Hospice at Home
Carlisle and North Lakeland

NHS
North Cumbria Integrated Care
NHS Foundation Trust

PEDAL

Plantar Exercise, DAily, for Lymphoedema

PEDAL; Plantar Exercise, Daily, for Lymphoedema, a single-centre, controlled, prospective, randomized feasibility trial

Version 2.1, dd 24 Nov 2021

Chief Investigator's Statement of Ownership and Content.

I, Dr Stacey Fisher, 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):___Dr Stacey Fisher_____

Signature:_____

Date: _____

RESEARCH PROTOCOL SUMMARY

TITLE:	**PEDAL; Plantar Exercise, Daily, for Lymphoedema, a single-centre, controlled, prospective, randomized feasibility trial**
Short title:	PEDAL trial
IRAS number	265968
Device description	StepIt plantar flexion rocker pedal device. CE-marked and licensed medical device. To be used in this study for indicated purpose, namely plantar flexion exercise.
Study design	Multi centre, controlled, prospective randomized feasibility trial
Primary objective	To assess the feasibility of conducting a full RCT in the future - Participants' compliance to StepIt exercise regime and total number of steps achieved - Recruitment and attrition rates, willingness of patients to be randomised, response rates to questionnaires, and degrees of missing data - Testing of eligibility criteria and ability/willingness of clinical staff to partake in recruitment of participants - Adequacy of duration of follow-up (e.g. in relation to lymphoedema status)
Secondary objectives	To determine the acceptability and efficacy of the step-it pedal as an adjuvant therapy for leg lymphoedema at 6 and 12 weeks post-baseline - Efficacy of StepIt pedal adjunct therapy vs standard care. Status leg volume difference. - Ankle circumference - Ankle range of motion - Lymphoedema-related quality of life - General quality of life - Patient feedback on use of the device (StepIt users only)
Patient population	A total of 24 participants, over the age of eighteen, with leg lymphoedema managed by the community lymphoedema team. Participants must have the capacity to provide informed written consent and complete patient reported outcome measures. Participants are recruited from the local Hospice at Home lymphoedema service caseload.

	- 12 Patient will receive treatment as usual (TaU) - 12 Patients will receive TaU plus StepIt exercise programme intervention Randomisation will not be stratified.
Sponsor	North Cumbria Integrated Care NHS Foundation Trust
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Organisations where research will take place	GP practices in North Cumbria CCG, and Hospice at Home Carlisle and North Lakeland, Carlisle, CA5 7NY
Planned timeline	Start date (first patient, first visit) 1 Jan 2020 Recruitment end date (last patient, first visit): 31 Dec 2022 Study end date (last patient, last visit): 31 Mar 2023 Overall trial completion date (closure): 31 May 2023
Protocol version, date	Version 2, 24 Nov 2021

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1. LAY SUMMARY

Chronic lymphoedema is a long-term medical condition that results in swelling of the limbs or other body parts. The cause of fluid build-up in particularly the arms and/or legs is problems with the lymphatic system, which is a network of glands and vessels that helps fight infection and remove excess liquid in the body. Lymphoedema of the legs is common in people who: may have another chronic condition such as heart failure, COPD, or vascular disease; are inactive for long periods; are overweight or obese; or have had cancer treatment to eg the pelvis. Oedema is a risk factor for serious complications such as cellulitis infection. There is some evidence to suggest that specific resistance exercise of the calf muscle – moving the front of the foot up and down by plantar flexion, similar to what a drummer does when using the foot pedal of a drum - may improve the calf muscle pump function and help reduce fluid build-up. It has been shown that at least in the short-term there is better blood flow and endurance if the calf muscle is exercised in this manner.

As yet there remains considerable uncertainty as to the effects of an exercise programme on leg lymphoedema symptom control. There is very limited research data available on the medium- to long-term effects of calf muscle exercising by lymphoedema patients on the volume of the legs. This study is a prospective, controlled, randomised, feasibility trial to determine if the use of a CE-approved plantar flexion pedal, developed by StepIt Ltd, will be of benefit to people with lymphoedema of the leg. This study initially aimed to assess the feasibility of conducting a full randomised clinical trial in the future. After analysis of results from data involving an initial 24 patients, one outcome measure will be change in leg volume at 6 and 12 weeks. Other outcome measures will include acceptability of use of the device, trial completion rates, and lymphoedema-related quality of life. Due to the swelling experienced by leg lymphoedema patients, physical activity may be hard to achieve for some patients. Initiating calf muscle exercises whilst sitting down may be a first step in increasing physical activity for this population and improving calf muscle pump function.

2. INTRODUCTION

Chronic lymphoedema is a condition where patients experience swelling of subcutaneous tissue due to insufficient drainage of interstitial fluid. The worldwide prevalence of lymphoedema is estimated to be 250 million people (Földi & Földi, 2012). The causes of lymphatic system pathology can be divided into two main types, primary and secondary lymphoedema. Primary lymphoedema is a congenital condition and occurs as a result of impaired lymph vessels or lymph node development; this can be present from birth or develop throughout life. In developed countries, secondary lymphoedema takes place as a consequence of damage to the lymphatic system due to cancer, trauma, inflammation, infection, and obesity. Lymphoedema is primarily caused by parasites in developing countries (Wynd et al ,2007). The arm is commonly affected in women after treatment for breast cancer. The leg can be affected as a result of a range of conditions, as outlined in Table 1. In homeostasis, an amount of fluid leaves the capillaries and flows into the interstitial; usually, most of this fluid is absorbed back into the blood stream and the lymphatic system pumps away the

remaining imbalance in fluid. An imbalance occurs when the microvascular (capillaries and venules) filtration rate exceeds lymph drainage over an extended period. The reasons for this may be a high filtration rate, low lymph flow or a combination of the two. The net result of this impaired drainage is a rise of proteins and solutes in the soft tissue, which can result in fibrosis and hardening of the soft tissue. The presence of oedema can have serious consequences, such as the development of cellulitis (Cox, 2006).

Table 1, Causes of lower limb oedema (from Rabe et al, 2018)

Cause of oedema	Associated disease state of condition
Increased capillary pressure (due to increased venous pressure)	Severe varicose veins
	Deep vein thrombosis
	Heart failure
Increased capillary permeability	Chronic venous insufficiency
	Allergic reaction
	Diabetes
	Drug-induced oedema
Decrease in plasma protein	Nephrotic syndomre
	Hepatic failure
Lymphatic obstruction	Filariasis or lymphatic agenesis
	Cancer treatment related oedema

Currently, chronic lymphoedema can be managed but not cured. The mainstay of interventions includes decongestive lymphatic therapy (DLT), which consists of manual lymphatic drainage (MLD), a specialised medical massage to soften and drain lymph fluid, and compressive bandaging. Patient compliance with treatments is paramount for their success. Patients are also advised to take regular exercise to control the lymphoedema symptoms. The latter proves a challenge in leg lymphoedema patients because of the morbidity associated with their condition (Bogan et al, 2007). This brings about the risk of a vicious circle where less exercise leads to further worsening of lymphoedema symptoms. Whilst exercise could be of particular benefit for this group of patients' research suggests that around 50% of sedentary adults who start an exercise programme stop within the first 6 months of involvement (Heinen *et al* 2007). Patients may be receptive to this form of exercise especially if they are elderly, frail, have limited mobility, have a fear of falling or are housebound.

This study will apply a StepIt rocker pedal for the first time in patients with leg lymphoedema in addition to the standard care. This is a small pedal device that can be used from a seated position and was first devised to help alleviate the risk of deep vein thrombosis for travellers on long haul flights; a reduction in swelling was demonstrated in people who sat in a sedentary position for lengthy periods (Bergqvist, 2009). Subsequently, the StepIt device has been trialled in a clinic setting in patients with peripheral arterial disease (PAD) and venous leg ulcers, respectively (Tebbutt et al, 2013; Jonker et al, 2019). In the study by Tebbutt et al, encouraging results were obtained - in terms of increase in maximum walking distance for PAD patients who used the StepIt pedal – when a 20-minute exercise regime was prescribed. Jonker et al showed a trend towards improved healing rates of VLUs with the same exercise regime as for PAD patients. The StepIt pedal specifically exercises the calf muscle by performing plantar flexion exercise.

There is evidence that exercise of specifically the calf muscle can improve physiological functioning of said muscle. Exercises such as heel raises, flexion, extension and rotation of the ankles have been shown to increase venous return (Padberg, Johnston & Sisto, 2004, Roaldsen *et al* 2006, Jull *et al* 2009). Up to a third of advanced chronic venous disease conditions present also involve lymphatic pathology, ie phlebolymphoedema, and therefore this group of patients is one of the most prevalent leg lymphoedema cases (Bunke et al, 2009). Goddard and colleagues (2008) showed that oedema could be reversed in patients through micromechanical stimulation of the plantar surface. There is limited empirical evidence that calf muscle exercise by patients themselves can aid in controlling lymphoedema symptoms. However, in a small case series, the combination of compression bandaging and exercise resulted in significant leg volume reduction (Rooney et al, 2018). The 20 minute exercise regime comprised of: walking/marching on the spot, ankle and foot rotation and exion, straightening/bending of leg whilst seated, marching whilst seated. Another study involved leg lymphoedema patients exercising in a pool, five times over three weeks, and a significant reduction in leg volume was achieved (Gianesini et al). An impoved in ankle movement range was also reported, an observation also made in VLU patients who exercise (Davies et al, 2007).

2.1 Research question

The aim of this initial randomised, controlled, prospective feasibility study is to determine the acceptability and efficacy of the step-it pedal as an adjuvant therapy for leg lymphoedema with a primary clinical outcome measure of leg volume. This is a pilot aiming to assess the feasibility of conducting a full randomised clinical trial in the future.

3. INVESTIGATIONAL DEVICE + INTERVENTION

The Step-It pedal is developed at Uppsala University Hospital through collaboration between Professor Christer Busch and vascular surgeon Professor David Bergqvist. The StepIt rocker pedal is designed to mimic the walking movement and make the foot bend and stretch. This design is aimed to stimulate the calf muscles and increases circulation in the legs, thereby decreasing the risk for blood clotting and circulation problems. The step-it pedal is 95mm by 230mm by 40mm, weights 212 gram and is made out of ABS-plastic with a silicon footpad (figure 1).

Resistance of the pedal is circa 6 kg and cannot be adjusted. There is no recommended tempo indicated for the pedal, simply because some patients will be more able to do the movements. The videos on the Step-It website show a frequency of roughly 1 second downwards, 1 second upwards motion (https://www.youtube.com/watch?v=nsAZm5TxEIY&feature=youtu.be and http://www.stepit.com/). However, in the leg lymphoedema target population , patients will be encouraged to work at a minimum of 2 second downwards, 2 second upwards motion frequency.

The StepIt pedal is to be used:

Two short sessions per day, and for each session: total of 5 minutes for each leg (easiest to perform 1 minute per leg, then changeover, to allow rest of each leg in between exercise), making it 10 minutes of exercise per session. Total per day will be 10 minutes per leg.

A standard pedometer will be clipped onto the front of the pedal to allow measurement of pedal movement activity.

Figure 1. Step-it pedal

4. STUDY HYPOTHESIS

4.1 Primary objective

- To assess the feasibility of conducting a full RCT in the future

4.2 Secondary objective

- To assess the acceptability and efficacy of the Step-It pedal as an adjuvant therapy for lymphoedema symptom control.

5. STUDY PROTOCOL

5.1 Study design and timeline

This concerns a multi-centre, controlled prospective randomized study. The study will be carried out at GP practices and the Hospice at Home (Carlisle and Lakeland) lymphoedema service clinics, and the study is sponsored by Cumbria by North Cumbria Integrated Care NHS Foundation Trust. The study will take place in local community setting with support and oversight from Clinical Lymphoedema Specialists and research staff.

Table 2. Anticipated timeline

Month	Setup	Recruitment	Analysis	Finalise
Oct-19	Submission for HRA approval			
Nov-19	NIHR portfolio adoption			

Dec-19	HRA and Trust approval	Start recruitment		
Jan-20		Start recruitment		
Dec-22		Finish recruitment		
Mar-23			Analyze data	
May-23				Finalise analysis & report

5.2 Participant identification & consent

Patients with leg lymphoedema will be screened for eligibility for this study by the Chief Investigator. 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: one control group receiving care as usual and one intervention group receiving care with the StepIt device. The eligible patient population is defined in the Inclusion and Exclusion criteria section. A delegated member of the research team will join the (non-research) lymphoedema care specialist to the first appointment provided the patient has consented to this verbally. During this visit /clinic 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 Clinical Lymphoedema Specialists or Research Nurses/Practitioners , the latter as long as the patient's verbal consent has been sought from the treating clinical staff. A screening form will be completed for potentially eligible patients to confirm that they indeed meet the trial criteria.

During the screening visit all patients get the opportunity to try out the Step-It pedal. This also functions as a screening tool, since those patients who cannot perform the required ankle/foot movements cannot enter the trial. Significant discomfort will also be a reason for exclusion. The outcomes of this screening exercise will be recorded in the screening log.

Patients will be given > 24 hrs to consider if they wish to take part, and can ask questions regarding the study. If they understand the nature of the study and are happy to take part, written informed consent will be obtained.

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.

5.3 Recruitment

Participants will be randomised to either the control group (standard care) or the intervention group (standard care plus use of a StepIt pedal) for 12 weeks. Patients in both groups will be given the usual lymphoedema management information, but those in the intervention group will be issued with a StepIt Pedal to use daily for foot and ankle exercises. The participants will be asked to report on their activity at the end of trial (self-reported compliance Likert scale question). At their discharge visits participants are also asked to provide their wider opinion on trial participation. All participants will have demographic data obtained and the following base line measures (Table 3):

Table 3. Baseline measures

Weeks	0	6#	12#
Leg volume	X	X	X
Ankle circumference	X	X	X
Ankle range of motion	X		X
Visual analogue pain score	X	X	X
LYMQOL-Leg	X	X	X
EQ-5D-5L	X	X	X
PEDAL experience questionnaire			X

 # Allowed to be up to 2 weeks early or late

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

Patients are in the study until they are discharged from the lymphoedema service, GP practice, or for the maximum period of 12 weeks; we anticipate most, if not all, patients not to be discharged during their trial participation period. The patient will be followed up as they would in normal clinical practice. The Clinical Lymphoedema Specialist will manage the leg lymphoedema as per routine care, and will conduct the measurement of the leg volume. In clinic, the Clinical Lymphoedema Specialist or Researcher will randomise the patient, hand out the StepIt pedal, and conduct the patient-reported outcome questionnaires at the various timepoints.

5.5 Outcome measures

5.5.1 Primary outcome measures

To assess the feasibility of conducting a full RCT in the future, the primary outcome measures are mainly:

<u>Trial-related outcome measures</u>

- Participants' compliance to StepIt exercise regime
- Recruitment and attrition rates, willingness of patients to be randomised, response rates to questionnaires, and degrees of missing data
- Testing of eligibility criteria and ability/willingness of clinical staff to partake in recruitment of participants

- Ability of site and clinicians to recruit and randomise patients, irrespective of care setting
- To assess any training requirements
- Adequacy of duration of follow-up (e.g. in relation to lymphoedema management and outcomes)
- Fitness for purpose of data collection methods including across and between care settings
- Adverse events

5.5.2 Secondary outcome measures

The primary outcome for this pilot trial will be the feasibility of conducting a full RCT in the future. However, this study also aims to provide preliminary results regarding the acceptability and efficacy of a simple StepIt pedal as an adjuvant therapy for lymphoedema symptom control.

Clinical outcome measures

- Leg volume (see notes below), at week 0, 6, 12
    - Measured only between 9.30am to 3.30pm
    - Where possible the same rater is used for each participant; name of rater will be recorded.
- Ankle circumference measurement, using lateral malleolus as reference point (Brodovicz et al, 2009), at week 0, 6, 12
- Clinician's oedema severity score (Table 4 below; Nieman et al, 2013)

Table 4, Clinician's oedema severity score

	0	1+	2+	3+	4+
Visible	No	yes	yes	yes	yes
Pitting	No	slight	>slight	>slight	'can't reach tibia'
Level	n/a	n/a	< knee	>knee	>knee

- Ankle range of motion (using goniometer)
- Pain score, at week 0, 6, 12
- Quality of life score, determined with EQ-5D-5L and LYMQOL-L Questionnaire, at week 0, 6, 12
- Participant opinion on trial participation, at week 12 (StepIt users only)
- Patient withdrawal rates due to change in management (e.g. need for surgery, hospital admission, infection, or other)
- Leg infection rates, primarily cellulitis

Leg volume measurement notes

The most optimal method for determining lymphoedema severity remains a bone of contention (Brodovicz et al, 2009; Hidding et al, 2016). However, leg volume measurement is considered an essential outcome to assess. Volumetric analysis using water displacement is considered the gold

standard direct method to measure limb volume, along with the more expensive perometry technique. However, due to potential issues arising when patients have a wound, eczema or cellulitis, water displacement measurements are less practical for legs compared to arms. Furthermore, in standard clinics, water displacement volumetry is a time-intensive method. The latest international consensus on management of lymphoedema recommends the measurement of leg volume using Kunhke's technique (Lee et al, 2015; Kunhke, 1978). Commencing at the ankle, with patient seated and leg elevated, the circumference is measured at 4 cm intervals, until seven measurements have been performed (total of 28 cm). The truncated cone formula is then used to calculate the volume for each segment, and the total, using: $V = (1/3) * \pi * h * (r1^2 + r2^2 + (r1 * r2))$

Brijker and colleagues demonstrated that there is diurnal variation in leg volume (as measured by both water volumetric displacement and ankle circumference) and therefore the timing of performing the measurement. Volume can differ 5% depending on the time of day, with an increase observed particularly between 8am and 10am; a subsequent was observed at 5pm. During trial participation, therefore, patients need to attend for an appointment between 9.30am-3.30pm.

6. SUBJECTS

6.1 Anticipated number of research subjects

This concerns a feasibility trial, and therefore the results from this study should inform a potential effect size for StepIt pedal exercise therapy, and also the degree in variance in lymphoedema volume changes (primary clinical outcome). To date, there is not sufficient published data to gain an insight in the effect that calf muscle exercise may have on lymphoedema symptoms. Guidance from a publication by Julious (2005) advises the use of 12 participants per treatment arm, and this approach will be taken here (see Table 5). Patient withdrawal rates before week 12 are not known at present and measuring this will be a primary aim

Table 5, sample size numbers required, based on hypothetical differences between published data and study outcomes

	Standard care (control) arm	**Standard care plus StepIt pedal arm**
Patients (n)	12	12

Since this concerns a randomised controlled trial, albeit in the shape of a feasibility study, reprting will be done in line with CONSORT guidelines (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 lost to follow-up (Appendix 2).

The patient attrition rate (withdrawal and loss to follow-up) will also be recorded, since this involves a study with at multiple visits, albeit incorporated into standard clinical appointments. Patients will be recruited from the adult (age 18+) population routinely seen by the evaluating clinical staff members.

6.1.1 Randomisation

A 1:1 allocation to the control and intervention group respectively will be applied. Following written consent patients will be allocated at random to the control or intervention group, using a non-restricted randomised sequence generated for the whole sample using a free ware randomisation programme, see https://www.randomizer.org/ . Sequential envelopes with each next randomisation allocation will be used to achieve concealment.

The researcher/lymphoedema care specialist will inform the patient what arm they have been allocated. As the study involves the Clinical Lymphoedema Specialist or Researcher consenting and following up patients and a self-administered intervention of necessity it is not possible to achieve blinding for the participants or the Clinical Lymphoedema Specialists.

6.2 Eligibility criteria

6.2.1 Inclusion criteria

- Over the age of 18
- Diagnosis of chronic leg lymphoedema (chronicity > 3 months). This includes primary or secondary lymphoedema.
- Lymphoedema can be present in one leg or both legs
- Newly presenting leg lymphoedema patients or existing patients.
- Same type of compression therapy for at least 2 months.
- Presence of leg ulcer is not an exclusion criterion
- Command of English , verbal and in writing
- Able to give informed consent

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
- Currently receiving, or within 6 months of receiving, chemotherapy or radiotherapy for cancer
- Surgery on lower limb within last three months
- Surgery within last month.
- BMI > 50 (ie extreme obesity; approximation using 'Malnutrition Universal Screening Tool' ('MUST') is allowed)
- Active infection in one or both of the legs treated with systematic antibiotics (or within one week of finishing antibiotics)
- Inability to comply with the StepIt pedal exercise, eg due to fixed ankle or other pathology that impedes using the StepIt pedal. This will be established during the screening/consent process by trialling the StepIt pedal and the movement involved in clinic.
- Commenced, or change in dosage of, diuretic medication in last

6.3 Early withdrawal of subjects + intervention suspension

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, but no further data collection will occur. If a patient does not attend a planned follow-up appointment 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.

If a patient needs to suspend the StepIt exercises then this does not change the planned follow-up dates for 6 and 12 weeks after baseline study visit. This may be eg hospital admission. If a patient develops an infection then the routine approach will be: rest of the legs (ie no StepIt exercises) for duration of antibiotics course + 1 week. Intervention suspension events will be recorded.

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 the StepIt intervention group will be asked to do the StepIt exercise; this will take more time and effort compared to standard management (treatment as usual). Any adverse events will be recorded, as outlined in sections below.

For the participants in the control group there is no direct benefit in taking part in this study. They will be cared for in exactly the same manner as they normally would. For participants in the Step It intervention group, there may be benefits in terms of improved lymphoedema symptoms compared to normal standard care. However, this has not yet been proven and established, and this study is aimed to assess this. 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 AEs need to be reported to the sponsor/host Trust R&D within one week of the investigator team becoming aware of them. For this purpose an AE report form is completed by the researcher and/or Chief Investigator. SAEs should be reported within one working day of becoming aware of the event, where possible.

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

- **Related**: The adverse event follows a reasonable temporal sequence from swabbing. 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.
- **Severity grading**: the Chief Investigator will also record if it concerns an AE or SAE.

This is recorded on the aforementioned AE reporting form. The forms are stored in the study site file.

Pseudo-anonymised copies of all adverse events forms will be shared with StepIt AB as soon as causality reporting has been performed and concluded.

8. STATISTICAL CONSIDERATION AND DATA ANALYSIS PLAN

8.1 Analysis of baseline characteristics

To determine the demographics and characteristics of the patients in the two arms the following data will be collated:

- Age
- Gender

- BMI
- Smoking status
- Type of lymphoedema:
- Lymphoedema severity (0 indicating currently no edema symptoms and 3 indicating the worst possible stage, according to the classification of the International Society of Lymphology. International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema. 2009 Consensus Document of the International Society of Lymphology. Lymphology 2009;42(2):51e60.
- Clinician's lymphoedema severity score
- Lymphoedema chronicity
- Type of compression used (or other type of bandaging, dressing and/or hosiery) prescribed for index leg(s)
- Leg elevation habits
- Significant comorbidities, including, (history of) cancer, diabetes, rheumatoid arthritis, heart failure, hypertension, CKD.
- Vascular profile of legs: presence of chronic venous insufficiency, peripheral arterial disease, venous, mixed or arterial leg ulcer, diabetic foot ulcer.

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 was the feasibility of conducting a larger scale randomised controlled trial. The secondary outcome statistics are other clinical and patient related outcomes measures.

The following descriptive statistics will be reported on:

- 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)

Lymphoedema control: Mann-Whitney U-test of change in leg volume (week 0 vs 12) between control and StepIt groups respectively.

8.3 Secondary outcome statistics

To evaluate the effect of the StepIt exercises on lymphoedema control in the control group will be compared with data from the StepIt group. The StepIt exercise data will be stratified into different groups according to coherence to treatment.

Efficacy is defined by the following parameters:

- Leg volume (indirect via circumference measurements)
- Ankle circumference
- Ankle range of motion

- Visual analogue pain score
- Quality of Life questionnaires scores

To compare the groups in terms of leg volume and ankle circumference, Mann-Whitney U-test or t-test will be applied , depending on distribution of data.

To assess ankle range of motion, the average differences between first and last visit will be calculated. The control and intervention group will be compared by applying Mann-Whitney U-test or unpaired t-test depending on the distribution of the data.

To measure patient-reported outcome measures on quality of life at first visit, second visit and final visit, the Mann-Whitney U-test will be performed. Data of the control and intervention group 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 StepIt and other covariates in leg lymphoedema symptom control. Other covariates include: lymphoedema severity and chronicity at baseline, ankle motion range, patient age, patient mobility, absence/presence of co-morbidities.

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 Trust will need to apply for a letter of access via the NIHR research passport scheme.

Patient identifiable data will only be used within each respective Trust; pseudo-anonymised data are shared with the wider members of the study 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 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 Carleton Clinic, Carlisle, North Cumbria Integrated Care NHS FT. 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 15 years in line with local archiving policy and procedures. Direct access to anonymised data only will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

As this concerns a pilot study, the trial will be monitored by the in-house research team who will convene on a monthly basis. A trial steering committee will not be convened for this trial.

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. StepIt Ltd has provided a non-restricted grant for this study by means of provision of the StepIt pedals free of charge

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 hospital as part of their normal care pathway. Patients randomised to the intervention group will be provided the StepIt device free-of-charge for the duration of the trial.

11. PUBLICATION AND DATA-SHARING POLICY

The study will be registered on the Clinical Trials Gov 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

A summary of the main findings can be supplied to participants on request and this will be stated in the patient information leaflet

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APPENDIX 1. TOOLS AND ASSESSMENTS

This appendix contains:

- EQ-5D-5L is a much used generic quality of life measurement tool (Herdman edt al, 2011)
- LYMQOL-Leg , validated quality of life questionnaire for leg lymphoedema (Keeley et al, 2010)
- Visual analogue pain scale

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 ❑

EQ-5D

- 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 = ☐

©EuroQoL Group 1990

LYMQOL-leg questionnaire (Keeley et al, 2010)

Lymphoedema Quality of Life Study (LYMQOL) LEG

If any of the items are not applicable to you, please write N/A in the relevant answer box(es).

(1) Has your swollen leg(s) affected:				
	Not at all	A little	Quite a bit	A lot
a) your walking				
b) your ability to go up and down stairs				
c) your ability to bend, e.g. to tie shoelaces or cut toenails				
d) your ability to kneel				
e) your ability to stand				
f) your ability to get into/out of a car				
g) Your ability to get on/of public transport, e.g. trains/buses				
h) your ability to get up from a chair				
i) your ability to drive a car				
j) your occupation				
k) your ability to do housework				
(2) Does the swelling affect your leisure activities/social life?				

Please give example(s) of this.

.....

.....

(3) How much do you have to depend on other people?				
(4) How much do you feel the swelling affects your appearance?				
(5) How much difficulty do you have finding clothes to fit?				
(6) How much difficulty do you have finding clothes you would like to wear?				
(7) Do you have difficulty finding shoes to fit?				
(8) Do you have difficulty finding socks/tights/stockings to fit?				
(9) Does the swelling affect how you feel about yourself?				
(10) Does it affect your relationship with your partner?				
(11) Does it affect your relationships with other people?				
(12) Does your lymphoedema cause you pain?				
If so, do you have pain in the foot/feet				
leg/legs				
hip(s)				
back				
elsewhere — if so, where?				
(13) Do you have any numbness in your swollen leg(s)?				
(14) Do you have any feelings of 'pins and needles' or tingling in your swollen leg(s)				
(15) Does (do) your swollen leg(s) feel weak?				
(16) Does (do) your swollen leg(s) feel heavy?				
(17) Does (do) your swollen foot (feet) feel 'old'?				
(18) Have you had any leakage of fluid from your leg(s)				
In the past week				
(19) Have you had trouble sleeping?				
(20) Have you had difficulty concentrating on things, e.g. reading?				
(21) Have you felt tense?				
(22) Have you felt worried?				
(23) Have you felt irritable?				
(24) Have you felt depressed?				

(25) Overall, how would you rate your quality of life at present? Please mark your score on the following scale:

Poor	0	1	2	3	4	5	6	7	8	9	10	Excellent

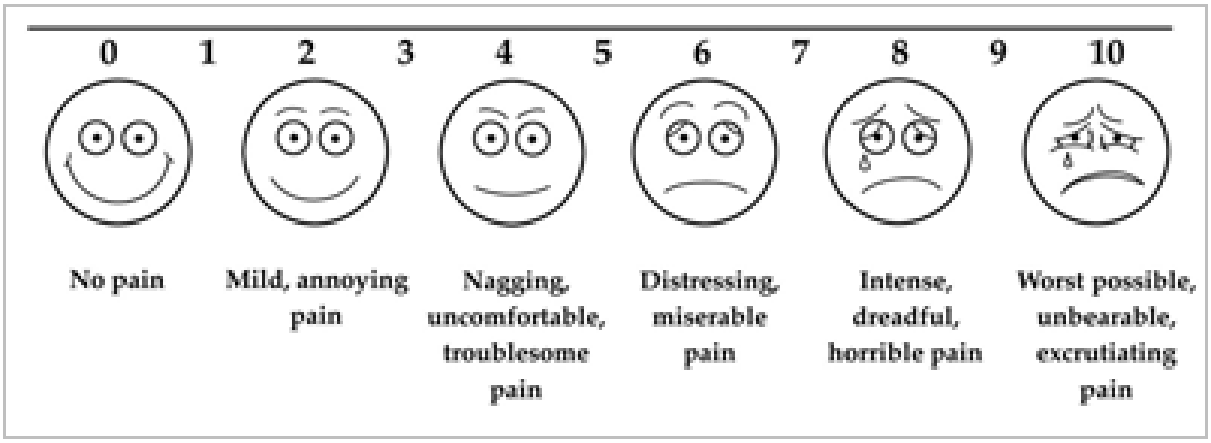
Thank you for completing this form.

If you have any comments or queries about it, please discuss these with..... Dr V L Keeley, Consultant

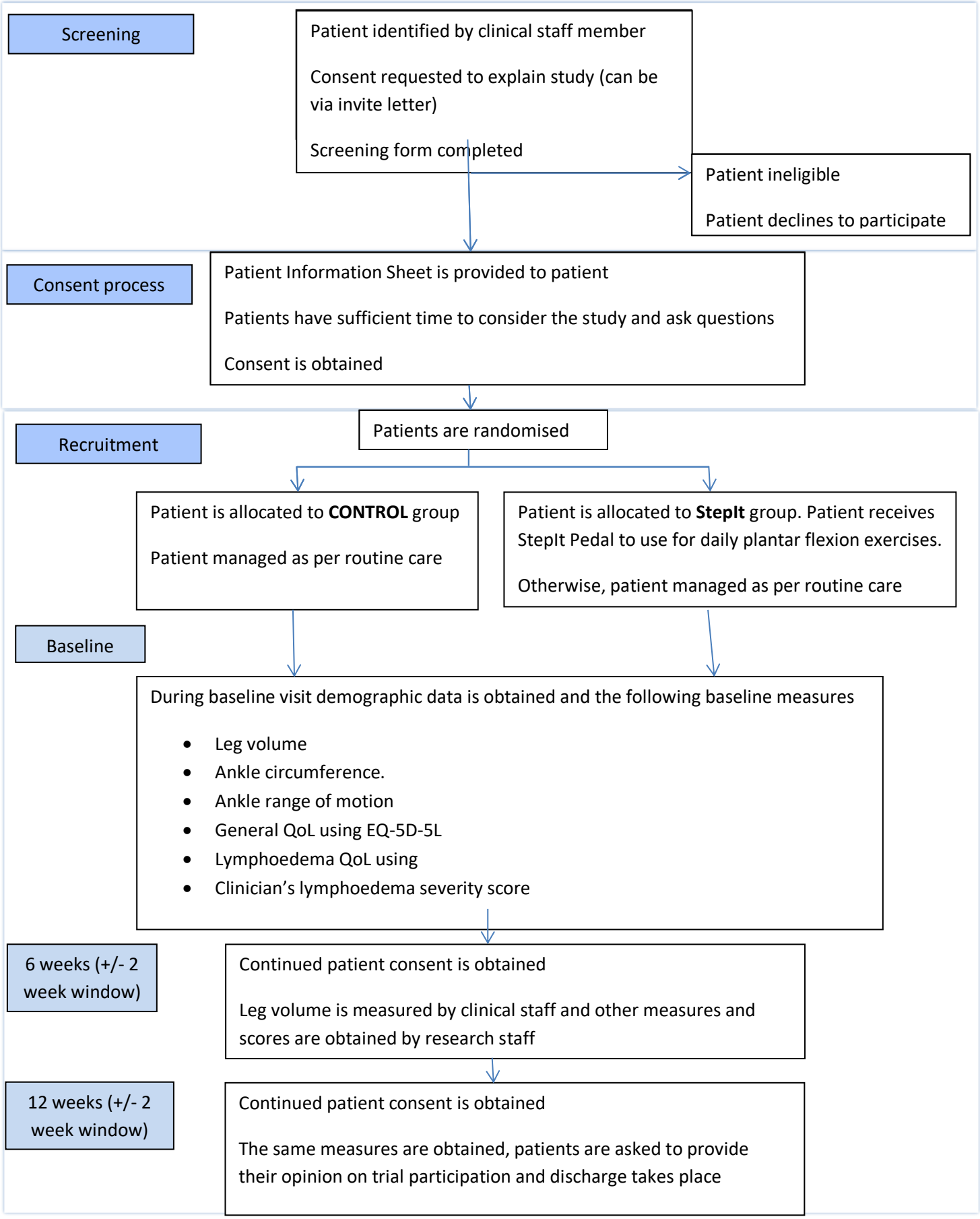
Visual analogue Pain score:

Please place a vertical line on the pain severity scale below, in answer to the question:

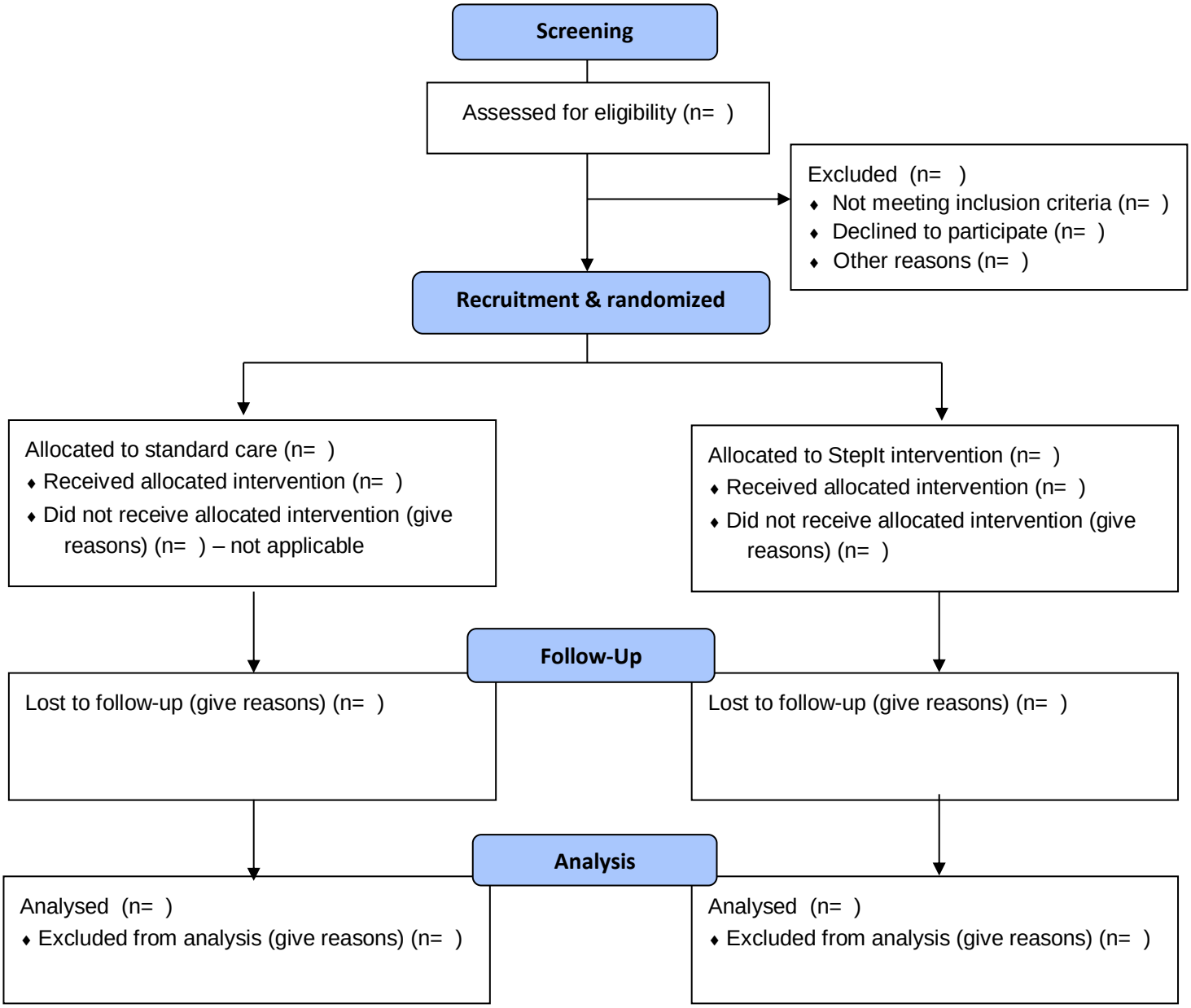
'How much pain have you experienced in your legs in the last week?'



APPENDIX 2. STUDY PARTICIPANT FLOWCHART



APPENDIX 3. CONSORT FLOWCHART



**Based on CONSORT Flowchart*