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

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ABSTRACT

Introduction:

Cellulitis represents a significant burden to patients' quality of life 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 management of chronic oedema using compression therapy effectively delays 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, quality of life 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 43 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, minimize affected limb volume and improve the quality of life of this population.

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

Trial registration number: ACTRN12617000412336 (Australia New Zealand Clinical Trials Registry)

ARTICLE SUMMARY

Strengths and limitations of this study

- ICTOC is the first randomised controlled trial to assess whether management of chronic oedema using compression therapy will delay the recurrence of lower limb cellulitis. It will provide clinicians with new evidence regarding best practice management for the prevention of cellulitis.
- 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.

Lymphoedema and chronic oedema are potent risk factors for developing lower limb cellulitis, and for its recurrence.[4 8 10 11] The terms lymphoedema and chronic oedema are often used interchangeably, although use of the term chronic oedema is becoming more common as an umbrella term to describe chronic swelling of tissues arising from multiple causes, including impaired lymphatic function.[12] It is broadly accepted that the relationship between cellulitis and chronic oedema is a vicious cycle.[8 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.[14] 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 13 15] 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[16], with a second study incidentally observing a reduction in 'infection' among patients receiving oedema management, although this was not a research objective.[17] 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.[16 17] 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.[18] Thus further research into the efficacy of prophylactic measures other than antibiotic, is warranted.[18]

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, minimize 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,[18] randomisation of participants will be stratified by prophylactic antibiotic use. For participants in the control group, once an episode of cellulitis has occurred, they will cross-over into the intervention group 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. 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 1: 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 in the same leg in the past 2 years (at the time of referral)
- Chronic oedema (oedema persisting ≥ 3 months) in the leg/s that have had recurrent cellulitis diagnosed (presence of oedema confirmed by a lymphoedema therapist through interview and physical examination)
- 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.[19]

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, 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.[3 4 10 20 21]

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.

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. Following the first episode of recurrent cellulitis, participants in the control group will be crossed over to receive compression therapy for the remaining duration of the trial. 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.[22] 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,[23-25] and is a valid measure of knee volume.[22] 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).[26]

Quality of life will be measured using LYMQOL, a validated, condition-specific quality of life tool for people with lower limb lymphoedema,[27] and the EQ-5D-3L, a generic preference-based measure of health related quality of life that comprises of five dimensions of health.[28] The EQ-5D can be used to calculate quality adjusted life years (QALYs) for the purpose of economic evaluation.[28] 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.[28]

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%[8] and compression therapy will reduce the 3-year incidence of recurrent cellulitis by 50%.[16 17] 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[29], 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.

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 10]

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[30].

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 generalized 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).

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.

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.

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Author contributions 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.

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Competing interests None

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

Trial status The ICTOC trial is currently in progress. Participant recruitment started in May 2017 and is expected to continue until December 2019.

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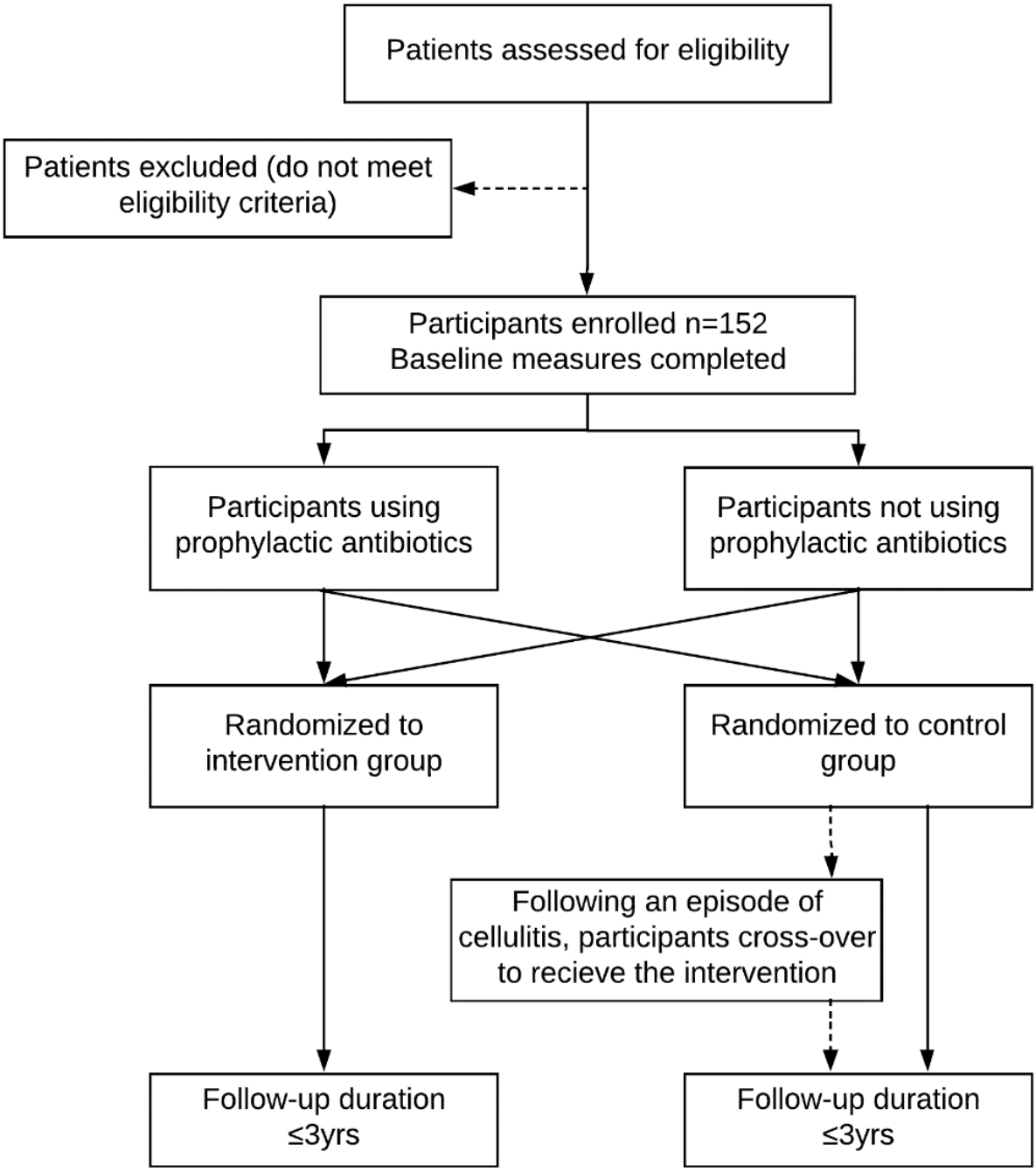
Figure 1: Anticipated participant flow through trial.



Reporting checklist for protocol of a clinical trial.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1,16
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13,16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if	10

		applicable (see Item 21a for data monitoring committee)	
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4,5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5,6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7

Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6,8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8, 11,12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9,12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6,8,10

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10,11
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13, 7-8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13,9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13-14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other	14

		details of the statistical analysis plan can be found, if not in the protocol	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	NA (Page 17)

Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	16
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA (Publishing protocol)
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA (not included in protocol)
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	NA

analysis in the current trial and for future use in ancillary studies, if applicable

BMJ Open

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

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

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References: 29

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Figures: 1

Competing interests: Nil

- **Trial registration number:** ACTRN12617000412336 (Australia New Zealand Clinical Trials Registry)
- **Date Registered:** 22/03/2017

ABSTRACT

Introduction: Cellulitis represents a significant burden to patients' quality of life 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 management of chronic oedema using compression therapy effectively delays 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, quality of life 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, minimize affected limb volume and improve the quality of life of this population.

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

Trial registration number: ACTRN12617000412336 (Australia New Zealand Clinical Trials Registry)

ARTICLE SUMMARY

Strengths and limitations of this study

- ICTOC is the first randomised controlled trial to assess whether management of chronic oedema using compression therapy will delay the recurrence of lower limb cellulitis. It will provide clinicians with new evidence regarding best practice management for the prevention of cellulitis.
- 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 principle cause of the 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 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] 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.[19] 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.[20] Thus further research into the efficacy of prophylactic measures other than antibiotic, is warranted.[20]

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, minimize 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,[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. 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 1: 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 in the same leg in the past 2 years (at the time of referral)
- 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.[22]

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.[3 4 12 23 24]

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.[25] 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,[26-28] and is a valid measure of knee volume.[25] 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).[29]

Quality of life will be measured using LYMQOL, a validated, condition-specific quality of life tool for people with lower limb lymphoedema,[30] and the EQ-5D-3L, a generic preference-based measure of health related quality of life that comprises of five dimensions of health.[31] The EQ-5D can be used to calculate quality adjusted life years (QALYs) for the purpose of economic evaluation.[31] 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.[31]

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%[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 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[32], 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 institutions 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 set 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.[3 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[33].

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 generalized 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[34], 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.

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Author contributions 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

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

Trial status The ICTOC trial is currently in progress. Participant recruitment started in May 2017 and is expected to continue until December 2019.

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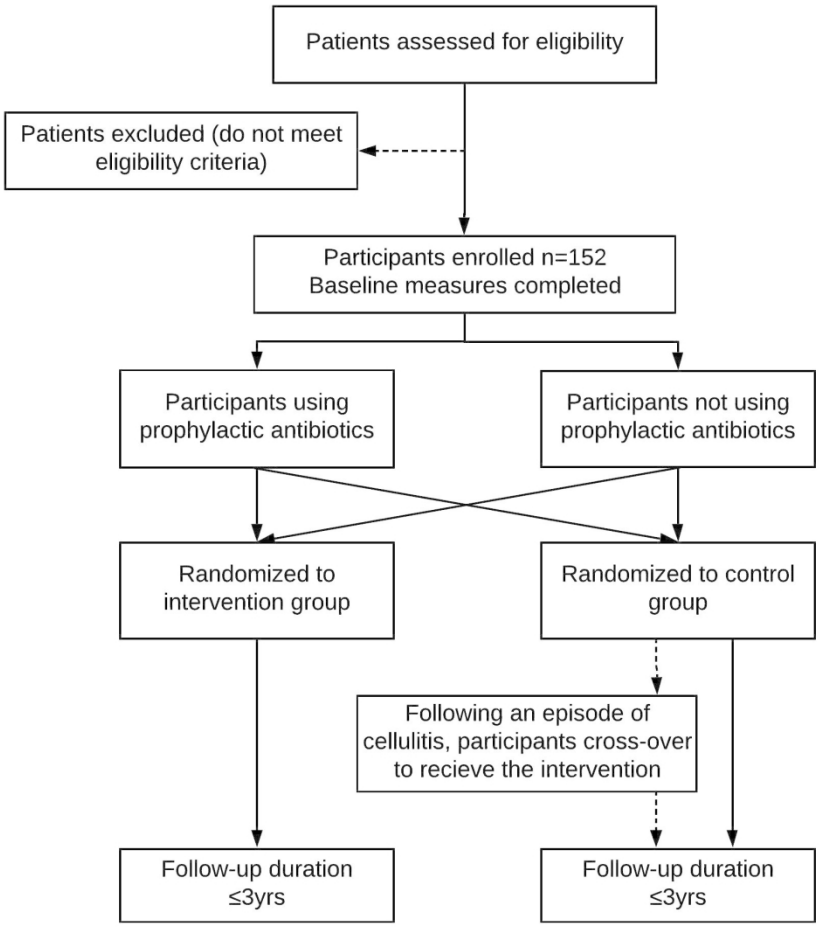

Figure 1: Anticipated participant flow through trial.

165x164mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1,16
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13,16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if	10

		applicable (see Item 21a for data monitoring committee)	
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4,5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5,6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7

Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6,8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8, 11,12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9,12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6,8,10

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10,11
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13, 7-8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13,9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13-14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other	14

		details of the statistical analysis plan can be found, if not in the protocol	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	NA (Page 17)

Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	16
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA (Publishing protocol)
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA (not included in protocol)
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	NA

analysis in the current trial and for future use in ancillary studies, if applicable

BMJ Open

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

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ABSTRACT

Introduction:

Cellulitis represents a significant burden to patients' quality of life 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 management of chronic oedema using compression therapy effectively delays 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, quality of life 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, minimize affected limb volume and improve the quality of life of this population.

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

Trial registration number: ACTRN12617000412336 (Australia New Zealand Clinical Trials Registry)

ARTICLE SUMMARY

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 principle cause of the 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 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] 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.[19] 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.[20] Thus further research into the efficacy of prophylactic measures other than antibiotic is warranted.[20]

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, minimize 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,[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. 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 1: 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.[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 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.[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. 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 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.[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 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).[31]

Quality of life will be measured using LYMQOL, a validated, condition-specific quality of life tool for people with lower limb lymphoedema,[32] and the EQ-5D-3L, a generic preference-based measure of health related quality of life that comprises of five dimensions of health.[33] The EQ-5D can be used

to calculate quality adjusted life years (QALYs) 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 upon 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 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 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.[3 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[35].

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 generalized 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[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. 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.

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Author contributions 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.

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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

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

Trial status The ICTOC trial is currently in progress. Participant recruitment started in May 2017 and is expected to continue until December 2019.

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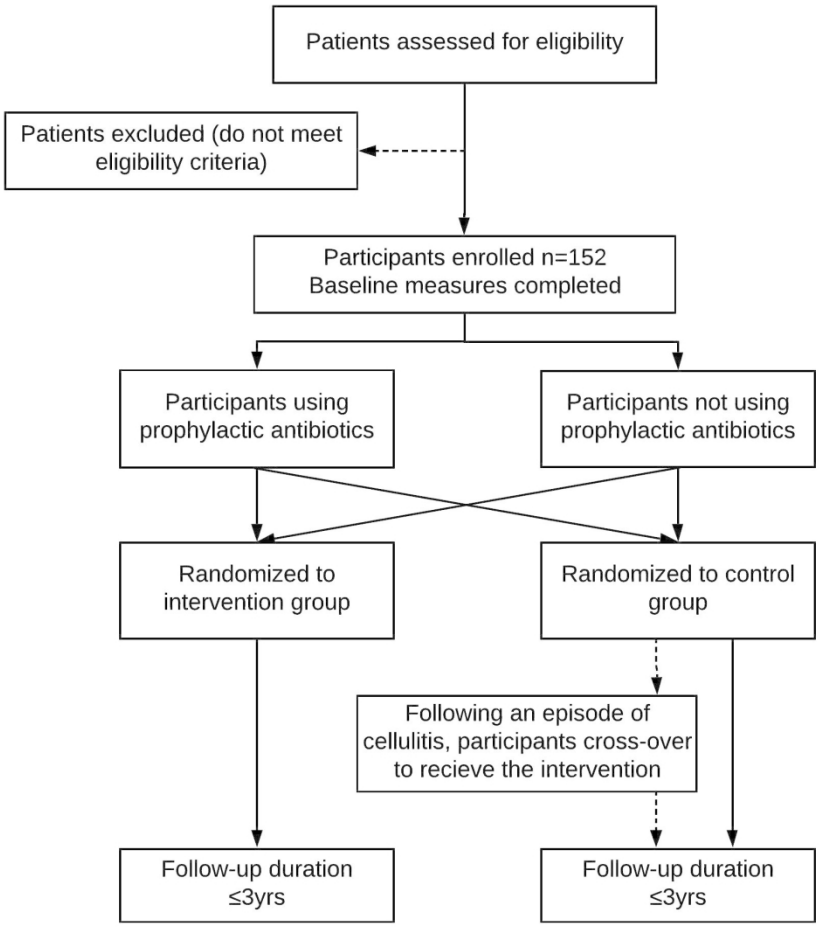

Figure 1: Anticipated participant flow through trial.

165x164mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1,16
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13,16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if	10

		applicable (see Item 21a for data monitoring committee)	
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4,5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5,6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7

Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6,8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8, 11,12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9,12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6,8,10

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10,11
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13, 7-8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13,9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13-14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other	14

		details of the statistical analysis plan can be found, if not in the protocol	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	NA (Page 17)

Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	16
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA (Publishing protocol)
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA (not included in protocol)
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	NA

analysis in the current trial and for future use in ancillary studies, if applicable