulitis): case-control study. BMJ 1999;318:1591-4.
11. Karppelin M, Siljander T, Vuopio-Varkila J, et al. Factors predisposing to acute and recurrent bacterial non-necrotizing cellulitis in hospitalized patients: a prospective case-control study. Clin Microbiol Infect 2010;16:729-34.
12. Moffatt C, Partsch H, Schuren J, et al. Compression therapy: a position document on compression bandaging. Frederiksberg, Denmark: International Lymphoedema Framework, 2012 (https://www.lympho.org/wp-content/uploads/2016/03/Compression-bandaging-final.pdf).
13. Swartz MN. Cellulitis. N Engl J Med 2004;350:904-12.
14. Chlebicki MP, Oh CC. Recurrent cellulitis: risk factors, etiology, pathogenesis and treatment. Curr Infect Dis Rep 2014;16:422.
15. Lymphoedema Framework. Template for practice: compression hosiery in lymphoedema. London: MEP, 2006 (https://www.lympho.org/wp-content/uploads/2016/03/Compression_hosiery.pdf).
16. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. Cochrane Database Syst Rev 2012;11:CD000265.
17. Keeley V, Crooks S, Locke J, Veigas D, Riches K, Hilliam R. A quality of life measure for limb lymphoedema (LYMQOL). J Lymphoedema 2010;5:26-37.
18. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-43.
19. Arsenault K, Rielly L, Wise H. Effects of complete decongestive therapy on the incidence rate of hospitalization for the management of recurrent cellulitis in adults with lymphedema. Rehabil Oncol 2011;29(3):14-20.
20. Ko DS, Lerner R, Klose G, Cosimi AB. Effective treatment of lymphedema of the extremities. Arch Surg 1998;133:452-8.
21. R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2018.
22. Pavlotsky F, Amrani S, Trau H. Recurrent erysipelas: risk factors. J Dtsch Dermatol Ges 2004;2:89-95.
23. Chira S, Miller LG. Staphylococcus aureus is the most common identified cause of cellulitis: a systematic review. Epidemiol Infect 2010;138:313-7.
24. Australian Commission on Safety and Quality in Health Care. Antimicrobial stewardship in Australian health care 2018. Sydney: ACSQHC, 2018 (https://www.safetyandquality.gov.au/sites/default/files/migrated/AMSAH-Book-WEB-COMPLETE.pdf).
25. Yasuhara H, Shigematsu H, Muto T. A study of the advantages of elastic stockings for leg lymphedema. Int Angiol 1996;15:272-7.
26. Pappas CJ, O'Donnell TF Jr. Long-term results of compression treatment for lymphedema. J Vasc Surg 1992;16:555-62.
27. Rathbun SW, Kirkpatrick AC. Treatment of chronic venous insufficiency. Curr Treat Options Cardiovasc Med 2007;9:115-26.
28. Nelson EA, Bell-Syer SE. Compression for preventing recurrence of venous ulcers. Cochrane Database Syst Rev 2014;9:CD002303.
29. Elwell R. The management and treatment of hyperkeratosis. Br J Nurs 2017;26:468-70.
30. Rich A. How to care for uncomplicated skin and keep it free of complications. Br J Community Nurs 2007;12:S6-S9.
31. Miteva M, Romanelli P, Kirsner RS. Lipodermatosclerosis. Dermatol Ther 2010;23:375-88.
32. Al-Niaimi F, Cox N. Cellulitis and lymphoedema. J Lymphoedema 2009;4:38-42.
33. Stephens M, Liao S. Neutrophil-lymphatic interactions during acute and chronic disease. Cell Tissue Res 2018;371:599-606.
34. Liao S, Cheng G, Conner DA, et al. Impaired lymphatic contraction associated with immunosuppression. Proc Natl Acad Sci U S A 2011;108:18784-9.
35. Ko LN, Garza-Mayers AC, St John J, et al. Effect of dermatology consultation on outcomes for patients with presumed cellulitis: a randomized clinical trial. JAMA Dermatol 2018;154:529-36.

CORRESPONDENCE

Compression Therapy to Prevent Recurrent Cellulitis of the Leg

TO THE EDITOR: Webb et al. (Aug. 13 issue)[1] present the results of a randomized, controlled trial of compression therapy in patients with chronic leg edema and recurrent cellulitis. Leg compression therapy plus education was significantly better than education alone (control) with regard to cellulitis prevention in a cohort of patients that was heterogeneous (as indicated by the distribution of characteristics in Table 1 of their article). It is apparent that a substantial proportion of patients had multiple factors contributing to chronic leg edema. Venous stasis due to morbid obesity was a frequent cause of leg edema, and the results of this trial are welcome for this group of patients with a challenging condition.

Chronic venous disease, which was apparently classified as clinical class C3 through C5 according to the clinical, etiologic, anatomical, pathophysiological (CEAP) classification system (with classes ranging from C0 [no signs of venous disease] to C6 [active ulceration]), was also frequent in the trial population. We are curious about the frequency of recurrent cellulitis among patients with chronic venous disease, given that cellulitis is often indistinguishable from dermatitis or hypodermatitis, which are recognized manifestations of CEAP clinical class C4 chronic venous disease.[2,3]

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No potential conflict of interest relevant to this letter was reported.

1. Webb E, Neeman T, Bowden FJ, Gaida J, Mumford V, Bissett B. Compression therapy to prevent recurrent cellulitis of the leg. N Engl J Med 2020;383:630-9.
2. Eklöf B, Rutherford RB, Bergan JJ, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004;40:1248-52.
3. Vasquez MA, Rabe E, McLafferty RB, et al. Revision of the Venous Clinical Severity Score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. J Vasc Surg 2010;52:1387-96.

DOI: 10.1056/NEJMc2029458

THE AUTHORS REPLY: In this pragmatic trial we accepted a diagnosis of cellulitis made by external treating physicians. We agree that misdiagnosis can occur,[1] particularly in patients who have clinical manifestations of chronic venous disease.[2] The randomized design of our trial supported the equal distribution of participants with chronic venous insufficiency across the two groups: 29% in the compression group and 26% in the control group. Of the 23 participants who had received a diagnosis of cellulitis, 6 (26%) had chronic venous insufficiency — specifically, 3 of 6 participants (50%) in the compression group and 3 of 17 (18%) in the control group.

In practice, several noninfectious conditions can be misdiagnosed as cellulitis. Our trial, within the limitations we acknowledged, showed that the use of compression therapy in patients with a previous diagnosis of cellulitis led to a lower risk of subsequent development of symptoms and signs consistent with cellulitis than education alone.

THIS WEEK'S LETTERS

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Since publication of their article, the authors report no further potential conflict of interest.

1. Ko LN, Garza-Mayers AC, St John J, et al. Effect of dermatology consultation on outcomes for patients with presumed cellulitis: a randomized clinical trial. JAMA Dermatol 2018;154:529-36.
2. Raff AB, Kroshinsky D. Cellulitis: a review. JAMA 2016;316:325-37.

DOI: 10.1056/NEJMc2029458

The "All of Us" Program and Indigenous Peoples

TO THE EDITOR: In his Perspective article (July 30 issue),[1] Fox raised compelling issues about medical research and considerations specific to Indigenous communities. He referenced the "All of Us" research program and our imperative to address these issues. We welcome this discussion. Indeed, Fox described challenges we have been navigating in collaboration with tribal leaders and the National Institutes of Health Tribal Advisory Committee.

To address persistent underrepresentation and eliminate health disparities, it is essential to rebuild trust with Indigenous communities. Listening to input from tribal communities strengthens research practices and will ultimately improve health.

Our recently posted preliminary report chronicles 14 months of tribal consultation on inclusion of American Indian and Alaska Native people.[2] Guided by a framework for ongoing engagement with tribal nations,[3] we seek to root the program in respect for tribal sovereignty, cultural sensitivity, data protection, and inclusive governance.

We are grateful to the tribal communities guiding this work and look forward to continued input from stakeholders, including Fox. Only through meaningful dialogue can All of Us chart a path toward respectful inclusion that benefits all participants.

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No potential conflict of interest relevant to this letter was reported.

1. Fox K. The illusion of inclusion — the "All of Us" research program and Indigenous peoples' DNA. N Engl J Med 2020;383:411-3.
2. All of Us research program tribal consultation report draft: draft for tribal leader input. Bethesda, MD: National Institutes of Health, August 2020 (https://allofus.nih.gov/sites/default/files/draft-tribal-consultation-report.pdf).
3. Considerations for meaningful collaboration with tribal populations: the Tribal Collaboration Working Group Report to the *All of Us* Research Program Advisory Panel. Bethesda, MD: National Institutes of Health, April 4, 2018 (https://allofus.nih.gov/sites/default/files/tribal_collab_work_group_rept.pdf).

DOI: 10.1056/NEJMc2028907

THE AUTHOR REPLIES: Although there have been considerable advances in biomedical research in recent decades, only marginal progress has been made in including underrepresented minorities in studies that will inform the future of precision medicine.[1-3] I appreciate the attention that the All of Us leadership has given to this issue.

While it is important to increase the representation of Indigenous and other minority communities in research, it is also important to recognize the limits of inclusion in facilitating the accrual of concrete benefits to those communities. As I outlined in my article, the benefits of publicly funded research continue to flow mainly to large corporations, and there is little attention paid to the development of mechanisms that will return some benefit to the communities involved in large-scale screening of genomic studies.[4]

Genomic data are a resource, but unless we approach their use more sustainably, we risk

APPENDIX F: Published copy of paper three

Compression Therapy is Cost-Saving in the Prevention of Lower Limb Recurrent Cellulitis in Patients with Chronic Oedema

LYMPHATIC RESEARCH AND BIOLOGY
Volume 00, Number 00, 2022
Mary Ann Liebert, Inc.
DOI: 10.1089/lrb.2022.0029

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Compression Therapy Is Cost-Saving in the Prevention of Lower Limb Recurrent Cellulitis in Patients with Chronic Edema

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Abstract

Background: Cellulitis is a common and often recurrent infection that causes substantial financial burden and morbidity. Compression therapy reduces the risk of recurrent cellulitis episodes for adults with chronic edema; however, little is known about the cost-effectiveness of the intervention.
Methods and Results: A cost analysis was undertaken during a randomized controlled trial (RCT) involving 84 participants with lower limb chronic edema and a history of recurrent cellulitis. The intervention group received compression therapy and education, while the control group received education only. A clinical audit and survey were used to measure health service and patient resource use for (1) the most recent episode of cellulitis, and (2) compression therapy over 18 months. Australian reference costs were used to calculate cellulitis and compression therapy costs, and the mean expenditure in both the RCT groups. Of the 84 RCT participants, 43 were surveyed and audited on the cost of cellulitis, and 40 on the cost of compression therapy. The mean cost of a hospitalized and nonhospitalized episode of cellulitis was $9071 and $506 from a health service perspective, and $4496 and $1320 from a patient perspective. The mean cost of compression therapy per participant over 18 months was $1905 and $421 from health service and patient perspectives, respectively. During the RCT, the mean annual cost per participant was $4972 in the experimental group and $26,382 in the control group, giving a cost-saving of $21,483 (95% confidence interval, 3136–48,176) per participant.
Conclusion: For patients with lower limb chronic edema and recurrent cellulitis, compression therapy is both efficacious and cost-saving. Trial Registration: ACTRN12617000412336.

Keywords: cellulitis, edema, lymphedema, recurrence, compression, cost

Introduction

Cellulitis is a common bacterial infection of the skin and subcutaneous tissue. It frequently reoccurs, with up to 47% of patients experiencing another infection within 3 years.[1] Cellulitis causes considerable financial burden for both patients and health services. Within the Australian emergency departments, cellulitis is the fourth most-common principal diagnosis, and the third most-common presentation requiring hospital admission.[2] In 2017–2018, there were

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128,129 emergency department presentations[2] and 72,150 hospital admissions[3] for cellulitis, which cost the Australian health system ~90 million and 327 million AUD, respectively.[3,4] Although only 7%–20% of cellulitis episodes require hospitalization,[5,6] it has been reported that 83% of medical expenditure for cellulitis is related to hospital admissions.[6]

Chronic edema, where swelling persists for 3 or more months, increases the risk of cellulitis and cellulitis recurrence.[1,7,8] There is a cyclical relationship between cellulitis and chronic edema, through which chronic edema increases the risk of cellulitis, and cellulitis can cause or worsen chronic edema.[9] An international cross-sectional study of patients with lower limb chronic edema observed that the lifetime prevalence of cellulitis was 37%, with 16% suffering an episode in the past 12 months.[10] Furthermore, controlled swelling was associated with reduced risk of cellulitis.[10] Two linked clinical trials investigating the impact of prophylactic penicillin on cellulitis recurrence found that preexisting edema was present in 46% of participants with a history of cellulitis, and 59% of participants with recurrent cellulitis.[11,12] Thus, as both chronic edema and cellulitis are common comorbid conditions, there is an urgent need to manage both conditions to improve health and relieve financial burden.

Compression therapy is the main modality used to manage chronic edema. Our recent randomized controlled trial (RCT) demonstrated that for patients with lower limb chronic edema experiencing recurrent cellulitis, compression therapy reduced the risk of further cellulitis episodes by 77% (hazard ratio, 0.23; 95% confidence interval [CI], 0.09–0.59; $p = 0.002$).[13] The RCT was designed to enroll 164 participants, however, it was stopped for efficacy following a planned interim analysis. As such, the trial had a total of 84 participants with a median follow-up time of 186 days instead of the planned 3 years.[13]

While we now know compression therapy is effective in preventing cellulitis, there is limited information on the associated costs involved. A retrospective cohort study conducted in Australia during the 2012–2013 financial year found that the mean hospital admission cost for an episode of cellulitis was $5196 for inpatient admissions and $5873 for hospital-in-the-home admissions. However, as patients hospitalized for cellulitis with concurrent edema have longer admissions,[14] hospital costs are likely to be higher in this population. While we have some knowledge of hospital admission costs for cellulitis, information on the broader health service and patient costs relating to cellulitis is scarce. Furthermore, chronic edema is considered a hidden epidemic, despite being very common, and the expense to the health system and patient is largely unknown. Improved knowledge of these costs is essential to guide policy and resource allocation.

Compression therapy can break the cycle of edema and cellulitis, but there is no information on the cost-effectiveness of this intervention. As part of the clinical trial assessing the impact of compression therapy on cellulitis recurrence, a cost analysis was undertaken[15] with the aim to describe and compare the cost of a recurrent cellulitis episode and the cost of compression therapy (over 18 months) from both health service and patient perspectives. Furthermore, the total costs arising in the experimental and control groups during the RCT were compared.

Methods

During the RCT, a cost analysis was undertaken to determine and compare the costs of cellulitis and compression therapy in patients with chronic edema who are experiencing recurrent cellulitis. Cellulitis and compression therapy costs were measured from both health service and patient perspectives. These costs were then applied to the experimental and control RCT groups, allowing comparison of costs.

RCT methods

The RCT protocol and results have been previously published,[11,13] but are summarized briefly here. The primary outcome of the RCT was time to cellulitis recurrence. Following enrollment, participants were randomized to receive either education on the prevention of cellulitis (control group) or the same education plus compression therapy (experimental group).[13] Trial group assignment was concealed, but after randomization therapists and participants were not blinded to treatment allocation for ethical and logistical reasons. To replicate standard clinical practice, participants were followed up six monthly, with the experimental group participants attending extra appointments to complete compression therapy with qualified lymphedema physiotherapists.

Following an episode of recurrent cellulitis, participants in the control group were crossed over to receive compression therapy. The trial was planned to continue for 3 years, or until 45 episodes of cellulitis occurred, and a planned interim analysis with stopping rules was completed after the 23rd episode of cellulitis. Although the trial was stopped early for efficacy, participants were followed up until 18 months postrandomization, allowing the cost of compression therapy to be measured across this time frame.

Participants

The cost analysis included two subsets of participants from the RCT who were surveyed regarding resource use: one group in relation to their most recent episode of cellulitis (cellulitis group), and the other regarding the use of compression therapy over 18 months (compression group). Participants were excluded from the cellulitis group if their most recent episode of cellulitis was over a year before enrollment in the trial.

Participants met the inclusion criteria for the RCT, which included having chronic edema and a history of two or more episodes of cellulitis in the same leg in the 2 years before trial referral. Exclusion criteria comprised the following: being <18 years of age; being medically unstable; receiving end-of-life care; having a chronic wound or wound requiring specialist treatment; being unable to tolerate compression; or already wearing effective compression garments regularly.

Outcomes

The primary outcomes of the costs analysis were the cost of an episode of cellulitis, and the cost of compression therapy over 18 months. Costs were categorized as health service or patient expenses. Paper surveys were developed to measure participant resource use and piloted on relevant patients before use in the trial. Participants were also asked to complete the Self-Administered Comorbidity Questionnaire, and to provide demographic information to allow description and comparison of the samples.

The cellulitis group participants were surveyed consecutively following enrollment into the trial. The survey captured resource use relating to their most recent episode of cellulitis, including medical appointment attendances, health service utilization, length of stay (LOS) in hospital, participant and family time away from work and leisure activities, duration that the participants required assistance with activities of daily living (ADLs), and use of antibiotics and pain relief. Medical records were audited at both the Australian Capital Territory (ACT) public hospitals to verify the details of reported hospital admissions. Participants' data were excluded if they reported hospitalization for cellulitis, but the medical record indicated that their admission was primarily for another condition.

The compression group participants were consecutively surveyed during a scheduled follow-up appointment after 18 months of compression therapy. The survey obtained information regarding participant and family time away from work and assistance provided for ADLs that were related to their compression therapy. Medical records were audited to determine the cost of prescribed compression garments, the number of appointments attended, and the number of compression bandages applied.

Resource costs

Australian national reference costs for the 2017/2018 financial year were applied to all resource items. Medications were costed using the Australian Pharmaceutical Benefit Scheme[16] (PBS) with the assumption that pension age participants (≥66 years) paid the concession price, with the PBS funding the surplus.[17,18] Health Information Services at the two local hospitals individually costed reported hospital admissions using the Australian Refined Diagnosis Related Groups[19] (AR-DRGs). For the three reported hospital admissions that occurred outside of the ACT, admission costs were calculated using a standard algorithm that incorporates the 2017/2018 National Efficient Price, the average price weights for the two cellulitis AR-DRGs (J64A: Cellulitis, Major Complexity; and J64B: Cellulitis, Minor Complexity), and the hospital LOS. Emergency department presentations were costed based on the National Hospital Cost Data Collection Cost Report.[4]

General practitioner appointment costs were based on the Medicare Benefits Scheme (MBS) prices,[20] while hospital outpatient, pathology, and allied health appointments were based on the Independent Hospital Pricing Authorities' (IHPA) Tier 2 Non-Admitted Services Classification prices.[3] The national average patient cocontribution was used for general practitioner and outpatient appointments.[21] Time off work was priced on the average Australian weekly earnings reported by the Australian Bureau of Statistics.[22] The National Disability Insurance Scheme price guide[23] was used to assign costs for assistance with ADLs. For participants reporting they required both assistance with ADLs and family to take time away from work, family time off work was subtracted from the number of days ADL assistance was provided to avoid doubling up on costs.

Travel for all appointments was assumed to be a 10 km round trip, with the price per km based on the Australian Tax Office's work-related car expenses.[24] The compression bandage and compression garment costs were recorded for each participant. A full list of the resource costs can be found in Supplementary Appendix Table S1.

The health service perspective included all costs related to government-funded health services, being hospital admissions, emergency department presentations, public outpatient services, and MBS and PBS rebates for appointments and medications. The patient perspective included all costs incurred by the participants and their family, including costs relating to appointments, travel, medications, assistance with ADLs, and the inability to work. Leisure time missed was recorded but not priced. Tables 2 and 3 show which costs were assigned to either the health service perspective or the patient perspective.

Descriptive analysis

Resource use and associated costs were reported as mean and standard deviation (SD). Costs were calculated and presented using Australian reference costs for the 2017–2018 financial year, with high-level costs being translated into US dollars (USD) using the average conversion rate for that financial year[25] to allow easier international comparison. Although some trial data collection and outcomes occurred before and after this time frame, due to the limited follow-up duration of the trial, discounting was considered redundant.

Mean total costs for compression therapy were given over 18 months, as well as over 0–6 and 7–18 months to show how treatment costs change over time. Mean total costs for cellulitis were also presented separately for hospitalized and nonhospitalized participants due to the large difference in resource use for these participants. The sensitivity analysis assessed the impact of outlier values. Winsorization was used, with all variable outliers over 3.29 SDs from the mean being replaced with the closest nonoutlier value.[26] All analyses were performed using R software (version 3.6.0).

Application of measured costs to the RCT

The outcomes from the costs analysis were used to calculate the total cost of the intervention and the cellulitis episodes for each trial group during the RCT. For both the RCT groups (experimental and control), the intervention cost was calculated for each participant based on the individual follow-up time frame, before being censored for an episode of cellulitis or the trial's cessation. For the experimental group participants, their follow-up duration within the initial 6-month period, and the subsequent 7- to 18-month period was costed separately based on mean compression therapy costs for these periods, before being summated. For the control group, the intervention cost was based on the number of appointments attended for education on cellulitis prevention. Hospitalized and nonhospitalized episodes of cellulitis occurring during the trial were costed separately.

Due to the large discrepancy in follow-up time between the two trial groups arising from more control group participants being censored following cellulitis episodes, the trial costs were presented per participant per year to allow direct comparison. Due the small sample size and skewed data, nonparametric bootstrap sampling with 1000 samples was used to calculate the mean annual cost per participant for each trial group, and subsequently the mean intergroup difference and 95% CIs.

Results

Participant characteristics

Data were obtained on the cost of compression therapy for 40 participants (compression group) and the cost of an episode of cellulitis for 43 participants (cellulitis group), with 18 participants contributing data to both groups. The majority of participants surveyed regarding compression therapy costs were those randomized to the experimental group, however, three control group participants who completed 18 months of compression therapy following crossover were also surveyed. Of participants surveyed on the cost of cellulitis, 21 were from the experimental group, and 22 were from the control group. The patient demographics of the compression and cellulitis groups in the cost analysis are shown in Table 1, and are similar to those of the RCT participants.[13]

For both groups, the mean number of cellulitis episodes per leg in the 2 years before referral to the trial was 2, the mean Self-Administered Comorbidity Questionnaire Score was 9 (out of a maximum score of 45), and obesity was the most common reported factor contributing to chronic edema. For the compression group, the mean age and body mass index (BMI) were 66 (SD: 12.9) and 39 (SD: 9.9), respectively, and chronic edema was bilateral in 78% of participants. The cellulitis group's mean age and BMI were 64 (SD: 14) and 42 (SD: 9.6), and 81% had bilateral chronic edema.

Table 1. Baseline Characteristics of the Participants

Characteristic	*Compression (N = 40)*	*Cellulitis (N = 43)*
Female sex, *n* (%)	19 (48)	17 (40)
Age		
Mean (SD)	66 (12.9)	64 (14)
Median (IQR)	69 (55–75)	65 (52–73)
Pension age (≥66 years), *n* (%)	23 (58)	21 (48)
Spousal status (single or *de facto*)		
De facto, *n* (%)	28 (70)	28 (65)
Body mass index		
Mean (SD)	39 (9.9)	42 (9.6)
Median (IQR)	39 (31–45)	41 (34–48)
Self-Administered Comorbidity Questionnaire		
Mean (SD)	9 (4.4)	9 (5.2)
Median (IQR)	9 (5–11)	9 (5–12)
Chronic edema: bilateral, *n* (%)	31 (78)	35 (81)
Duration of edema, *n* (%)		
1–5 Years	17 (43)	13 (30)
>5 Years	23 (58)	30 (70)
Episodes of cellulitis per leg in 2 years before trial referral		
Mean (SD)	2 (1.4)	2 (1.3)
Median (IQR)	2 (0–2)	2 (0–2)
Hospital admission for cellulitis in 2 years before trial referral		
Mean (SD)	1 (0.9)	1 (0.7)
Median (IQR)	1 (0–1)	1 (0.5–1)
Prophylactic antibiotics, *n* (%)	2 (5)	2 (5)
Factors contributing to chronic edema, *n* (%)		
Obesity	26 (65)	30 (70)
Surgery/trauma	14 (35)	13 (30)
Venous hypertension	11 (28)	14 (33)
Immobility	4 (10)	4 (9)
Primary lymphedema	3 (8)	3 (7)
Cancer	0 (0)	0 (0)
Other	6 (15)	5 (12)
Comorbidities, *n* (%)		
Tinea pedis	14 (35)	15 (35)
Diabetes	10 (25)	14 (33)
Chronic venous insufficiency	10 (25)	13 (30)
Congestive heart failure	7 (18)	11 (26)

IQR, interquartile range; SD, standard deviation.

Cellulitis group costs

The resource use and costs associated with an episode of cellulitis are shown in Table 2. Of the 43 cellulitis group participants, 27 (63%) presented to the emergency department, 24 (56%) were admitted to hospital, 41 (95%) had one or more general practitioner appointments, 23 (53%) required nonprescription pain relief, and 15 (35%) required prescription pain relief for their most recent episode of cellulitis. The total mean cost for a nonhospitalized episode of cellulitis was $1826, whereas the mean cost for a hospitalized episode was 7.4 times higher, being $13,567.

Health service costs. The mean cost to health services for an episode of cellulitis was $5287 ($4289 USD). However, on average, cellulitis episodes requiring hospitalization cost $9071, which is almost 18 times higher than nonhospitalized episodes, which cost an average of $506. The highest cellulitis-related costs were for hospital utilization, with emergency department presentations costing a mean of $640 per participant and the average hospital admission costing $7057 per hospitalized participant. General practitioner and other health care appointments were the next biggest contributor to cost, with antibiotics and pain relief medications adding comparatively minimal expense. Resource use and costs were generally positively skewed (Supplementary Appendix Table S2), with a few participants with substantially higher resource utilization increasing mean values. For example, 22 of 24 hospital admissions cost between $3300 and $7500, however, 2 admissions costing more than $24,000 resulted in the mean and median costs for hospitalization being $7057 and $5831.

Patient costs. The mean patient cost for an episode of cellulitis was $3092 ($2509 USD), with hospitalized patient costs being $4496, compared with $1320 for nonhospitalized patients. The highest costs were for patient and family time off work and assistance with ADLs, and general practitioner and other health care appointments were the next biggest contributor. Patient and family time off work, assistance with ADLs, and the overall combined resource costs were positively skewed (Supplementary Appendix Table S2). A total of 17 (40%) participants were employed, with 13 reporting they required time off work. Those who were employed took a mean of 15 days off work (range 0–45 days). Furthermore, 26 (60%) participants needed assistance with ADLs or family to take time off work.

Table 2. Measured Resource Use and Cost for Recurrent Cellulitis Episodes

Measured resources (per episode of cellulitis)	*Cellulitis episodes,* n = *43*			
	Number, mean (SD)	*Health service costs ($), mean (SD)*	*Patient costs ($), mean (SD)*	*Total cost ($), mean (SD)*
Hospital utilization				
Emergency department Presentations	1 (0.6)	640 (516)	—	640 (516)
Hospital LOS for cellulitis episodes requiring admission (days)[a]	8 (7.9)	7057 (5883)	—	7057 (5883)
Health care appointments				
General practitioner	3 (3.1)	105 (116)	106 (117)	211 (233)
Other	2 (4.9)	614 (1208)	66 (144)	680 (1296)
Antibiotics (prescriptions purchased)	2 (1.3)	11 (15)	34 (29)	46 (27)
Pain relief (days used)				
Prescription	5 (8.6)	8 (22)	20 (47)	28 (55)
Nonprescription	5 (8.4)	—	4 (7)	4 (7)
Travel for health care (number of trips)	7 (6.7)	—	43 (44)	43 (44)
Assistance with ADLs[b] (days)	8 (11.3)	—	644 (991)	644 (991)
Time off work (days)				
Patient	6 (11.2)	—	1945 (3715)	1945 (3715)
Family	1 (2.3)	—	238 (758)	238 (758)
Leisure time missed (days)				
Patient	14 (18.7)	—	—	—
Family	4 (8.9)	—	—	—
Combined resources per episode of cellulitis				
All episodes ($n = 43$)	—	5287 (6344)	3092 (4483)	8379 (8442)
Hospitalized episodes ($n = 24$)	—	9071 (6254)	4496 (5493)	13,567 (7944)
Nonhospitalized episodes ($n = 19$)	—	506 (842)	1320 (1551)	1826 (2106)

All costs are in 2017–2018 Australian dollars. The average exchange rate for the 2017–2018 financial year: $1 AUD = $0.8113 USD.[25]
[a]LOS calculations only included patients who were hospitalized ($n = 24$).
[b]For ADL assistance calculations, reported family time away from work was subtracted from the reported number of days that ADL assistance was required to avoid doubling up on costs.
ADLs, activities of daily living; LOS, length of stay.

Compression group costs

The mean resource use and costs for compression therapy are shown in Table 3. Of the 40 compression group participants, 23 (58%) received compression bandaging to reduce their edema before the provision of compression garments. These participants attended extra appointments, usually early on in their treatment course. The total mean cost for compression therapy over 18 months was $2326 ($1887 USD), with $1229 attributed to the first 6 months and $1117 to the following 12 months. These figures indicate that compression therapy is more expensive during the initial intensive treatment phase, and after 6 months, ongoing maintenance costs for compression therapy are reduced for both the health service and the patient.

Health service costs. Health service costs for compression therapy are greatest in the first 6 months of treatment, after which ongoing maintenance costs were 57% lower. The mean health service cost of compression therapy was $1905 ($1546 USD) per participant over 18 months, with $1038 of that expenditure occurring within the first 6 months and $887 occurring in the following 12 months. The greatest expense was for lymphedema service appointments, being $1045 over 18 months, however, appointment costs reduced substantially after the initial 6-month period. Compression garments were the second biggest expense, costing $795 per participant over 18 months. For the 65% of participants for whom compression garments were government funded, the mean cost of compression garments was 1.5 times higher, being $1223 per participant. Participants with unilateral edema cost 36% less than those with bilateral edema.

Patient costs. The mean patient cost for compression therapy was $421 ($342 USD) per participant over 18 months, with the first 6 months costing $191 and the following 12 months costing $230. Although only 35% of compression garments were patient funded, they were still the greatest contributor to the overall cost for participants. The mean patient cost for compression garments was $242, with $118 being spent in the first 6 months and $124 in the following 12 months. The mean patient cost for compression garments was much higher among self-funding participants, being $691 over 18 months. Assistance with ADLs and time off work costs were positively skewed, with the mean sitting above the interquartile range (Supplementary Appendix Table S3).

Only four participants required up to 1 day off work, and two participants required assistance with ADLs for compression therapy. Of these two participants, one required 10 minutes of assistance per day over the 18-month period to apply and remove compression garments, which substantially positively skewed the total patient expenditure, particularly for those with unilateral edema.

Table 3. Measured Resource Use and Cost for Compression Therapy over 18 Months

Measured resources (per participant)	*Compression therapy,* n = *40*			
	Number, mean (SD)	*Health service costs ($), mean (SD)*	*Patient costs ($), mean (SD)*	*Total cost ($), mean (SD)*
Garment sets purchased				
0–6 Months	2 (0.2)	292 (259)	118 (189)	410 (180)
7–18 Months	3 (1.2)	503 (543)	124 (205)	627 (456)
Compression bandages applied				
0–6 Months	3 (3.1)	59 (73)	—	59 (73)
7–18 Months	0 (0.8)	6 (19)	—	6 (19)
Lymphedema service appointments				
0–6 Months	4 (2.1)	686 (325)	—	686 (325)
7–18 Months	2 (1.4)	378 (223)	—	378 (223)
Travel for health care (number of trips)				
0–6 Months	4 (2.1)	—	29 (14)	29 (14)
7–18 Months	2 (1.4)	—	16 (9)	16 (9)
Assistance with ADLs[a] (hours)				
0–6 Months	1 (4.8)	—	37 (219)	37 (219)
7–18 Months	2 (9.6)	—	74 (437)	74 (437)
Time off work (days)				
Patient	0 (0.2)	—	23 (78)	23 (78)
Family	0 (0)	—	0 (0)	0 (0)
Leisure time missed (days)				
Patient	0 (1.4)	—	—	—
Family	0 (0.1)	—	—	—
Combined resources per participant All participants ($n = 40$)				
0–18 Months	—	1905 (1097)	421 (825)	2326 (1169)
0–6 Months	—	1038 (539)	191 (320)	1229 (582)
7–18 Months	—	887 (708)	230 (515)	1117 (737)
Participants with unilateral edema ($n = 9$)				
0–18 Months	—	1322 (592)	740 (1548)	2062 (1566)
Participants with bilateral edema ($n = 31$)				
0–18 Months		2074 (1158)	328 (455)	2403 (1046)

All costs are in 2017–2018 Australian dollars. The average exchange rate for the 2017–2018 financial year: $1 AUD = $0.8113 USD.[25]
[a]For ADL assistance calculations, reported family time away from work was subtracted from the reported number of days that ADL assistance was required to avoid doubling up on costs.

Sensitivity analysis

After winsorizing all identified outlier values, no mean total health service costs changed by more than 5%. For an episode of cellulitis, the average patient cost among hospitalized participants changed from $4496 to $4250 (5% change). For compression therapy, the patient cost over 18 months reduced from $421 to $317 (25% change). This change was particularly large for participants with unilateral edema, where the average patient cost for compression therapy over 18 months reduced from $740 to $315 (57% change). This reduction in the cost of compression therapy for patients was related to one participant with unilateral edema who required high levels of assistance with ADLs (daily assistance for garment application and removal).

RCT outcomes and costs

RCT outcomes. During the RCT, 23 episodes of cellulitis occurred before the interim analysis and subsequent stopping of the trial for efficacy. Six episodes of cellulitis occurred in the experimental group, and 17 occurred in the control group, giving an incidence rate ratio of 0.21 (95% CI: 0.08–0.55, $p = 0.0005$). Of those participants who experienced cellulitis, three and six required hospital admission in the experimental and control groups, respectively.

Measured costs applied to the RCT. The mean annual costs per participant for both the experimental and control groups are shown in Table 4. The mean annual health service cost per person was $3616 in the experimental group and $14,527 in the control group, giving a mean intergroup difference of $10,963 (95% CI, $1000–$24,590). The mean yearly patient costs were $1356 and $11,856 per person in the experimental and control groups, respectively, providing a mean intergroup difference of $10,521 (95% CI, $1806–$24,933). The mean total (health service and patient) annual cost per person was $4972 ($4034 USD) for the experimental group and $26,382 ($21,404 USD) for the control group, giving an intergroup difference of $21,483 (95% CI, $3136–$48,176). Therefore, the mean total expenditure per participant was 81% lower in the experimental group. This reflects the higher incidence and costs related to cellulitis management in the control group (90% of total costs) versus the experimental group (48% of total costs).

Table 4. Measured Costs Applied to the Randomized Controlled Trial

Perspective	*Mean annual cost per participant ($)*		*Mean intergroup difference, $ (95% CI)*
	Experimental group, n = *41*	*Control group,* n = *43*	
Health service	3616	14,527	10,963 (1000–24,590)
Patient	1356	11,856	10,521 (1806–24,933)
Total (health+patient)	4972	26,382	21,483 (3136–48,176)

The mean annual cost per participant, and the mean intergroup difference and 95% CI were calculated using nonparametric bootstrap sampling with 1000 samples. All costs are in 2017–2018 Australian dollars. The average exchange rate for the 2017–2018 financial year: $1 AUD = $0.8113 USD.[25]

CI, confidence interval.

Discussion

This is the first analysis to demonstrate that compression therapy is a cost-saving treatment for preventing cellulitis in patients with recurrent cellulitis and comorbid lower limb chronic edema. While this trial assessed costs in Australian currency (AUD), the cost-savings presented may be proportionate to other countries with similar health systems. Daily costs incurred during the trial were 81% lower in the experimental group than in the control group. Compared with the control group, health service and patient-specific costs in the experimental group were 75% and 89% lower, respectively. These results provide strong justification for health care systems to invest in compression therapy for these patients, as the benefits are clear from both health and economic perspectives.

During the RCT, total expenditure on cellulitis was calculated to be $147,648, of which 83% related to hospitalized participants. The reported mean LOS for cellulitis-related hospitalizations varies from 4.7 to 12.1.[5,6] The mean and median hospital LOS of 8 and 6.5 observed in the cellulitis group is on the higher end of reported Australian statistics,[3,27] however, an above-average LOS in this population was expected as research has shown that edema is a risk factor for increased LOS for cellulitis-related admissions.[14] In addition, hospital admissions have been observed to be longer for recurrent versus primary episodes of cellulitis.[28] The increased LOS found in this population, and the high expenditure related to hospitalization, highlights the importance of preventing cellulitis infections in this patient group.

Total expenditure on compression therapy during the RCT was $50,551 across 41 participants, with health services funding 84% and patients funding the remaining 16%. Government funding schemes differ between countries, and therefore, the proportion of compression therapy expenditure funded by health services may also vary. Health service and patient costs for compression therapy were substantially higher in the first 6 months compared with the following 12 months. This was expected as initiating compression therapy involves multiple appointments for education, and for measurement and fitting of compression garments. Furthermore, some patients also require a series of compression bandages to reduce limb volume before optimal measurement and fit of compression garments. Although these interventions may be required on an ongoing basis to manage chronic edema, the frequency and consequently cost are usually much lower after the initial intensive treatment phase. After the initial 6-month period, the measured 12-month cost of compression therapy per patient, being $887 and $230 from health service and patient perspectives, respectively, may be indicative of ongoing annual costs. Thus, provision of compression therapy has high upfront costs, but ongoing maintenance costs appear to be lower.

In addition to preventing cellulitis, compression therapy provides many other health benefits for patients with chronic edema or venous disease. Compression therapy is a primary treatment modality for both chronic edema[29] and chronic venous insufficiency,[30] a common condition[31] and a known cause of chronic edema.[32] Compression therapy has been found to increase the rate of healing for venous ulcers,[33] reduce the rate of venous ulcer recurrence,[34] reduce limb volume,[13] improve skin condition,[29] improve quality of life for patients with chronic venous disease,[35] and may prevent post-thrombotic syndrome.[36] Furthermore, it is used to manage conditions that mimic cellulitis, such as lipodermatosclerosis.[37] Therefore, the health and financial benefits of compression therapy for patients with chronic edema and cellulitis may be greater than that found in our trial. Thus, we believe our analysis presents a conservative perspective on the cost-savings of compression therapy in these patients.

A limitation of this trial was the early cessation for efficacy, as this limited the sample size and duration of the follow-up period. Although outliers were identified, they were accurate, and we believe they would occur in standard practice. Therefore, although we assessed their impact in the sensitivity analysis, their inclusion in the primary analysis is appropriate.

This cost analysis indicates that compression therapy is cost-saving from both a patient and health service perspective for patients with chronic edema and recurrent cellulitis. The health and economic benefits demonstrated by this research provide clinicians, health services, and policy makers with strong justification to support the funding of compression therapy in the prevention of lower limb recurrent cellulitis. Further research with more participants and a longer follow-up duration will allow for a robust analysis of its longer term cost-effectiveness.

Ethics Approval

The study was approved by the ACT Health, Calvary Public Hospital Bruce, and the University of Canberra Human Research Ethics Committees. The trial was registered before commencement (ACTRN12617000412336). All participants were given written and verbal information on the trial, and signed a consent form before participating in the trial.

Acknowledgments

The Calvary Public Hospital Bruce Physiotherapy Team, specifically Gemma Arnold, Marie-Michelle Coulombe, Emma May, Abby Benton, Caitlin Norris, Joshua Pogson, Alicia Palmer, Nievelle Chand, Sarah Toohey, Ashlee Cashion, and Bhavleen Singh, who all assisted with data collection and/or trial administration.

Authors' Contributions

E.W.: trial design and implementation, funding acquisition, contribution of original material, analysis and interpretation of data, creating initial draft, and approving the final article. V.M. and B.B.: trial implementation support, contribution of original material, and interpretation of data. T.N.: trial design input, trial implementation support, and statistical support. V.M., B.B., T.N., F.B., and E.P. provided supervision, contributed to refinement of the article, and approved the final article.

Author Disclosure Statement

The authors have no competing interests to declare.

Funding Information

Calvary Public Hospital Bruce was the primary sponsor, funding clinician time to initiate and manage the trial. Haddenham Healthcare was a secondary sponsor, providing two sets of free compression garments for each trial participant. Haddenham Healthcare had no role in designing this trial, trial implementation, analyses, data interpretation, or publication or dissemination of results. Haddenham Healthcare had no access to trial data.

Supplementary Material

Supplementary Appendix Table SA1
Supplementary Appendix Table SA2
Supplementary Appendix Table SA3

References

1. Cox NH. Oedema as a risk factor for multiple episodes of cellulitis/erysipelas of the lower leg: A series with community follow-up. Br J Dermatol 2006; 155:947–950.
2. Australian Institute of Health and Welfare 2018. Emergency department care 2017–2018: Australian hospital statistics. https://www.aihw.gov.au/getmedia/9ca4c770-3c3b-42fe-b071-3d758711c23a/aihw-hse-216.pdf.aspx?inline=true (accessed September 10, 2021).
3. Independent Hospital Pricing Authority. National Hospital cost data collection report, public sector, Round 22 (financial year 2017–2018). February 2021. https://www.ihpa.gov.au/publications/national-hospital-cost-data-collection-report-public-sector-round-22-financial-year (accessed June 11, 2021).
4. Independent Hospital Pricing Authority. National Hospital cost data collection: What is the cost of Australia's emergency care patients? 2020. https://www.ihpa.gov.au/sites/default/files/publications/round_22_nhcdc_infographics_emergency.pdf (accessed June 11, 2021).
5. Challener D, Marcelin J, Visscher S, et al. Hospital costs for patients with lower extremity cellulitis: A retrospective population-based study. Hosp Pract (1995) 2017; 45:196–200.
6. Goettsch WG, Bouwes Bavinck JN, Herings RM. Burden of illness of bacterial cellulitis and erysipelas of the leg in the Netherlands. J Eur Acad Dermatol Venereol 2006; 20:834–839.
7. Inghammar M, Rasmussen M, Linder A. Recurrent erysipelas-risk factors and clinical presentation. BMC Infect Dis 2014; 14:270.
8. Karppelin M, Siljander T, Vuopio-Varkila J, et al. Factors predisposing to acute and recurrent bacterial non-necrotizing cellulitis in hospitalized patients: A prospective case-control study. Clin Microbiol Infect 2010; 16:729–734.
9. Chlebicki MP, Oh CC. Recurrent cellulitis: Risk factors, etiology, pathogenesis and treatment. Curr Infect Dis Rep 2014; 16:422.
10. Burian EA, Karlsmark T, Franks PJ, et al. Cellulitis in chronic oedema of the lower leg: An international cross-sectional study. Br J Dermatol 2021; 185:110–118.
11. Thomas KS, Crook AM, Nunn AJ, et al. Penicillin to prevent recurrent leg cellulitis. N Engl J Med 2013; 368:1695–1703.
12. Thomas K, Crook A, Foster K, et al. Prophylactic antibiotics for the prevention of cellulitis (erysipelas) of the leg: Results of the UK Dermatology Clinical Trials Network's PATCH II trial. Br J Dermatol 2012; 166:169–178.
13. Webb E, Neeman T, Bowden FJ, et al. Compression therapy to prevent recurrent cellulitis of the leg. N Engl J Med 2020; 383:630–639.
14. Morpeth SC, Chambers ST, Gallagher K, et al. Lower limb cellulitis: Features associated with length of hospital stay. J Infect 2006; 52:23–29.
15. Webb E, Neeman T, Gaida J, et al. Impact of Compression Therapy on Cellulitis (ICTOC) in adults with chronic oedema: A randomised controlled trial protocol. BMJ Open 2019; 9:e029225.
16. Australian Government Department of Health. Schedule of pharmaceutical benefits. January 2018. https://www.pbs.gov.au/info/publication/schedule/archive (accessed July 13, 2021).
17. Australian Government Department of Health. Pharmaceutical benefits: Fees, patient contributions and safety net thresholds. https://www.pbs.gov.au/info/healthpro/explanatory-notes/front/fee (accessed July 13, 2021).
18. Australian Government Department of Social Services. Age pension. https://www.dss.gov.au/seniors/benefits-payments/age-pension (accessed July 16, 2021).
19. Independent Hospital Pricing Authority. Australian Refined Diagnosis Related Groups version 10.0 final report. https://www.ihpa.gov.au/what-we-do/admitted-acute-care/ar-drg-version-10 (accessed July 16, 2021).
20. Australian Government Department of Health. Medicare benefits schedule book: Operating from 1 January 2018. 2017. www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/90CB91EE0B6FB8A9CA2586140082584E/$File/201801-MBS.pdf (accessed July 13, 2021).
21. Australian Government Department of Health. Annual Medicare statistics. 2020. https://www1.health.gov.au/internet/main/publishing.nsf/Content/Medicare%20Statistics-1 (accessed July 13, 2021).

22. Australian Bureau of Statistics. Average weekly earnings, Australia, May 2018. August 2018. https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/6302.0Main+Features1May%202018 (accessed July 16, 2021).
23. National Disability Insurance Agency. NDIS price guide: Australian Capital Territory, Northern Territory, South Australia, Western Australia. 2017. file:///C:/Users/lizzi/Downloads/PB%20Price%20Guide%20201718%20ACT%20NT%20SA%20WA%20PDF_1.pdf (accessed July 23, 2021).
24. Australian Government Australia Taxation Office. Car expenses. May 2021. https://www.ato.gov.au/Individuals/Income-and-deductions/Deductions-you-can-claim/Transport-and-travel-expenses/Car-expenses (accessed July 16, 2021).
25. Australian Tax Office. Rates for financial year ending 30 June 2018. https://www.ato.gov.au/Tax-professionals/TP/Financial-year-ending-30-June-2018 (accessed February 1, 2022).
26. Mowbray FI, Fox-Wasylyshyn SM, El-Masri MM. Univariate outliers: A conceptual overview for the nurse researcher. Can J Nurs Res 2019; 51:31–37.
27. Kameshwar K, Karahalios A, Janus E, et al. False economies in home-based parenteral antibiotic treatment: A health-economic case study of management of lower-limb cellulitis in Australia. J Antimicrob Chemother 2016; 71: 830–835.
28. Cannon J, Dyer J, Carapetis J, et al. Epidemiology and risk factors for recurrent severe lower limb cellulitis: A longitudinal cohort study. Clin Microbiol Infect 2018; 24:1084–1088.
29. Lymphoedema Framework. Best Practice for the Management of Lymphoedema. International consensus. London: MEP Ltd.; 2006.
30. Nicolaides A, Kakkos S, Baekgaard N, et al. Management of chronic venous disorders of the lower limbs. Guidelines According to Scientific Evidence. Part I. Int Angiol 2018; 37:181–254.
31. SAGE GROUP. Chronic venous disease (CVD): Epidemiology, costs and consequences. http://thesagegroup.us/pages/reports/CVD-report.php (accessed November 23, 2021).
32. Moffatt C, Keeley V, Quere I. The concept of chronic edema—A neglected public health issue and an international response: The LIMPRINT study. Lymphat Res Biol 2019; 17:121–126.
33. O'Meara S, Cullum N, Nelson EA, et al. Compression for venous leg ulcers. Cochrane Database Syst Rev 2012; 11: CD000265.
34. Nelson EA, Bell-Syer SE. Compression for preventing recurrence of venous ulcers. Cochrane Database Syst Rev 2014; 9:CD002303.
35. Demczyszak I, Sutkowska E, Jasiak M, et al. The impact of compression garments on the quality of life in patients with chronic venous disease. Fizjoterapia 2017; 24:19–22.
36. Appelen D, van Loo E, Prins MH, et al. Compression therapy for prevention of post-thrombotic syndrome. Cochrane Database Syst Rev 2017; 9:CD004174.
37. Miteva M, Romanelli P, Kirsner RS. Lipodermatosclerosis. Dermatol Ther 2010; 23:375–388.

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