North Cumbria Integrated Care NHS Foundation Trust

PEACH trial

PEACH trial; Prospective Evaluation of Applied 'Lite' Compression for leg ulcer Healing, a pragmatic, multi-centre randomized controlled non-inferiority trial

Version 1.1, dd 2 December 2022

Chief Investigator's Statement of Ownership and Content.

I, Jane Todhunter, confirm that this protocol is my work and is owned by me. The protocol conforms with standards outlined in the Declaration of Helsinki 1964.

Name (PRINT):___Jane Todhunter_____

Signature:_____

Date: _____

RESEARCH PROTOCOL SUMMARY

TITLE:	**Prospective Evaluation of Applied 'Lite' Compression for leg ulcer Healing, a pragmatic multi-centre randomized controlled trial**
Short title:	PEACH trial
IRAS number	280418
Device description	Andoflex™ TLC Calamine Lite Two-Layer Compression System. Compression of ('Lite' compression) 20-30 mmHg, primarily intended for patients with an ABPI of 0.5 to 0.8. Layer 1 is a soft foam roll impregnated with calamine that is designed to soothe and calm skin with multiple wounds or other skin conditions. Layer 2 is a short stretch compression bandage that sticks to itself and features Easy HandTear Technology. Absorbs 20xs its dry weight vs. traditional Unna Boot, and contains 50% more active ingredients than traditional Unna Boot. It provides a two-step short stretch performance with high working pressure and low resting pressure. Visual indicators are provided for ease of application - ovals become circles when the intended compression is achieved. 3M™ Coban™ 2 Lite Two-Layer Compression System This provides ('Lite' compression) 25-30 mmHg compression, primarily intended for patients with ABPI 0.5 – 0.8. Coban 2 Lite Layer Compression Systems are indicated for the treatment of venous leg ulcers, lymphedema and other conditions where compression is appropriate, such as post-operatively. Each of the above systems is supplied as a kit that includes two rolls: a Comfort Layer roll and a Compression Layer roll. They have been shown to provide sustained therapeutic compression for up to 7 days.
Study design	Multi-centre, controlled, prospective randomized non-inferiority trial
Primary objective	To determine the relative efficacy of two-layer Lite compression bandaging for the management of leg ulcers, measured through wound status (healed vs non-healed) at 12 weeks post-baseline

Secondary objectives	To determine the efficacy of two-layer Lite compression bandaging for the management of leg ulcers at 6 and 12 weeks post-baseline - Wound status (healed vs non-healed at 6 weeks) - Healing rate (ulcer size, PUSH score) - Quality of Life (EQ-5D-5L) - Leg ulcer related quality of life score (VEINES-QoL) - Leg ulcer related pain and pruritus levels - Infection rates, withdrawal rates
Patient population	Pragmatic approach to allow inclusion of wider cohort of patients than those with pure venous leg ulcers (VLU). Therefore, patients with leg ulcer who are suitable for reduced (ie 'Lite') compression are considered for inclusion. Specifically, these are: - VLU - Mixed venous and arterial leg ulcers Suitability for reduced compression is an ABPI of 0.5 -0.8 depending on holistic assessment. ABPI measured within last 3 months is part of the decision making to use reduced (Lite) rather than full compression. Only if ABPI or other diagnostic method (eg pulse palpation and ultrasound diagnostics, toe pressure assessment or arterial imaging) is not available or applicable then provision of solely a clinical assessment is allowed.
Sample size	A total of 92 participants, over the age of eighteen, with leg ulcers. Power beta of 80%, one-sided alpha p-value of 0.025, non-inferiority limit 15%. Assumption of 15% difference in absolute percentage healed ulcers in intervention (Andoflex) arm versus control (Coban2) arm. Therefore, 97.5% confidence interval for Andoflex to be no more than 15% worse than mean ulcers healed percentage for Coban2. Sample size with 10% attrition rate included: 92 patients Of which: - 46 Patients to receive Andoflex TLC Calamine Lite - 46 Patients to receive Coban2 Lite Participants must have the capacity to provide informed written consent and complete patient reported outcome measures. Participants are recruited from the local community nursing caseload and identified in hospital clinics.

	Randomisation will be stratified for ulcer size, with cut-off PUSH score of up to and including 10, or 11 and above.
Sponsor	North Cumbria Integrated Care NHS Foundation Trust
Manufacturer & funder	Milliken Healthcare Inc UK-based contact: Claire Stephens, Clinical Specialist EMEA , Milliken Healthcare Division, +44 7553 897753 , claire.stephens@Milliken.com
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Organisations where research will take place	North Cumbria Integrated Care NHS Foundation Trust Cumberland Infirmary, Newtown Road Carlisle, CA2 7HY GP Practices within North Cumbria CCG (can be identification centre or recruiting centre) Up to 2 other NHS Trusts, exact sites to be determined (once trial has been listed on National Institute for Health Research National Portfolio) – amendment to be submitted to HRA once additional site identified.
Planned timeline	First patient, first visit: 1Oct2022, Last patient, first visit: 28Apr2024 Last patient, last visit: 31Jul2024 Trial end date: 31Sep2024
Protocol version, date	Version 1.1, 2Dec2022

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1. LAY SUMMARY

Leg ulcers are a challenging condition to manage and treat; there is a high risk of the wounds becoming chronic, infected and needing surgical intervention. Apart from having a significant negative impact on patients' lives, it is also an economic burden to the National Health Service. Compression bandaging is the main treatment option for leg ulcers, and patient compliance with this therapy is key to maximise chances of wound healing and minimise the risk of complications. In recent years, compression bandaging has become more functional and comfortable for patients, but in a recent study we showed that itching and other undesirable symptoms related to having a leg bandaged are still an issue. Initial data has demonstrated that a novel bandage called Andoflex TLC Calamine (Milliken Healthcare Inc) reduces discomfort and possibly accelerates leg ulcer healing. In this pragmatic randomised controlled trial, leg ulcer patients who may benefit from reduced compression therapy will be allocated by chance to one of two bandages: Andoflex TLC Calamine Lite or 3M's Coban 2 Lite. The aim is to determine how effective each bandage is at promoting leg ulcer healing over a period of 12 weeks. In total, 92 patients are planned to be enrolled and for clinical reasons these patients cannot be administered full compression bandaging and are hence administered reduced (or 'Lite') compression bandaging. Outcome measures will be wound healing rates and also patient reported quality of life.

2. INTRODUCTION

Leg ulcers can occur for various reasons, see Figure 1. Though venous leg ulcers (VLUs) are the most common type of leg ulcers, contributing to the majority of leg ulcers, there are many patients who have ulcers due to a mixed venous-arterial or other underlying condition (SIGN 2010, Graham *et al* 2003). The natural history of the disease – particularly in those patients who have venous insufficiency and or other chronic disease affecting the vasculature such as diabetes and peripheral arterial disease - is a continuous cycle of healing and breakdown over decades. VLUs are associated with considerable expense, morbidity and impaired quality of life (Persoon *et al* 2004). A positive relationship has been observed between VLU occurrence and specific modern lifestyle risk factors such as sedentary lifestyles and obesity (Brand *et al* 1998). Table 1 shows annual NHS cost for treating VLUs compared to other chronic wound treatments.

Table 1. Chronic wound treatment costs to the NHS (Posnett & Franks 2008)

	Annual incidence	Cost per patient	Annual NHS cost (2005–2006)
Venous leg ulcers	108,600	£1,500–1,800	£168–198m
Foot ulcers	57,000	£5,200	£300m
Pressure ulcers	410,000	£4,300–6,400	£1.8–2.6bn
TOTAL	575,600	£4,000–5,400	£2.3–3.1bn

Figure 1, Different causes of leg ulcers (Agale 2013)

Vascular	Venus
	Arterial
	Mixed
Neuropathic	Diabetes
	Tabes
	Syringomyelia
Metabolic	Diabetes
	Gout
	Prolidase deficiency
Haematological	Sickle cell disease
	Cryoglobulinemia
Trauma	Pressure
	Injury
	Burns
Tumors	Basal cell carcinoma
	Squamous cell carcinoma
Infection	Bacterial
	Fungal
	Protozoal
Panniculitis	Necrobiosis lipoidica
	Fat necrosis
Pyoderma	Gangrenosum
Special	Hypertensive ulcer

Despite extensive research the exact manner in which particularly venous leg ulcers develop, is not yet fully understood however it is agreed that prolonged venous hypertension caused by chronic venous insufficiency is a common aetiological factor (Eberhardt & Rafetto 2005, White & Ryjewski 2005). The mainstay of treatment of leg ulcers is compression bandaging (O'Brien *et al* 2012), however up to 15-30% do not respond to this current gold standard treatment and remain unhealed even after 6 months of treatment (Moffett *et al* 2006, O'Meara, Cullum & Nelson 2009). Depending on the degree of venous insufficiency, any arterial impairment and other clinical and patient-specific factors, the applied compression can be as high as 40 mmHg. Since many patients' leg ulcer pathologies are not suitable to receive full compression, there is paucity in evidence managing leg ulcers with reduced compression bandaging (20-30 mmHg).

The first 'gold' standard bandaging for chronic venous insufficiency (CVI) was Unna's boot, though the application of bandaging and other products goes back thousands of years (Rubin et al, 1990; Thomas , 1997). This concerned a gauze dressing impregnated with Zinc oxide and calamine lotion. The bandaging was then further developed to be elasticated and provide better compression, for a time using four layers around the leg. The modern compression bandaging products (incl Coban2 and OptiFlex) are two-layer short stretch compression bandaging systems (Hanna et al , 2008). Milliken Healthcare Inc has combined one of the elements of Unna's boot, namely the skin soothing ingredients Zinc Oxide (ZnO) and Calamine, and the favoured two-layer design. One of the Milliken products contains ZnO (Andoflex Zn) and the other Calamine (Andoflex TLC Calamine).

Treatment success in CVI is highly dependent on achieving high levels of patient compliance. Unfortunately, compliance rates are often poor in this population (Heinen et al , 2007). Undesirable effects of compression bandaging play a role in this. Apart from bandage slippage, the most common undesirable effects of wearing compression bandaging are skin-related. Dryness and redness of the skin are commonly reported, and pruritus develops in as many as 1 in 3 patients (Reich-Schupke et al, 2009). Unna's boot has been shown in the past to be effective at controlling pruritis in different conditions, including burns-related long-term itch (Shohrati et al, 2007). A recent study by Jonker and colleagues (2020) showed that patients deem the Andoflex TLC Calamine compression bandaging more comfortable, and less itchy, than Coban2 compression bandaging; there was also a trend towards improved healing rates with Andoflex TLC Calamine.

The aim of this pragmatic randomised, controlled, prospective trial is to determine the efficacy of two types of two-layer compression bandaging (Andoflex TLC Calamine Lite and Coban 2 Lite), with a primary outcome measure of healed ulcer at week 12. Secondary outcome measures will be other ulcer characteristics, and patient-reported quality of life.

3. INVESTIGATIONAL DEVICES

Two different two-layer compression bandages will be appraised. Apart from Andoflex TLC Calamine Lite, provided free of charge by Milliken Healthcare Inc as part of the non-restricted research grant for this study, the other bandage (Coban 2 Lite) will be purchased by the relevant healthcare provider via the conventional Trust NHS supply chain. Coban 2 is a first-line product listed in North Cumbria Integrated Care NHS Trust's current formulary (Appendix 3). Therefore, Coban2 Lite effectively is the treatment as usual arm.

3.1 Andoflex TLC Calamine Lite

Full product information on the Andoflex TLC Calamine 2-layer compression system can be found on the Milliken Healthcare Inc website https://andoverhealthcare.com/product/Andoflex-tlc-calamine/ . Andoflex® TLC Calamine (known as AndoFlex® TLC Calamine in the UK) is manufactured by and is a registered trademark of Andover Healthcare, Inc., a subsidiary of Milliken Healthcare Products, LLC

There are two pressure options, with the Lite version applied in this trial: compression of either (standard compression) 35-40 mmHg or ('Lite' compression) 20-30 mmHg, for patients with an ABPI of ≥ 0.8 or ≥ 0.5 respectively. Layer 1 is a soft foam roll impregnated with calamine that is designed to soothe and calm skin with multiple wounds or other skin conditions. Layer 2 is a non-latex short stretch compression bandage that sticks to itself and features Easy Hand Tear Technology, eliminating the need for scissors. Absorbs 20xs its dry weight vs. traditional Unna Boot, and 50% more active ingredients than traditional Unna Boot. It provides a two-step short stretch performance with high working pressure and low resting pressure. Visual indicators are provided for ease of application - ovals become circles when the intended compression is achieved.

3.2 Coban 2 Lite

Full product information on the 3M Coban 2-layer compression system can be found on the 3M website: https://www.3m.com/3M/en_US/company-us/all-3m-products/~/3M-Coban-2-Layer-Compression-System?N=5002385+3293321927&rt=rud

From the literature: the product provides sustained therapeutic compression for up to 7 days, and it is clinically proven to significantly reduce slippage, to encourage longer wear. The compression layer is designed to be applied at full stretch, reducing application variability.

- Enables a more normal lifestyle – The thin, lightweight, breathable sleeve allows patients to wear their own shoes, so they can return to their regular daily activities
- Easy to use – Application is fast, and easy to teach and learn.
- Not made with natural rubber latex

Engineered with Intelligent Compression Dynamics to stay in place and deliver comfortable, effective, therapeutic compression for venous leg ulcers and other conditions requiring compression

Again, there are two pressure options with the Lite version used in this trial: either (standard) 35-40 mmHg or ('Lite' compression) 25-30 mmHg compression, for patients with ABPI ≥0.8 or ≥ 0.5 respectively This provides 25-30 mmHg compression for patients with ABPI greater than or equal to 0.5. Coban2 Layer Compression Systems are indicated for the treatment of leg ulcers, lymphedema and other conditions where compression is appropriate, such as post-operatively. Each system is supplied as a kit that includes two rolls: a Comfort Layer roll and a Compression Layer roll.

3.3 Medical Device management and use of different compression bandage brands

Bandages will be stored in the clinic rooms at the temperature recommended by the respective manufacturers. No requirement for involvement pharmacy or clinical trials pharmacist. Standard available stocks of dressings to be used, including Andoflex TLC Calamine provided free of charge by Milliken Healthcare Inc as part of the research grant.

4. STUDY HYPOTHESIS

4.1 Primary objective

To determine the efficacy of two-layer Lite compression bandaging for the management of leg ulcers, measured through wound status (healed vs non-healed) at 12 weeks post-baseline

4.2 Secondary objective

To determine the efficacy of two-layer Lite compression bandaging for the management of leg ulcers at 6 and 12 weeks post-baseline

- Wound status (healed vs non-healed at 6 weeks)
- Healing rate (ulcer size, PUSH score)
- Leg ulcer related quality of life score (VEINES-QoL)

- Leg ulcer related pain and pruritus levels
- Generic quality of Life (EQ-5D-5L)

5. STUDY PROTOCOL

5.1 Study design and timeline

This concerns a multi-centre, controlled prospective randomized study. The study will be carried out in Cumbria by North Cumbria Integrated Care NHS trust and North Cumbria CCG. Up to two other NHS Trusts will be considered for inclusion in the trial as recruitment sites once the trial has been listed on the National Institute for Health Research national portfolio. The study will take place in local community and hospital settings with support and oversight from research staff. Research delivery staff will be delegated to provide support with data collection and processing.

Table 2. Anticipated timeline

Month	Setup	Recruitment	Analysis	Finalise
Sep-22	Submission for HRA approval			
Sep-22	NIHR portfolio adoption			
Oct-22	HRA and Trust approval	Start recruitment; first patient, first visit		
May-24		Finish recruitment		
Jul-24		Last participant, last visit		
Aug-24			Analyze data	
Sep-24				Finalise analysis & report

5.2 Participant identification & screening

Patients who are referred to the local clinical team with a leg ulcer will be screened for eligibility for this study by the direct care team. The research team will then be informed on potential participants and the patient information sheet will be added to the appointment letter. All eligible patients will be invited to take part until the required numbers have been achieved. Patients will be recruited sequentially and randomised into two groups: either the Andoflex or Coban2 bandaging described in section 3 of this protocol. The eligible patient population is defined in the Inclusion and Exclusion criteria section.

There may be occasions where the consent may be delegated to a member of the research team; this is an option as long as the patients has given verbal consent for this when asked by the direct care team first. During the first appointment, the study will be discussed in further detail and the participant has the opportunity to ask questions that they may have. If potential participants meet the eligibility criteria, the patients can be consented by the direct care team personnel or this may

be delegated to the research delivery team (again, as long as the patient's verbal consent has been sought for the latter arrangement). A screening form will be completed for potentially eligible patients to confirm that they indeed meet the trial criteria.

Participants will receive no incentives and consent will be regarded as a process and not a one off event. Participants are free to withdraw from the study at any time without the need to give any reasons for withdrawal. Their standard care will not be affected by either declining to participate in the study or withdrawing during participation – patients would still be managed with the two layer Lite compression bandage type even if not in the trial.

5.3 Recruitment

Participants will be randomised to one of two treatment arms. Patients in both groups will be given standard advice on leg ulcers and their management. Stratification by wound size (PUSH score up to and including 10 or PUSH score of 11 or higher) will take place.

All participants will have demographic data obtained and the following measures (table 3):

Table 3. Baseline measures

Weeks	0	2	4	6#	8	10	12#
Baseline measures (demographics, medical history, vascular history)	X						
Ulcer wound status + bandage use status	X			X			X
Ulcer size measured with wound grid	X			X			X
PUSH score	X			X			X
Visual analogue pain score	X			X			X
Visual analogue pruritus score	X			X			X
EQ-5D-5L	X			X			X
VEINES-QoL	X			X			X
Photo of ulcer (or original index site); subject to consent by patient	X			X			X

 # Allowed to be up to 2 weeks early or late. For all follow-up dates, calculation is based on original enrolment date for patient, even if deviation for one or more follow-up timepoints.

The Pressure Ulcer Scale for Healing (PUSH) tool, see Appendix 1 is a standardised method of assessing and monitoring the severity and healing of both pressure ulcers and venous leg ulcers (Stotts et al, 2001; Ratliff & Rodeheaver 2005). Concerns have been raised regarding the criterion validity and intra-rater reliability of the tool (Pillen et al 2009) however in the absence of other valid tools it provides a comprehensive parallel assessment of the ulcer along with measuring size alone.

VEINES-QoL is a patient reported outcome measure score that focuses on lower limb health, and can be used in patients both with, or without a leg ulcer (Launois 2015)

During the recruitment process the research team acts as a contact point and coordinator for patients requiring information and support. If concerns are raised on participants (mental) wellbeing

based on the home visits or outcome of the assessments, referral of patients/families on to other professional agencies will be done as appropriate and according to the Trust guideline.

5.4 Follow-up and Standard care

Patients are in the study for the planned 12 weeks, even if the index leg ulcer has healed prior to that time point. Apart from the specific research measurements and assessments, the patient will be followed up as they would in normal clinical practice. The vascular or community nurse will redress the leg ulcer as per routine care, and will conduct the measurement of the leg ulcer (grid measurement and PUSH score). The researcher will visit the patient at baseline, week 6 and 12 of study participation to randomise the patient and conduct the questionnaires.

Patients identified in the community (primary care or non-vascular surgery dept) can be invited to participate in the study via the vascular surgery department.

Standard wound care will be provided throughout the trial period, as well as meeting any other medical needs that arise. The SIGN guidelines for leg ulcer care form the framework for management of the leg ulcers (https://www.sign.ac.uk/media/1058/sign120.pdf).

5.5 Outcome measures

5.5.1 Primary outcome measures

Wound status (healed vs non-healed)

In line with the definition used by the VENUS6 trial team, the primary outcome of this trial is time to healing of the reference ulcer, and the definition is: complete epithelial cover in the absence of a scab (eschar) with no dressing required. There is no minimum length of time that the index site has to have been in said condition for when participant present for follow-up study visit.

5.5.2 Secondary outcome measures

Clinical outcome measures

- VLU size, measured with Convatec grid tool
- Size and characteristics of VLU, determined with PUSH score
- Pain score
- Pruritus score
- Quality of life score, determined with VEINES QoL score and EQ-5D-5L score.
- Patient withdrawal rates due to change in management (e.g. need for surgery)
- Leg ulcer infection rates

6. SUBJECTS

6.1 Anticipated number of research subjects

Locally, we have healing data available from two previous trials involving venous leg ulcers, namely the PREVUE and APRICOT trials (Jonker et al 2020a, and Jonker et al 2020b). One caveat is that those

studies concerned pure venous leg ulcers and that compression bandaging could be full (40 to 50mmHg) or Lite (20 to 30 mmHg). Nonetheless, from these studies we know that the study follow-up time points are valid and APRICOT compared Andoflex vs Coban2.

Below a summary is given for the sample size needed. The primary outcome, wound status (healed vs non-healed) is used for sample size calculation. The non-inferiority related sample size calculation has been performed using the calculator at https://www.sealedenvelope.com/power/binary-noninferior/ . Power calculations for sample size assume 80% power and 2.5% one-sided confidence interval. The non-inferiority limit is set at 15% in favour of the Coban2 control bandage. The result is shown in Table 4. Since some patients may withdraw over the course of the 12-week trial period, a 10% dropout rate is calculated into the sample size. A 1:1 allocation to the two types of compression bandage will be applied.

Table 4, Sample size calculations

Sample size calculation		
	Intervention Bandage (Andoflex)	Control Bandage (Coban2)
Ulcer healed	65%	50%
Ulcer not healed	35%	50%
	Power beta of 80%, Alpha p-value of 0.05, Non-inferiority limit 15% Sample size required without any drop-out: 84 patients Sample size with 10% attrition rate included: 92 patients Total of 92 patients: - 46 Patients to receive Andoflex - 46 Patients to receive Coban2	

The CONSORT guidelines require a statement on the number of patients assessed for eligibility (Schulz, Altman & Moher 2010). The number of patients screened but who did not meet the inclusion criteria or who declined to participate will be recorded, as will any patients who are lot to follow-up (Appendix 5).

6.1.1 Randomisation and Blinding

Following written consent patients will be allocated at random to the one of two treatment arms, using a non-restricted randomised sequence generated for the whole sample using a free ware randomisation programme, see https://www.sealedenvelope.com/. The randomisation will be stratified by ulcer size, with one group being those with a PUSH score of up to and including 10, or a PUSH score of 11 or higher.

Each next randomisation allocation will be obtained from the sealedenvelope.com account for this PEACH trial. The randomisation will be stratified by ulcer size, with one group being those with a PUSH score of up to and including 10 (LOW PUSH randomisation), or a PUSH score of 11 or higher (HIGH PUSH RANDOMISATION).

Each next randomisation allocation will be obtained from either the LOW PUSH or HIGH PUSH the sealedenvelope.com account for this PEACH trial. The PUSH score is done as part of standard clinical practice and is a swift method (appr. 1 minute to obtain).

Since it will not be known up front how many patients will be LOW PUSH or HIGH PUSH, a total of 60 randomisations will be generated for each stratification, in blocks of 10 randomisations within said stratification. This means 6x10 randomisations for LOW PUSH and also 6x10 randomisations for HIGH PUSH. If one of the stratifications reaches 60 then only the other stratification can be recruited into going forward. It is recognised that random selection does not guarantee representativeness but variables which may affect the outcome variable are more likely to be balanced out and reliability enhanced (Thomas 1990).

As the study involves different looking bandages, it is not possible to achieve blinding for the participants. However, statistical analysis is carried out blinded to group allocation, by persons who have not had contact with study participants.

6.2 Eligibility criteria

6.2.1 Inclusion criteria

- Aged 18 years or over
- Underlying pathology of leg ulcer is venous or mixed venous-arterial. Recognised co-morbidities that may contribute to the development of leg ulcers (e.g. diabetes, rheumatoid arthritis, peripheral vascular disease) are not an exclusion criterion.
- At least one leg ulcer (in case of multiple defined ulcers, single largest measurable ulcer will be classed as index ulcer). Leg ulcer defined as any break in the skin on the lower leg that has been present for 2 weeks (from NICE 2013)
- Tolerating compression bandaging
- Mental ability to give consent
- An ankle–brachial pressure index (ABPI) of ≥ 0.5 – 0.8 taken within the previous 3 months. Where an ABPI measure is not viable, use of locally-approved alternative diagnostic assessments to rule out significant peripheral arterial disease and/or ischaemia, i.e. by pulse palpation and ultrasound diagnostics, toe pressure assessment or arterial imaging. If ABPI or other diagnostic methodology is not indicated or feasible, recorded clinical assessment by qualified clinical staff is allowed (diagnosis and rationale for reduced compression to be recorded at baseline).
- Patient is allowed to be on compression therapy prior to enrolment.

6.2.2 Exclusion criteria

- Under the age of 18 years
- Unable to fully understand the consent process and provide informed consent due to either language barriers or mental capacity
- Limited life expectancy, i.e. undergoing palliative care, or other condition that in opinion of researcher contraindicates participation

- Active infection in leg ulcer treated with antibiotics within last 1 week (does not apply for prophylactic antibiotic regimes)
- Is not willing or able to wear any compression device
- Pure foot ulcer, ie any ulcer that commences below malleolar region (particularly plantar, digital regions)
- Enrolled in other interventional research study related to patient's leg ulcer
- Previous participation in PEACH trial
- Awaiting surgical intervention related to vascular system of the lower limbs, planned within three months
- Wound size that is too small (typically < 1 cm^2), or too large (larger than single wound grid or extending round the leg) to measure accurately
- Known intolerance or allergy to materials used in compression bandaging (including zinc oxide, calamine).

6.3 Early withdrawal of subjects

Patients have the right to withdraw from the trial at any time and without giving any reason. If a patient withdraws from the trial, any and all information gathered prior to the withdrawal will be included in the analysis, though no further data collection will occur. If a patient does not attend planned follow-up appointments then two more attempts will be made to contact the patient regarding the study. If still no contact can be made then the patient is deemed lost to follow-up and any collected study data will be retained. Appendix 2, INTERVENTION DEVIATION AND LEG ULCER INFECTION, covers study withdrawals in more detail.

7. SAFETY

7.1 Potential risks & benefits to study participants

There is no anticipated personal safety risk associated with taking part in this study. If the research team learns of important new information that might affect patient's desire to remain in the study, he or she will be told. Appropriate precautions are in place to ensure medical and personal information is kept safe through adhering to appropriate governance regulations. Participants in both the treatment arms will be allocated a compression bandage that is used for its intended licensed purpose and that is available via standard care routes. Any adverse events will be recorded, as outlined in sections below.

Apart from being allocated to a different type of compression bandage, all patients will be commenced on a compression therapy that aims to achieve 20-30 mmHg of pressure; therefore, all patients will receive the indicated clinical care they would receive when not in the trial too. They will otherwise be cared for in exactly the same manner as they normally would. Some bandage types may be more comfortable and more effective at controlling symptoms associated with vascular pathology and this present trial aims to establish whether this holds true. Participants cannot claim payments, reimbursement of expenses or any other benefits or incentives for taking part in this research.

7.2 Safety definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or other clinical investigation participant taking part in a trial of a medical device, which does not necessarily have to have a causal relationship with the device under investigation. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the device, whether or not considered related to the device.
Serious Adverse Event	A serious adverse event is any untoward medical occurrence that: - results in death - is life-threatening - requires inpatient hospitalisation or prolongation of existing hospitalisation - results in persistent or significant disability/incapacity - consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

7.3 Procedures for recording adverse events

All SAEs need to be reported to the sponsor/host Trust R&D **within one working day** of the investigator team becoming aware of them.

The relationship of each adverse event to the trial must be determined by a medically qualified individual according to the following definitions:

- **Related**: The adverse event follows a reasonable temporal sequence from intervention. It cannot reasonably be attributed to any other cause.
- **Not Related**: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

8. STATISTICAL CONSIDERATION AND DATA ANALYSIS PLAN

8.1 Analysis of baseline characteristics

To determine the demographics and characteristics of the patients, the following baseline data will be collated:

Patient details

- Age
- Sex
- Height, Weight, BMI
- Smoking status
- Postcode (deprivation score)
- Mobility status: does not walk / walks with assistance (stick/frame) / walks without assistance.

Medical history and status:

- Significant comorbidities, including CEAP Clinical score, Peripheral Arterial Disease, Diabetes (type I, type II, +/- neuropathy), Heart failure, Eczema, Rheumatoid Arthritis , Psoriasis, Other dermatitis, , Multiple Sclerosis, Cancer
- Any previous leg ulcers within last 2 years.

Index leg and ulcer status

- Leg ulcer aetiology determining need for compression bandaging
- ABPI (within last 3 months)
- CEAP Clinical score.
- Compression therapy prior to enrolment, and duration of compression (if applicable)
- Ulcer location: above calf / calf / below calf (gaiter) / spanning malleolar region / predominantly below malleolar region
- Chronicity of ulcer (in weeks)
- Ulcer size (PUSH score / measuring grid)
- If leg ulcer healed at week 6, status of index location at week 12 (ie any recurrence of ulcer?)

Compression care characteristics

- Location of regular leg care: home (self-care) / home (district nurse) / GP practice / secondary care (hospital)
- Frequency of care (change of compression bandaging: …. per week.
- 'Prescribed' compression length of time / per day: …. hours/day (<6hrs / 6-12 hrs/ 12-24hrs/ continuously)
- Specific dressing used on wound ? yes/no (if yes, which?)
- Skin care product used on index leg before application of compression bandaging?
    - No
    - Yes, namely: eg Sudocrem, Desitin, or other cream/ointment/paste/emollient

Any differences in distribution will be established with Chi-squared test or ANOVA as indicated.

8.2 Primary outcome statistics

The primary objective for this pilot study wound healed status at week 12. For non-inferiority analysis, patients who withdraw prior to completion of the study or do not attend week 12 appointment will be assigned the worst-case healing outcome (not healed at week 12).

The test for non-inferiority concerns the proportion of patients attaining ulcer closure by week 12 for both treatment groups, and the associated 97.5% one-sided confidence interval for the difference. Non-inferiority of Andoflex is considered valid if the lower limit of the 95% confidence interval for the difference between treatment means (Andoflex – Coban2) is not more negative than -15%. That is, non-inferiority for Andoflex is demonstrated when a maximum of 15% fewer patients using this bandage, compared with patients using Coban2, have healed by week 12 of treatment. This approach was taken in previous non-inferiority trials for ulcers (Harding et al, 2012; Moffatt et al, 2019), and is outlined in papers by Oczkowski (2014) and Flight (2016).

For comparative performance (superiority) analysis, any statistically significant difference (p-value < 0.05) between the two treatment arms will be determined with Chi-squared test. This will be done since Dunn et al postulate that non-inferiority and superiority trials effectively aim to answer the same hypothesis (Dunn et al, 2018)

Analysis will be performed on a per protocol and also an intention to treat basis. Multiple imputation (default five imputations) will be applied for missing values for the outcome measures, and inferential statistics will be performed on pooled data. Data will first be collated in Microsoft Excel, followed by analyses performed using SPSS v20.

8.3 Secondary outcome statistics

To evaluate the effect of the different reduced compression bandages on leg ulcer healing, data from the two treatment arms will be compared.

Ulcer healing and more general health measures is assessed by the following parameters:

- Ulcer status (healed vs non-healed)
- Ulcer size (cm^2, measured with wound grid)
- PUSH score
- Visual analogue pain score
- Visual analogue pruritus score
- VEINES-QoL
- EQ-5D-5L

To assess the Ulcer size, PUSH score, visual analogue pain score, and visual analogue pruritus score, which are measured every 6 weeks, per treatment arm the average difference between time points will be calculated per treatment group (Wilcoxon test). To compare between the groups, Mann-Whitney U-test will be applied.

To measure patient-reported outcome measures on quality of life (VEINES-QoL and EQ-5D-5L) at baseline, week6 and week 12; the Wilcoxon test will be applied within treatment arms (over time) whereas the Mann-Whitney U-test will be performed between treatment arms. Data of the two treatment arms will be compared by applying the Mann-Whitney U-test.

Subject to sufficient data being available, Cox proportional hazards regression analysis will be conducted to investigate the role of the compression bandage itself and other covariates in leg ulcer healing rates. Other covariates include: leg ulcer size and chronicity at baseline, patient age, ulcer aetiology (pure venous vs other), absence/presence of co-morbidities, ulcer location, history of recurrent ulcers.

The following descriptive statistics will be reported on where possible:

- Number of patients screened
- Number of patients eligible/ineligible, and percentage of patients consented into the trial
- Number of patients completed the trial/discontinued (plus reasons if discontinued)

9. DATA HANDLING AND MONITORING

Data arising from this study is confidential. Identifiable information can only be accessed by delegated members of the study team. Anyone in the research team who does not have a substantive contract with North Cumbria Integrated Care NHS Foundation Trust will need to apply for a letter of access via the NIHR research passport scheme, should they require access to identifiable study data.

Patient identifiable data will only be used within each respective Trust and by the core research team. All identifiable data is stored on password protected NHS computer systems. Anonymised data will be shared and stored using security-enabled systems such as password-protection and encryption of e-mails and files. The requirements of the Data Protection Act, GDPR, and NHS Code of Confidentiality will be followed at all times. All researchers will be fully trained in NHS Confidentiality and GCP. Participants' GP practices will be informed that they are taking part in the study.

All paper data will be held in secure locked environments in the office of the Research & Development department in the Carlisle, Whitehaven and Penrith hospital locations. Data released (e.g. by publication) will contain no information that could lead to the identification of an individual participant. Upon completion of the study the site files will be archived for a period of 10 years in line with local archiving policy and procedures. Direct access to data only will be granted to authorised representatives from the sponsor / host institution, grant funder and medical device provider (Milliken Healthcare Inc) and the regulatory authorities to permit trial-related monitoring, audits and inspections.

This investigator-initiated trial will be monitored in terms of conduct of the study by the in-house research team, led by the Chief Investigator, who will convene on a monthly basis in person or via phone/e-mail. A trial steering committee will not be convened for this trial. The study can be audited by the in-house R&D department as part of their rolling audit programme of sponsored and hosted

research studies. As part of the research grant agreement, anonymised study data will be shared with Milliken Healthcare Inc for review and for potential publication purposes. No identifiable data, including on potential exemplar case photos, will be contained in any of this data.

10. GOVERANCE OF STUDY

10.1 Approvals

This study will be conducted in compliance with the protocol approved by the Health Research Authority, National Research Ethics Service, and local Trust R&D Approval, and according to Good Clinical Practice standards including the Declaration of Helsinki (1964, Amended Oct 2013). No deviation from the protocol will be implemented without the prior review and approval of the aforementioned review bodies, except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported according to policies and procedures

10.2 Sponsor & Indemnity

North Cumbria Integrated Care NHS Foundation Trust is the sponsor of this study and therefore NHS indemnity applies for design, conduct and management of the study. Milliken Healthcare Inc has provided a grant for this study by means of provision of the Andoflex TLC Calamine Lite dressing free of charge and a monetary grant worth £8526.

Patients will not be given financial incentives for taking part in the study. Travel expenses are not offered in this study since patients are seen at their home by community nurses or in clinic as part of their normal care pathway.

11. PUBLICATION AND DATA-SHARING POLICY

The study will be registered on the ISRCTN website, in line with CONSORT guidelines on good practice in clinical research.

The results of this study will potentially be disseminated through:

- Peer-reviewed manuscript in scientific journal
- Conference paper
- Internal report

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APPENDIX 1. OUTCOME MEASURE TOOLS AND ASSESSMENTS

This appendix contains:

- The PUSH tool that will be used to assess ulcer (from Stotts et al, 2001)
- The VEINES Quality of Life survey (from Lamping et al, 2003)
- Visual analogue pain scale and the visual analogue pruritis scale (used in APRICOT study; Jonker et al, 2020)
- Patient feedback and compliance (non-validated)
- EQ-5D-5L quality of life score (from Herdman edt al, 2011)

NATIONAL PRESSURE ULCER ADVISORY PANEL

Pressure Ulcer Scale for Healing (PUSH)
PUSH Tool 3.0

Patient Name_____ Patient ID# _____

Ulcer Location _____ Date _____

Directions:

Observe and measure the pressure ulcer. Categorize the ulcer with respect to surface area, exudate, and type of wound tissue. Record a sub-score for each of these ulcer characteristics. Add the sub-scores to obtain the total score. A comparison of total scores measured over time provides an indication of the improvement or deterioration in pressure ulcer healing.

LENGTH X WIDTH (in cm^2)	**0** 0	**1** < 0.3	**2** 0.3 – 0.6	**3** 0.7 – 1.0	**4** 1.1 – 2.0	**5** 2.1 – 3.0	**Sub-score**
		6 3.1 – 4.0	**7** 4.1 – 8.0	**8** 8.1 – 12.0	**9** 12.1 – 24.0	**10** > 24.0	
EXUDATE AMOUNT	**0** None	**1** Light	**2** Moderate	**3** Heavy			**Sub-score**
TISSUE TYPE	**0** Closed	**1** Epithelial Tissue	**2** Granulation Tissue	**3** Slough	**4** Necrotic Tissue		**Sub-score**
							TOTAL SCORE

Veines QoL questionnaire

INSTRUCTIONS
HOW TO ANSWER:
Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

Below are some questions about your views about your legs. This information will help keep track of how you feel and how well you are able to do your usual activities.

1. During the past 4 weeks, how often have you had any of the following leg problems?

	(check one box on each line)	Every day	Several times a week	About once a week	Less than once a week	Never
1.	Heavy legs	1	2	3	4	5
2.	Aching legs	1	2	3	4	5
3.	Swelling	1	2	3	4	5
4.	Night cramps	1	2	3	4	5
5.	Heat or burning sensation	1	2	3	4	5
6.	Restless legs	1	2	3	4	5
7.	Throbbing	1	2	3	4	5
8.	Itching	1	2	3	4	5
9.	Tingling sensation (e.g.pins and needles)	1	2	3	4	5

2. At what time of day is your **leg problem** most intense ? *(check one)*

1 On waking
2 At mid-day
3 At the end of the day
4 During the night
5 At any time of day
6 Never

3. Compared to one year ago, how would you rate your **leg problem** in general now? *(check one)*

1 Much better now than one year ago
2 Somewhat better now than one year ago
3 About the same now as one year ago
4 Somewhat worse now than one year ago
5 Much worse now than one year ago
6 I did not have any leg problem last year

4. The following items are about activities that you might do in a typical day. Does your **leg problem** now limit you in these activities? If so, how much ?

	(Check one box on each line)	I do not work	YES, Limited A Lot	YES, Limited A Little	NO, Not Limited At All
a.	Daily activities at work	0	1	2	3
b.	Daily activities at home (e.g. housework, ironing, doing odd jobs/repairs around the house, gardening, etc...)		1	2	3
c.	Social or leisure activities in which you are standing for long periods (e.g. parties, weddings, taking public transportation, shopping, etc...)		1	2	3
d.	Social or leisure activities in which you are sitting for long periods (e.g. going to the cinema or the theater, travelling, etc...)		1	2	3

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your **leg problem**?

	(check one box on each line)	YES	NO
a.	Cut down the **amount of time** you spent on work or other activities	1	2
b.	**Accomplished less** than you would like	1	2
c.	Were limited in the **kind** of work or other activities	1	2
d.	Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

6. During the past 4 weeks, to what extent has your leg problem interfered with your normal social activities with family, friends, neighbors or groups? *(check one)*

1 Not at all
2 Slightly
3 Moderately
4 Quite a bit
5 Extremely

7. How much leg pain have you had during the past 4 weeks? *(check one)*

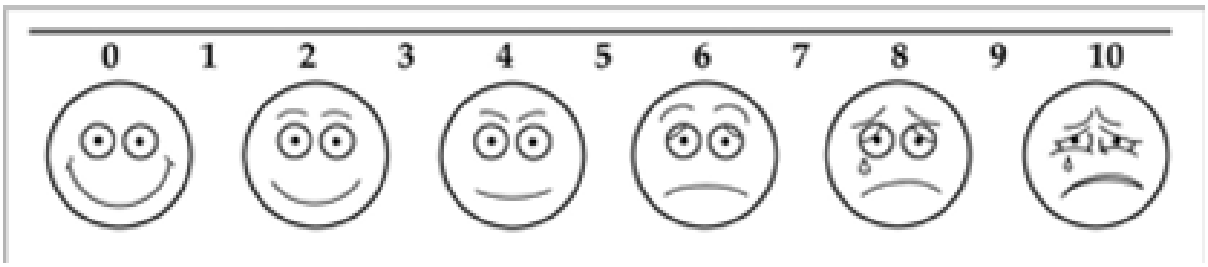
1 None	4 Moderate
2 Very mild	5 Severe
3 Mild	6 Very severe

8. These questions are about how you feel and how things have been with you during the past 4 weeks as a result of your **leg problem**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks -

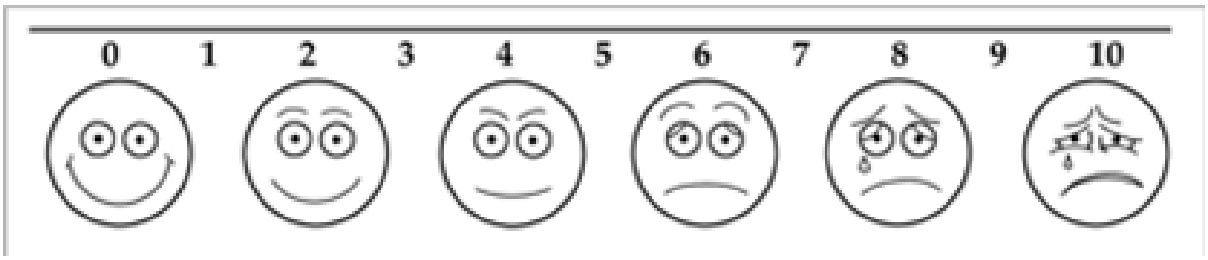
	(check one box on each line)	**All of the Time**	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
a.	Have you felt concerned about the appearance of your leg(s) ?	1	2	3	4	5	6
b.	Have you felt irritable ?	1	2	3	4	5	6
c.	Have you felt a burden to your family or friends ?	1	2	3	4	5	6
d.	Have you been worried about bumping into things ?	1	2	3	4	5	6
e.	Has the appearance of your leg(s) influenced your choice of clothing ?	1	2	3	4	5	6

Visual analogue Pain and Pruritus visual analogue scores:

Pain visual analogue scale Instructions: “Please think about any **leg pain** you may have had over the past **2 weeks** and draw a vertical line along the scale that best describes it best.”



Pruritus visual analogue scale Instructions: “Please think about any **leg itching** you may have had over the past **2 weeks** and draw a vertical line along the scale that best describes it best.”



Quality of life: EQ-5D-5L

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work ,study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

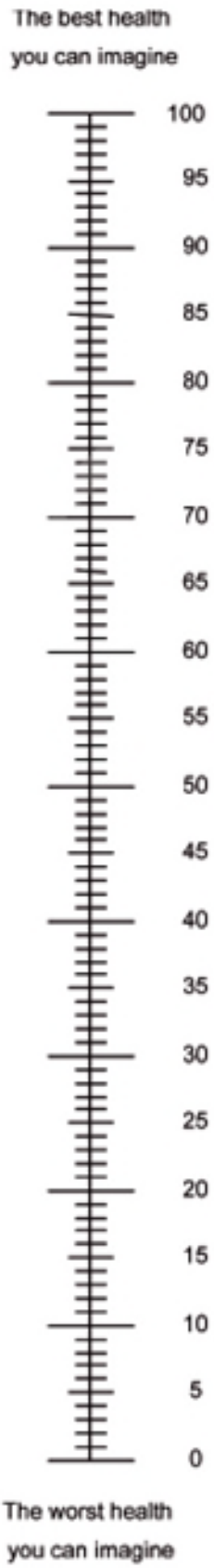
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderate anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is **TODAY.**
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.

  0 means the worst health you can imagine
- Mark an **X** on the scale to indicate how your health is **TODAY.**
- Now, please write the number you marked on the scale in the box below



YOUR HEALTH TODAY =

APPENDIX 2. INTERVENTION DEVIATION AND LEG ULCER INFECTION

There may be incidences where a participant may either:

- Develop a reaction to the allocated dressing/bandage
- Becomes completely non-compliant (possibly due to bandaging being uncomfortable, or eg hospital admission)
- Improve to such an extent that compression bandaging is no longer indicated.

In such instances the patient and/or clinician can opt to stop or pause treatment with the bandage in question. If this occurs, this needs to be recorded (date and reason), and the decision can then be made to either:

- Discontinuation due to improvement in symptoms (including wound healed). Participant will still continue to be assessed as per planned dates and timepoints.
- Change over to an alternative compression bandage that is not the originally allocated type. This is allowed but only if there are clinical indications to do so or at patient request if they cannot tolerate the allocated bandage type. Patient can later in trial period be transferred back to original allocated bandage type if required.
- Pausing or discontinuation of compression bandaging when not clinically indicated. Even if leg ulcer persists and patient no longer wears compression bandage, they can still continue in the trial if they wish. Outcome measures will continue to be recorded as per planned dates and timepoints.
- Pause of compression therapy due to adverse event. Patient can remain in trial provided they are capable to continue with follow-up schedule and completion of outcome measures. If not possible, see next point regarding 'Withdraw patient from study'.
- Withdraw patient from study.
    - At the request of the patient
    - For clinical reasons, eg if the leg has deteriorated to such an extent that emergency surgical or medical intervention is required which means return to use of compression bandage in reasonable time frame is not feasible. In this case, this needs to be reported as a (Serious) Adverse Event if discontinuation is due to deterioration of the index wound or index leg only.

When overall trial participation for a patient is finished early, the participant will still be asked to complete the relevant questionnaires (provided they have capacity to do so):

- Week 6 VEINES QoL questionnaire (if patient withdrawal before week 6)
- Week 12 VEINES QoL questionnaire (if patient withdrawal > week 6 and < week 12)

Infection and use of antibiotics during trial

Patients do not have to withdraw from the study if infection occurs, as long as clinically there is a reason to continue with compression bandaging and it is deemed safe to do so. This applies for both oral and intravenous antibiotics use. If a treating clinician determines that compression bandaging should stop then this will be classed as an intervention deviation – see above.

APPENDIX 3 – CUMBRIA WOUND FORMULARY (2019)

Retention Bandages	Mollelast / Actiwrap (finger & Toe) K-Band K-Lite
Padding	Flexiban (to use with Actico) Profore #1, (Cellona-Lymphoedema)
Tubular Bandage	Comfi-fast Comfi-fast Garments Comfigrip
Full Compression Bandages – Short Stretch	Actico
Multi-layer Compression Bandages	Coban 2, Coban 2 Lite
Compression Hosiery Applicator	Actiglide
Waterproof dressing protection	Limbo Sealtight
Dressing Packs	Polyfield Patient Pack Dressit
Skin Protection	Cavilon Cream Cavilon no-sting barrier Film Proshield Plus Skin Protectant
Compression Hosiery	Jobst Elvarex Custom Fit, Jobst Elvarex Soft Custom Fit, Sigvaris Optiform Hold Custom Fit, Sigvaris Optiform Flex Custom Fit, Haddenham (Veni, Star Cotton, microfine Toe caps)Juzo Soft, Medi, Mediven plus, Mediven Elegance, Jobst for Men, Ambition and Explore, Juzo, BSN
Protease Modulator	Urgostart Plus
Leg Wraps & Liners	Haddenham Easywrap Strong & Light, Jobst, BSN, Farrow wrap (Classic, lite, strong, 4000) Jobst Farrow Hybrid liner, Sigvaris Transition liner, Sigvaris Complete Liner, Juzo adjustable

APPENDIX 4. STUDY PARTICIPANT FLOWCHART (BASED ON COHORT)