Supervised exercise training as an adjunct therapy for venous leg ulcers: a randomised controlled feasibility trial

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Title: Supervised exercise training as an adjunct therapy for venous leg ulcers: a randomised controlled feasibility trial

Running Title: Exercise in adults with venous ulcers

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What's already known about this topic?

- Almost 70% of all leg ulcers have a venous component. Furthermore, up to 30% of venous leg ulcers (VLU's) don't respond to compression alone, remain open after a year's treatment, needing an average of 51 treatment visits to heal. Therefore, adjunct therapies to compression are needed, which would improve healing outcomes. Exercise can form part of the therapeutic pathway, however, research evidence to determine whether exercise training has an effect on ulcer healing and QoL is limited, and further work is needed.

What does this study add?

- The findings support the feasibility and acceptability of supervised exercise training as an adjunct therapy for adults with VLU's. Our preliminary data also support the potential effectiveness of exercise training in improving ulcer healing. An appropriately-powered, multi-centre trial is required to confirm the clinical and cost-effectiveness of the intervention.

Abstract

Background: Almost 70% of all leg ulcers have a venous component. Venous leg ulcers (VLU's) are typically painful and heal slowly, resulting in an impaired quality of life (QoL), social isolation and reduced work productivity. Compression therapy offers high healing rates, however, improvements aren't usually sustained. Exercise is a low-cost, low-risk, and effective strategy for improving physical and mental health. However, little is currently known about the feasibility and efficacy of supervised exercise training used in combination with compression therapy in this patient group.

Objectives: To assess the feasibility of a 12-week supervised exercise programme combining aerobic, resistance and flexibility exercises as an adjunct therapy to compression in patients with VLU's.

Methods: This was a two-centre, two-arm, parallel-group, randomised feasibility trial. Thirty-nine patients with venous ulcers were recruited and randomised 1:1 either to exercise (3 sessions per week) and compression therapy or compression only. Progress/success criteria included exercise attendance rate, loss to follow-up and patients' preference. Baseline assessments were repeated at 12 weeks, 6 months and 1 year following baseline, with healing rate and time, ulcer recurrence and infection incidents also being documented. Intervention and healthcare utilisation costs were calculated. Qualitative data was collected to assess participants' experiences.

Results: Overall, 72% of the exercise group participants attended all scheduled exercise sessions. No serious adverse events, and only two exercise-related adverse events (e.g., increased ulcer discharge) were reported. Loss to follow-up was 5%. At 12-months median ulcer healing time was lower in the exercise group (13 vs 34.7 weeks). Total NHS costs were calculated as £813.27 for the exercise and £2,298.57 for the control group.

Conclusions: Our findings support the feasibility and acceptability of both the supervised exercise programme in conjunction with compression therapy and the study procedures. The next step will be the design and implementation of an appropriately-powered, multi-centre trial.

Introduction

Almost 70% of all leg ulcers have a venous component.[1] Occurrence of venous leg ulcers (VLU's) increases with age, with the annual UK prevalence in those over 65 years being estimated at about 3%.[2] VLU's arise from venous valve incompetence and calf muscle pump insufficiency, which leads to venous stasis and hypertension. This results in microcirculatory changes and localised tissue ischaemia.[3,4] The natural history of VLU's is of a continuous cycle of healing and breakdown over decades[5]: VLU's are typically painful and heal slowly, resulting in an impaired quality of life (QoL), social isolation and reduced work productivity.[6] Treatment of this major health problem results in a considerable cost to the National Health Service (NHS): each ulcer costs up to £1,981 per year[7] and estimated total healthcare costs total between £198-£400 million per year[8,9], with 65% of those occurring in the community.[10]

Lower-limb compression therapy is an established first-line therapy for VLU's[11], with approximately 50% of VLUs closing within 24 weeks.[10] Nevertheless, recurrence rates remain high (up to 56% within 4 years[12]). Furthermore, up to 30% of VLU's don't respond to compression alone[11], remain open after a year's treatment [13], needing an average of 51 treatment visits to heal.[10] Therefore, it is important to develop adjunct therapies to compression, which would improve healing outcomes.

Lifestyle factors, including nutrition, exercise and smoking, are mentioned in guidelines on the management of VLU's[14], but receive relatively little emphasis. Exercise training might enhance ulcer healing and other aspects of health and is routinely prescribed for other cardiovascular disease (e.g., peripheral arterial disease[15] and coronary artery disease[16]). In patients with VLU's, supervised calf muscle exercise has been shown to increase calf muscle pump function and improve lower-limb haemodynamics[17,18], as well as mobility and QoL.[19-21] A recent systematic review suggested further research to determine whether exercise training has an effect on ulcer healing and QoL.[22]

Our team recently completed "FISCU", (Feasibility of Implementing Supervised exercise training alongside Compression therapy in people with venous Ulceration - an NIHR-funded study; PB-PG-0213-30029)[5] to assess the feasibility of a 12-week supervised exercise programme combining aerobic, resistance and flexibility exercises as an adjunct therapy to compression in patients with VLU's. We report on rates of screening, eligibility, recruitment, retention, outcome completion, exercise adherence, and adverse events. We also report on reasons for exclusion and non-consent, sample characteristics, the distribution and completeness of potential primary outcomes as well as providing information on preliminary data on effectiveness and health care resource use.

Methods

A full description of methods is available in our previously published protocol paper.[5] The study was a two-arm, parallel-group, randomised controlled feasibility trial conducted in two U.K. sites (Lincoln and Sheffield). Ethics approval was granted by the NHS National Research Ethics Service, Yorkshire and the Humber (Sheffield) Committee (14/YH/0091), and all participants provided written informed consent prior to enrolment. The trial was prospectively registered (Current Controlled Trials ISRCTN10205425).

Participants
Participants were recruited from community nursing and tissue viability teams or services, community and outpatient leg ulcer clinics, and newspaper advertisement. Inclusion and exclusion criteria are given in Table 1.

Randomisation, allocation concealment and blinding
Following baseline assessments, participants were randomly assigned 1:1 to an intervention group or a control group. Participants were stratified by ulcer size (maximum ulcer diameter 1 – 3 cm or >3 cm in any direction). Outcome assessors were blinded to group allocation.

Interventions
All participants received standard compression therapy directed by experienced tissue-viability nurses, following standard local practice. Patients were reviewed in clinics as considered clinically necessary, with no interference by the study team.

Participants randomised in the exercise group were invited to attend three sessions of supervised exercise each week for 12 weeks (total of 36 sessions) at one of the two study exercise training facilities (Sheffield Hallam University and University of Lincoln). For details on the exercise components see Online Supplement 1.

Study schedule and assessments
In Visit 1, after written informed consent has been obtained and eligibility confirmed (which included a medical examination), the following baseline measurements were recorded at one of the two research centres (Sheffield Hallam University, University of Lincoln):
-Demographic data, including age, sex, and socioeconomic status.
-Clinical history, current medications, stature, body mass, ankle and calf circumference.
-Ulcer size.
-ABPI: A Doppler-determined measurement of ABPI was performed according to the procedures of Aboyans *et al.*[23], unless a reading <3 months old could be obtained from clinical records, following patient's consent.
-Baseline exercise history.
-Health-related QoL questionnaires: EQ-5D-5L[24,25] and VEINES-QOL.[26]
-Lower-limb cutaneous microvascular function (methods[27, 28] and results reported elsewhere).
-Physical fitness, using 3 items from the Senior Fitness Test (6-minute walking test, chair sit and reach, chair sit and stand[29]) and ankle range of motion assessed using a bi-plane ankle goniometer.
All participants were given a resource use diary to complete at home for the duration of the study (to conduct Health Economics' analysis).
Participants were then randomised to one of the two groups, as described above.
At 12 weeks and 12 months, participants had the following measures and tests repeated: physical fitness, microvascular function, ulcer-related clinical data (size, status and recurrence) and medications, body mass and health-related QoL questionnaires. A copy of the resource use diary was also taken. A postal assessment involving the completion of health-related QoL questionnaires was also undertaken at 6 months.

Feasibility and acceptability outcomes
Recruitment rates were measured as rate of invited participants who are eligible and consenting. Acceptability of allocation was assessed by examining reasons for dropout in

discontinuing participants and comparing attrition rates between the two study groups. Suitability of measurement procedures was evaluated by completion rates and reasons for missing data. Attrition rate was established as discontinuation of intervention and loss to follow-up measurement for all conditions. The acceptability of the exercise programmes was assessed by using session attendance and compliance data and participant feedback via one-to-one semi-structured interviews conducted with a sub-group of participants after the 3-month follow-up visit (see 5; detailed analysis will be presented elsewhere). The safety of exercise training was also assessed by exploring reasons for dropout from the exercise programme and the number and type of adverse events that occurred in each group.

Sample size

Sample size calculation (see Online Supplement 1) was based on willingness for randomisation and aimed to recruit 80 participants within an 18-month recruitment period.

Data analysis

All analyses were conducted on intention to treat basis (ITT), conducted in SPSS version 24 (IBM, USA). Missing data were reported by trial arm with description of underlying reasons.

Baseline

Summary tables report all baseline variables, clinical, fitness and patient-reported outcome variables. Continuous variables were summarised with descriptive statistics. Frequency counts and percentages were provided for categorical data.

Feasibility and acceptability

For success criteria see Table 2. Outcomes used to assess the feasibility and acceptability of key trial parameters were rates of eligibility, recruitment, retention, outcome completion, exercise adherence, and adverse events.[5] Group preference, reasons for exclusion and non-consent, sample characteristics and the distribution of potential primary outcomes are presented.

Clinical, fitness and patient-reported outcomes

Descriptive statistics are presented for clinical, fitness and patient-reported outcomes at each time point.

Economic evaluation

A prospective economic evaluation was rehearsed to develop and refine the methods for a subsequent definitive trial (see Online Supplement 2).

Results

Figure 1 shows the flow of participants through the trial. Recruitment took place between July 2014 and May 2016, with all follow-up data collection completed by May 2017. The trial was extended for 3 months to allow extra recruitment time.

Screening, eligibility and recruitment

A summary of feasibility and acceptability data is presented in Table 3. All success criteria were met (e.g., 72% of participants completed all exercise sessions, loss to follow-up was 5%, patients' preference to the exercise group was 44%, while median ulcer healing time

was chosen as the primary outcome for the definitive trial). Of 514 patients screened for participation, 109 met eligibility criteria and 39 (24 male, 15 female) were recruited, giving eligibility and recruitment rates of 21% and 36%, respectively. Sites 1 and 2 recruited 38 and 1 participants, respectively. Reasons for non-consent and exclusion are shown in Figure 1.

Group allocation, group preference and participant characteristics
Eighteen participants were allocated to exercise and 21 to usual care. Seventeen (69%) of 27 participants expressed a preference for exercise (12 expressed no preference). Participant characteristics at baseline are shown in Table 4; the groups were well balanced for most variables except QoL.

Retention
Retention rate was 95%. Two of 39 participants formally left the study; one from the exercise group for ulcer pain before the 3-month assessment, one control group for non-ulcer related health reasons before the 6-month assessment. All others completed all assessment sessions. Five participants withdrew from exercise training due to family commitments and non-ulcer related health reasons.

Exercise attendance and safety data
Of the 18 exercise participants, 13 (72%) completed all sessions, overall session completion rate of 79% (512/648). No bandage slippage/misplacement was detected during exercise sessions. We observed two exercise-related adverse events (both excessive discharge from the ulcer). Actions taken included the removal of resistance exercises and postponement of exercise sessions.

Physical function and body mass
Participants in the exercise group showed higher mean values at all 3 months in all tests (Table 5). Results stabilised at 12 months at all tests except plantar flexion. The reduction in weight was modest for the exercise group in relation to the baseline [(103.9 (24) at baseline vs 99.8 (28.4) at 12 months]. In contrast there was an increase in weight in the control group [(102.6 (25.6) vs 105.7 (25.2) at 12 months].

Ulcer related data
Median ulcer size was similar at 12 months (Table 6), but healing rate was higher in the intervention group (83% vs 60%), with shorter median ulcer healing time (13 (3.9 to 52) vs 34.7 weeks (4.3 to 52)). Recurrence rates were low in both groups (2 intervention vs 1 control).

Health-related QoL
Participants in the intervention group started the study with a higher EQ5D utility score than the control group (Table 7; 0.8022 (0.17) vs 06010 (0.35)). This difference was maintained throughout the study. Similar difference was observed with EQ-Visual Analogue Scale, VEINES-QOL (overall score and symptom score) and pain score, although for VEINES-QOL and pain score the difference between groups was increased from 3 months onwards.

Health Economic data
There was no missing data for procedure costs. Mean cost per participant was £610.22, including staff time, room hire and patient reimbursement. Total NHS costs (based on NHS National Tariff Schedules and calculated based on visits and usage of NHS resources) were calculated as £813.27 for the exercise and £2,298.57 for the control group.

Personal costs were calculated using a diary with "out of pocket" expenses being estimated at £113.63 and £174.58 for the exercise and control group respectively.

The "per patient" cost-savings to NHS from the exercise intervention was £875.08. Similarly, the "per patient" less "out of pocket" expenses to participants, as a result of participation in exercise intervention was £60.95. The combined per "per patient" total cost-savings was £936.03 (Table 8; Online Supplement 2).

Discussion

Our study successfully assessed a series of feasibility study aspects, including recruitment, baseline and follow-up measurements, as well as the feasibility and preliminary effectiveness of a supervised exercised programme for people with venous leg ulcers. Our main finding was that the study procedures were feasible and acceptable.

The feasibility and acceptability of using a supervised exercise regime as an adjunct therapy to compression therapy, had been an area of uncertainty prior to this study. Indeed, during the preliminary study stages, such a notion was met with scepticism by some clinicians and patients, who believed that exercise may be either inappropriate or harmful and may delay rather than promote healing - an attitude that has been documented in the literature as well.[30,31] Nevertheless, the majority of the eligible patients had a positive attitude towards undertaking exercise in addition to following a therapeutic pathway based on compression therapy. This was irrespective of whether they consented to take part and reasons for non-participation will help make the programme more accessible (i.e., by choosing appropriate venues). Our feasibility data show few adverse events, with no bandage misplacement or slippage incidents, one of the biggest concerns of collaborating clinicians.

Exercise attendance was 79% with 72% completing all sessions. This is high considering that many participants were old, frail and had no previous exercise experience. This was achieved without employing any specific adherence-enhancing components or provision of behavioural change support, which could have potentially improved attendance rates and the effect of the intervention even further.[32] This suggests a great interest and self-motivation from our participants, which will be a decisive factor for the success of a definitive trial and any wider roll-out of the intervention. Despite our success however, it is our plan to incorporate cognitive-behavioural strategies as part of any future trial to optimise exercise adherence and increase any potential, positive effect.

In respect to practicality our intervention was primarily delivered within a university setting, at some distance from the clinics that our participants were treated. The high attendance rate, suggests that this didn't have a negative impact on the outcome, although it may have impacted recruitment rate. Recruitment rate may be improved in the definitive trial, where 12-week exercise referral schemes[33] will be utilised for the intervention delivery. Delivery with an option of times in community-based venues increases accessibility but comes with a number of challenges (as adherence and success varies) [34], recent research suggests that these schemes can offer QoL and physical activity gains.[35]

Our study suggests the feasibility of collecting of economic data using diaries to collect data on patients' usage of NHS resources, healthcare visits prescriptions and out-of-pocket expenses. The findings suggest potential savings to both the NHS (e.g., £875.08 per patient) and the patients (e.g., £60.95 reduction in out-of-pocket expenses). Nevertheless, as this

was a collection exercise only, an appopriate Health Economics analysis in the definitive trial will provide responses in that area as well.

Overall, no major difficulties were identified in the design or implementation of trial procedures. For example, the blinding procedures ran as intended, the rates of retention and outcome completion (including the 6-month postal assessment) was very good, and from a point onwards there was an excellent communication between clinical and research teams, which allow smooth recruitment. There was an imbalance between groups in EQ-5D-5L data, which didn't affect the success of our study but may need to be considered in planning the definitive trial.

Designing, setting up and managing a definitive, multi-centre study has other challenges besides recruitment rate, data collection and exercise delivery. One important issue is the recruitment of a sufficient number of sites which will: a) deliver the required number of participants, b) have experienced clinicians to act as local Principal Investigators, c) have dedicated tissue viability services, which will support and promote the study and d) have a good communication level between exercise deliverers, tissue viability clinics, local stakeholders (e.g., NHS Trusts) and the main research team. It is therefore, advisable that a cost-effective use of a clinical trials unit is implemented, which would safeguard data quality and guarantee database management, in addition to costing dedicated personnel (e.g., a trial co-ordinator and a trial manager) for day-to-day study management and involving experienced research sites in previous, similar studies (which would safeguard a consistent delivery of the trial protocol).

Our findings support the feasibility and acceptability of both the supervised exercise programme in conjunction with compression therapy and the study procedures and all our originally-set, success criteria[5] were met. In addition, our results suggest that there may be significant potential benefit in healing rates and that, if this were confirmed in a full trial, the introduction of supervised exercise for VLU may well also be cost-saving for the NHS. The next step will be the design and implementation of an appropriately-powered, multi-centre trial is required to provide answers on the clinical and cost-effectiveness of the intervention, and measure its impact.

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Conflicts of interest
None.

Figure Legends
Figure 1. The flow of participants through the trial.

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Inclusion Criteria	Exclusion Criteria
Patients who: • are at least 18 years of age • have at least one venous leg ulcer of primarily venous aetiology (determined by a clinician) with a maximum diameter of at least 1 cm • have an ankle brachial pressure index (ABPI) of at least 0.8 (recorded within the previous 3 months) • are able and willing to tolerate lower-limb compression.	Patients who: • are unsuitable or unable to exercise (determined by a clinician) • are unable or unwilling to tolerate lower-limb compression • have insulin-controlled diabetes mellitus • are pregnant • have coexisting skin conditions, vasculitis, deep venous occlusion or malignant/atypical ulceration • require major surgery • have a leg ulcer with a maximum diameter of less than 1 cm • have had an ulcer at the same site within the previous 3 months • are unable or do not wish to consent to participation in the trial.

Table 1: Study inclusion and exclusion criteria.

Criterion
• An appropriate primary outcome variable is defined. • At least 67 % of randomly assigned patients in the exercise group are compliant with the intervention (defined as at least 75 % of the scheduled sessions are completed as planned). • Loss to follow-up at 12 months is less than 20%. • Patient preferences are not so strong that they result in the conclusion that a randomised controlled trial is not a feasible design.

Table 2: Criteria for success/progression.

Methodological issues	Findings	Evidence
What factors influenced eligibility and what proportion of those screened were eligible?	Tissue Viability Clinics see a variety of patient wounds the majority of which are not ulcers or of venous origin.	109 out of 514 screened were eligible. The most common reasons for non-eligibility being ulcer not of venous origin or other type of wound present=206. The main reasons for non-consent were mainly of social origin (e.g., work commitments or difficulty travelling; n=52).
Was recruitment successful?	Recruitment was slower than anticipated	39 participants were recruited within a 21-month period.
Were eligible patients recruited?	Conversion rate to recruitment was within our primary targets.	39 out of the 109 (36%) eligible participants were recruited in the study.
Were participants successfully randomised and did randomisation yield equality in groups?	Randomisation process worked well.	Similar sized groups, well-balanced on stratification and most other variables; however, quality of life scores were higher at baseline in exercise group.
Were blinding procedures adequate?	Blinding of outcome assessors and ulcer healing assessments worked well.	Two different assessors were used at follow-up sessions. No discussions were reported between participants and assessors on their study experience during follow-up sessions. Assessment of digital ulcer photographs was completed by a team member unaware of the association between study id numbers and group allocation.
Did participants adhere to the intervention?	We experienced a very high attendance rate.	Overall, 13/18 (72%) of the exercise group participants attended 100% of the scheduled exercise sessions. 512/648 (79%) of the scheduled sessions were completed.
Was the intervention	Qualitative and quantitative	Out of the 27 participants

acceptable to the participants?	data from exercise participants suggests that the intervention was acceptable.	who expressed a preference for a specific group before allocation (12 of the study participants didn't express a preference), 17 (69% amongst those expressing preference; 44% amongst all) preferred exercise. Patient interviews (reported elsewhere) have also suggested a high degree of satisfaction.
Was the intervention safe?	Our preliminary safety data appears favourable.	Two non-serious adverse events (excess fluid discharge from ulcer) were noted during the study. No bandaging was affected during the exercise sessions.
Were outcome assessments completed?	Outcome completion rates were very high.	See results.
Was it possible to calculate intervention and healthcare utilisation costs?	Yes.	Cost of exercise programme: £610.22 per participant Total costs per participant were £2412.2 (including Out of Pocket expenses) and £1537.1 for control and exercise, respectively.
Was retention to the study good?	Retention was very high.	Retention rate = 95%.
Did all components of the protocol work together?	From the point that the recruitment procedures were modified, components had strong synergy.	There were no major difficulties identified in the various processes and the researchers' ability to implement them. For example, if participants were recruited, there was excellent collaboration between the care and the research team in regards to data capture (e.g. tracing, ulcer photography).
Was an appropriate outcome defined for the definitive trial?	Yes.	Based on our study and previous research experience, a reduction in ulcer healing time appears to be the most appropriate outcome for the definitive trial.

Table 3: Summary of trial feasibility and acceptability data.

Baseline characteristics	**Intervention (18)**	**Control (21)**	**Combined (39)**
1. Male gender, n (%)	9/18 (50%)	14/21 (67%)	23/39 (59%)
2. Age in years, mean (SD)	65.4 (14.9)	61.9,10.9	63.5,12.8
3. Working, n (%)	8/18 (44%)	6/21 (29%)	14/39 (36%)
4. White ethnicity, n (%)	17/18 (94%)	21/21 (100%)	38/39 (98%)
5. Body mass, mean (SD)	102.1 (29.4)	104.9 (24.3)	103.6(26.5)
6. Blood pressure, heart rate, mean (SD) BP – Systolic (mmHg) BP - Diastolic (mmHg) Heart Rate (beats/minute)	 143 (20) 79 (10) 72 (13)	 140 (18) 84 (13) 69 (11)	 141 (19) 81 (12) 70 (12)
7. Smoking status, n (%)	4 (22%)	5 (24%)	9 (24%)
8. Alcohol consumption, units/week, mean (SD)	8 (13)	9 (14)	8 (13)
9. Key medications names (% yes) Anti-platelet/Anti-coagulant Statin ACE-inhibitor Beta-blocker Calcium channel blocker Diuretic	 7 (39%) 3 (17%) 1 (6%) 3 (17%) 1 (6%) 4 (22%)	 5 (25%) 5 (25%) 1 (5%) 6 (29%) 2 (10%) 3 (15%)	 12 (31%) 8 (21%) 2 (5%) 9 (23%) 3 (8%) 7 (18%)
10. Comorbidities, n (%) Hypertension History of other CVD Non-insulin-dependent diabetes History of cancer Hypercholesterolemia	12/18 (67%) 7 (39%) 1 (6%) 4 (22%) 2 (11%) 1 (6%)	16/21 (76%) 4 (20%) 8 (39%) 4 (20%) 1 (5%) 2 (10%)	28/39 (72%) 11 (28%) 9 (23%) 8 (21%) 3 (8%) 3 (8%)
Ulcer Related			
1. Had ulcer before, n (%)	11/18 (61%)	14/21 (67%)	25/39 (64%)
2. Duration of reference ulcer, mean months (SD)	12.7(19.9)	7.1 (8.1)	7.9(14.8)
3. Time since diagnosis of reference ulcer, mean months (SD)	8.9(13.7)	6.1(8.0)	7.4(10.9)
4. Previously had ulcer at same site (>3 months ago), n(%)	3/18 (17%)	3/21 (14%)	6/39 (15%)
5. Ulcer size, median length in cm(range) median width in cm(range) median area in cm^2(range)	2.6(1.2 to 13.5) 1.9(0.9 to 10.1) 4.9(1.9 to 136.4)	2.8(1.2 to 11.8) 1.9(1.1 to 6.5) 5.7(1.3 to 56.6)	2.7(1.2 to 13.5) 1.9(0.9 to 10.1) 5.0(1.3 to 136.4)
6. ABPI, mean (SD)	1.0(0.1)	1.1(0.2)	1.1(0.2)
Physical activity and Fitness			

1. Walking with difficulty, n(%)	8/18 (44%)	10/21 (48%)	18/39 (46%)
2. Walking, n (%): None <1hr 1-3hr 3+hr	5 (28%) 3 (17%) 6 (33%) 4 (22%)	7 (33%) 5 (24% 5 (24%) 4 (19%)	12 (31%) 8 (21%) 11 (28%) 8 (21%)
3. Exercise/Physical activity other than Walking, n (%)	14/18 (78%)	16/21 (76%)	30/39 (77%)

Table 4: Summary of baseline demographics.

	Exercise Group			Control Group		
Test	**Baseline**	**3 months**	**12 months**	**Baseline**	**3 months**	**12 months**
6-minute walk distance (m)	276 (100)	290 (123)	291 (122)	280 (141)	284 (138)	273 (146)
Chair sit-to-stand (repetitions)	8 (4)	10 (4)	9 (4)	9 (4)	9 (4)	8 (4)
Chair sit-and-reach (score)	-6.4 (11.4)	2.6 (16.0)	2.2 (11.8)	-2.8 (13.6)	-0.8 (11.3)	-1.7 (11.9)
Plantar flexion (degrees)	18.7 (21.0)	22 (15.9)	17.6 (12.8)	15.1 (9.1)	19.0 (22.3)	14.7 (9.4)
Dorsiflexion (degrees)	20.5 (14)	22.9 (14.8)	18.9 (15.8)	20.3 (16.5)	18.7 (24.2)	17.4 (15.3)
Ankle range of movement (degrees)	39.2 (19.9)	44.9 (21.3)	36.6 (20.8)	35.4 (19.7)	37.7 (43.2)	32.1 (18.9)

Table 5: Physical fitness/function indices. Data are mean (SD).

	Exercise				Control			
	Baseline	**3 months**	**6 months**	**12 months**	**Baseline**	**3 months**	**6 months**	**12 months**
Ulcer size (Median length in cm; range) (Median width in cm; range) (Median area in cm^2; range)	2.6(1.2 to 13.5) 1.9(0.9 to 10.1) 4.9 (1.9 to 136.4)	0 (0 to 5) 0 (0 to 6.5) 0 (0 to 26)	N/A	0 (0 to 5.5) 0 (0 to 3.4) 0 (0 to 18.7))	2.8(1.2 to 11.8) 1.9(1.1 to 6.5) 5.7(1.3 to 56.6)	1.3 (0 to 10.2) 1 (0 to 7.7) 1.5 (0 to 78.5)	N/A	0 (0 to 14) 0 (0 to 10.5) 0 (0 to 147)
Whether healed (%)		53% (9/17)	65% (11/17)	83% (14/17)		14% (3/21)	40% (8/20)	60% (12/20)
Time of ulcer healing (median in weeks; range)				13 (3.9 to 52)				34.7 (4.3 to 52)
Reoccurrence of ulcer (%)		0% (0/17)	6% (1/17)	12% (2/17)		0% (0/20)	12% (2/17)	5% (1/19)

Table 6: Ulcer related data.

	Exercise				Control			
	Baseline	**3 Months**	**6 Months**	**12 Months**	**Baseline**	**3 Months**	**6 Months**	**12 Months**
EQ-5D-5L utility score	0.8022 (0.17)	0.8567 (0.15)	0.8147 (0.21)	0.7874 (0.28)	0.6010 (0.35)	0.5698 (0.42)	0.5740 (0.40)	0.5825 (0.41)
EQ-VAS score	69.03 (15.13)	75.35 (15.38)	71.47 (21.34)	75.53 (20.37)	57.43 (19.84)	64.33 (22.74)	58.70 (26.21)	56.20 (27.58)
VEINES-QOL: Main	53.68 (24.62)	69.53 (26.13)	67.49 (27.75)	67.23 (29.86)	42.65 (24.70)	47.24 (29.57)	51.79 (33.62)	52.46 (34.81)
VEINES symptom sub-Domain	62.03 (26.52)	75.18 (24.76)	73.24 (26.26)	73.41 (31.73)	53.17 (28.82)	54.60 (32.11)	58.13 (30.05)	58.53 (33.58)
Pain score	24.44 (27.3)	15.9 (27.7)	16.5 (28.4)	7.9 (22.8)	30.95 (31.6)	22.1 (32.8)	28.0 (36.3)	30.5 (36.6)

Table 7: Summary of health status, disease-specific quality of life and pain data (Mean, SD).

Summary of Annual Costs to NHS, Out of Pocket Expenses of Treatment and Exercise Study Cost by Group						
Cost Type	**Total**			**Per Patient**		
	Exercise	**Control**	**Combined**	**Exercise**	**Control**	**Combined**
I. NHS Healthcare professional	£12,724.00	£34,573.00	£47,297.00	£748.47	£1,646.33	£1,244.66
II. A&E	£0.00	£2,110.00	£2,110.00	£0.00	£100.48	£55.53
III. Inpatient Care	£0.00	£9,365.00	£9,365.00	£0.00	£445.95	£246.45
IV. Diagnostic Tests	£257.00	£746.00	£1,003.00	£15.12	£35.52	£26.39
V. Medicine (Free prescriptions)	£844.60	£1,476.00	£2,320.60	£49.68	£70.29	£61.07
Total Cost to NHS	£13,825.60	£48,270.00	£62,095.60	£813.27	£2,298.57	£1,634.09
Cost to Patients						
1. Travel	£1,081.66	£2,341.68	£3,423.34	£63.63	£111.51	£90.09
2. Medicine	£229.10	£413.44	£642.54	£13.48	£19.69	£16.91
3. Equipment	£621.00	£911.00	£1,532.00	£36.53	£43.38	£40.32
Total OOP expenses	£1,931.76	£3,666.12	£5,597.88	£113.63	£174.58	£147.31
Intervention Study Cost						
1. Exercise intervention delivery	£10,984.00	NA	£10,984.00	£610.22		£610.22
2. Including study Outcome measures cost	£14,051.17	£3,255.17	£17,306.33	£780.62	£155.01	£455.43

Table 8: Summary of Annual Costs to NHS, Out of Pocket Expenses of Treatment and Intervention Study Cost by Group.