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Title: A multi-centre, prospective, randomised controlled feasibility study of plantar resistance exercise therapy for venous leg ulcers – results of the PREVUE study.

Running title: Plantar resistance exercise for venous leg ulcers –PREVUE study

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Abstract

Objectives. To evaluate the feasibility of an interventional study involving a seated plantar resistance exercise programme, using a SteplIt pedal, aimed at promotion of venous leg ulcer (VLU) healing.

Methods. Thirty-two VLU patients, recruited from community, GP and hospital settings, were randomised to either a standard care or adjuvant SteplIt exercise programme arm for up to 12 weeks. The exercise involved a twice daily routine of ten times one-minute of exercise, i.e. two-second push and two-second lift repetitions (equating to 300 daily 'steps').

Results. Complete healing of the VLU was observed in 10 out of 15 (67%; SteplIt cohort) and 7 out of 17 (41%; control cohort) respectively (p-value 0.18, Fisher's exact test). Baseline differences between the two cohorts were longer wound chronicity, less VLU-related pain, and better VLU-related quality of life in the SteplIt cohort. One adverse event, involving increased wound exudate and slough production, was observed in a participant using SteplIt, and no study withdrawals were recorded in either arm. SteplIt users whose wound had completely healed by week 12 were more likely to be compliant with the exercise programme (self-reported) and more positive about the trial experience; however, all would recommend the device to others.

Conclusions: seated plantar resistance exercise shows promise and may accelerate VLU wound healing. The SteplIt pedal is well-received by patients, and its efficacy may depend on the degree of patient compliance with the exercise programme. Further larger scale studies are indicated to allow more concrete inferences to be made on the clinical and potential health economics impact that this device may have.

A multicentre randomised research trial assessing the effectiveness and acceptability of a calf muscle exercise device for supportive treatment of venous leg ulcers, ISRCTN75319519, <https://doi.org/10.1186/ISRCTN75319519>

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Background

Venous leg ulcers (VLUs) are the most common type of leg ulcers, affecting 1-3% of the population over 60 years and this incidence is expected to increase with an aging population.^[1,2] The economic burden of VLUs is considerable, with annual care costs in the UK alone reaching £200 million.^[3] A positive relationship has been observed between occurrence and specific modern lifestyle risk factors such as sedentary lifestyles and obesity.^[4] The natural history of the disease is a continuous cycle of healing and breakdown over decades and VLUs are associated with considerable; expense, morbidity and impaired quality of life.^[5]

Despite extensive research, the exact manner in which VLUs develop is not yet fully understood. However, prolonged venous hypertension caused by chronic venous insufficiency is a common aetiological factor.^[6,7] The mainstay of treatment of VLUs is the reversal of venous hypertension through compression bandaging,^[8] however up to 15-30% do not respond to this current gold standard treatment and remain unhealed even after six months of treatment.^[9,10] Venous return is also facilitated by the action of the foot and calf muscle pump; previous studies have shown that patients with VLUs have histopathological changes of degeneration in the calf muscle and impaired calf muscle function.^[11, 12, 13] There is evidence that exercise of said muscle can improve physiological functioning. Exercises such as heel raises, flexion, extension and rotation of the ankles have been shown to increase venous return,^[14, 15, 16, 17, 18] in addition, clinical guidelines recommend supervised ankle exercises and walking.^[1]

Patients with venous leg ulcers report multiple co-morbidities and are more likely to be sedentary than age matched controls.^[5, 15] 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 six months of involvement.^[19] There is therefore an unmet need for a calf muscle exercise option for patients who may be receptive to exercise but may struggle with more strenuous walking or other exercises that involve standing for longer periods. This may be the case for patients who are elderly, frail, have limited mobility, have a fear of falling or are housebound. The present study offered a plantar resistance rocker pedal, called Steplt, to patients with VLUs in an adjuvant therapy to compression therapy. The aim of this prospective, randomised, controlled, feasibility study was to determine the acceptability and initial efficacy of the Steplt pedal with a primary clinical outcome measure of complete VLU healing.

Methods

Study design

The PREVUE feasibility study (short for PlantaR flexion Exercise for Venous Ulcer Evaluation) was a multi-centre, prospective, randomised controlled trial of an adjuvant Steplt exercise regime versus standard compression bandaging wound care involving patients with VLUs. Patients were enrolled in two NHS hospital Trusts, two GP practices and one community care NHS Trust in England. Full research governance clearance was obtained from the National Research Ethics Service (reference 17/WA/0103), Health Research Authority (reference 222694) and local NHS Trusts, and the study is registered on the International Standardised Clinical Trial Number registry under reference ISRCTN75319519.

Eligibility criteria were that patients were aged 18 years or older, with a clinical diagnosis of VLU (ie a clinical severity score of C6 on the CEAP venous disease classification score^[20]) and mental and linguistic capacity to participate. Additional exclusion criteria were limited life expectancy such as palliative care, not being able to tolerate compression, and an active infection of the VLU that required further treatment with e.g. antibiotics. All regular clinical criteria for compression bandaging applied. Written informed consent was obtained and participants were in the trial for 12 weeks, with study visits at week 0, week 6 and week 12. Following written consent, participants were allocated 1:1 at random to the control or StepIt intervention group, using a non-restricted randomised sequence generated for the whole sample using a freeware randomisation programme, see <https://www.randomizer.org/>. The randomisation was stratified for VLU size, with one group being those with a PUSH score of 8 or lower and the other with a PUSH score of 9 or higher. Sequential envelopes with each next randomisation allocation were used to achieve concealment. As the study involved a self-administered intervention it was not possible to achieve blinding for the participants. Due to the pilot nature of this study, the researcher was not blinded either to the subjects' intervention.

Procedures

The StepIt rocker pedal is a small pedal device that can be used from a seated position and was first devised with the aim to help alleviate the risk of deep vein thrombosis for travellers on long haul flights.^[21] It has also been shown to have some potential effectiveness in patients with peripheral arterial disease.^[22] This design is aimed to stimulate the calf muscles through plantar resistance and hence increase circulation in the legs. Resistance of the pedal is circa 6 kg and cannot be adjusted. There is no recommended

tempo indicated for the pedal; however, in the VLU target population for the PREVUE trial, patients were encouraged to work at – or towards - a two-second downwards, two-second upwards motion frequency. In the study by Tebbutt et al^[22], encouraging results were obtained - in terms of increase in maximum walking distance for peripheral arterial disease patients who used the SteplIt pedal – when a 20-minute exercise regime was prescribed. Therefore, for this study a similar approach was taken: the overall exercise programme was to exercise on the pedal with the index leg for one minute – then rest it for one minute – and to repeat this 10 times. In the rest period patients were allowed to exercise the other leg if desired. This regime was to be done twice daily (e.g. morning and evening). At a minimum recommended 2-second down and 2-second up pace this equates to at least 300 pedal movements for the index leg per day. Participants were asked not to exceed the recommended regime – to standardise the intervention and to minimise the risk of any patients potentially injuring themselves through excessive overuse - and to be seated on a chair or sofa whilst exercising. They were also asked to complete a paper daily compliance diary and also had the option to be reminded bi-weekly about the exercise regime by periodical text message from the trial team.

Outcomes

Since this concerns a feasibility study, aimed to determine the feasibility of a larger trial in the future, the primary objectives were to determine if patients could be recruited to the trial, and to determine which healthcare sites were best suited to this kind of trial.

Furthermore, participant compliance with the SteplIt exercise regime, the suitability of the exercise programme itself, and adequacy of the follow-up period in relation to clinical outcomes were assessed. The primary clinical outcome in relation to the efficacy of the

StepIt pedal in relation to wound healing was complete healing at week 12. Wound healing was measured at weeks 0, 6, and 12, using a transparent wound measurement sheet and calculation of the area with Acrobat reader. A semi-quantitative measure of wound size was also made using the PUSH score.^[23,24] At all three study visits, including before randomisation at baseline, the following outcome measures were determined in addition to wound size: ankle range of motion, both plantarflexion and dorsiflexion, visual analogue pain score in relation to the VLU, Quality of life score as determined by Charing Cross Venous Ulcer Questionnaire (Smith *et al* 2010).^[25] Any adverse events, withdrawal, lost to follow-up and VLU infection rates were also recorded at follow-up. Serious adverse events were pre-defined in the protocol and the study was managed in accordance with good clinical practice.

Statistical analysis

No formal a priori sample size calculation was performed since this concerns a first feasibility trial of StepIt for VLUs. However, the recommended 12 participants per group was applied and an additional 30% attrition rate was anticipated in view of the twelve week follow-up period and multiple visits, resulting in a sample size of 32.^[26] Data was analysed on an intention-to-treat basis, using the last value carried forward principle for the PUSH score variable, which was applicable for one control participant at week 12. Due to missing data at week 0, only per protocol data was analysed for wound size (cm²) and pain levels.

Statistical analyses were two-sided and a p-value <0.05 was considered significant. Due to the non-normal distribution of wound size data in particular, non-parametric tests were used for statistical analysis.

Results

From June 2017 to and including November 2018, 53 VLU patients were considered of which 32 were randomised (Figure 1). CONSORT^[27] data is presented in Figure 1. A total of 31 out of 32 (97%; one case lost to follow-up) completed the 12-week trial period and there were no withdrawals. One adverse event occurred in the SteplIt cohort; a participant experienced a marked increase in exudate and slough produced by the VLU within one month of commencing the trial, and SteplIt exercise was suspended for a week as a precaution.

Figure 1, CONSORT flowchart of PREVUE feasibility trial

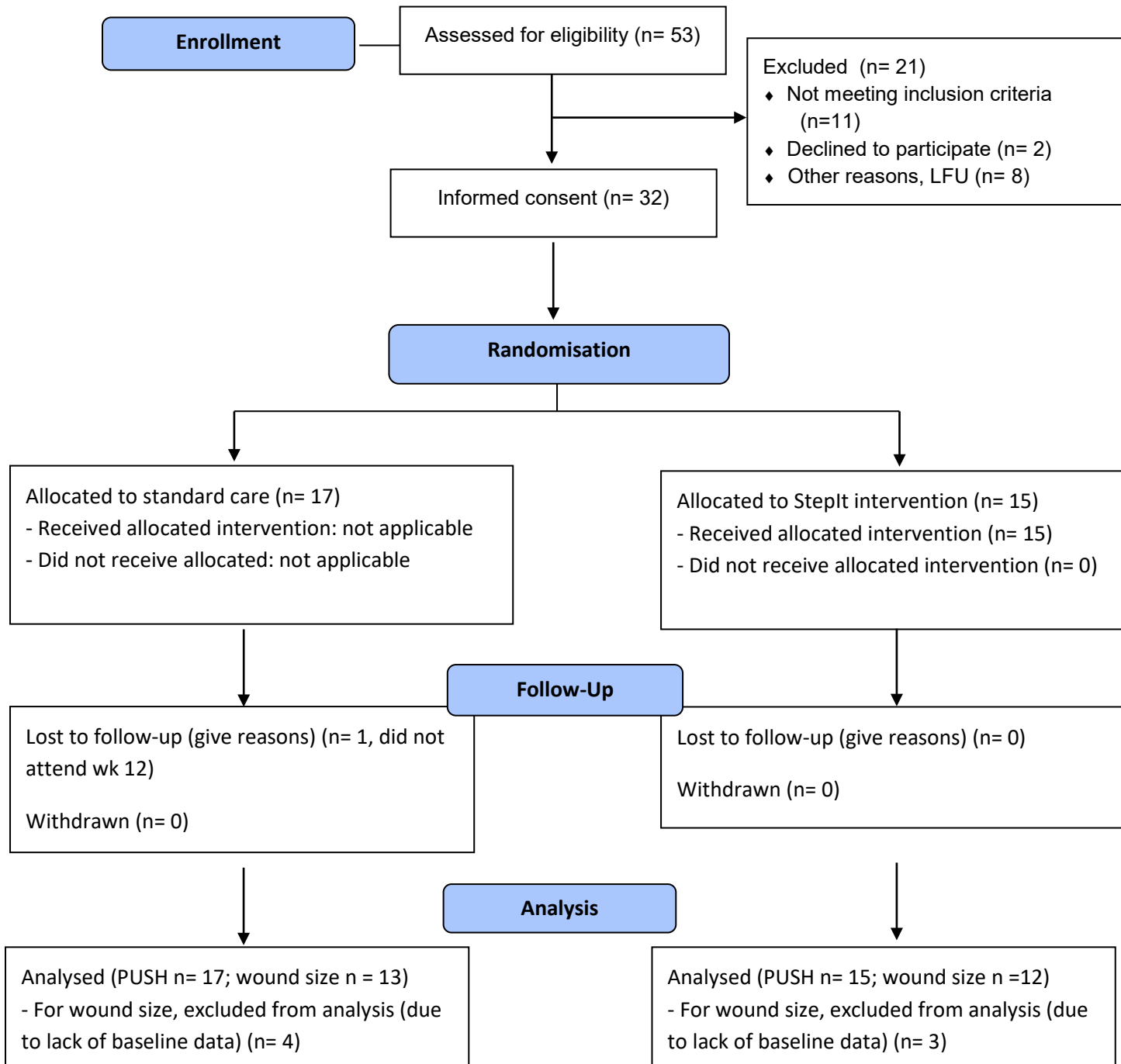


Table 1 shows information on demographics and clinical parameters at baseline for both the control and Steplt arm. On average, the VLUs of participants in the Steplt arm were significantly older than those in the control arm. Conversely, control patients experienced a poorer quality of life related to the wound at baseline (week 0). It was more challenging to obtain all relevant data in the community setting compared to GP practice and hospital settings; this contributed to not all demographic and clinical data being collated for all patients. Recruitment figures were as follows per setting: district nursing, 6 patients; GP practices, 5 patients; hospital (vascular surgery & dermatology departments), 21 patients. The PUSH score was obtained for all participants, whereas the wound size (using a measurement sheet) was not in all cases. In Table 2 the PUSH score is presented for the different time points and treatment arms. At no time point was there a significant difference between control and Steplt cohorts, though the p-value reduced as the trial progressed. The 'wound healed' status for control versus Steplt arms was compared at week 12 (see Table 3). A positive trend was observed for those who were randomised to the Steplt arm, though the result was not significant at a p-value of 0.18. At week 0, there was no difference in wound size between control (median 4.39 cm², interquartile range [IQR] 9.49) and Steplt (3.76 cm², IQR 5.80), p-value 1.00. Again, at week 12 there was no significant difference observed, and the median and IQR value were 0.12 cm², 0.88, for the control arm and 0 cm², 3.23, for Steplt (p-value 0.73). Figure 2a and 2b respectively outline the wound healing trajectory for each individual participant when plotted for PUSH score at week 0, 6 and 12. This illustrates the trend towards accelerated VLU healing in the Steplt cohort. Patients with VLU have a limited range of ankle movement because of decreases in

both plantar flexion and dorsiflexion.^[28] This decreased ankle mobility is associated with delayed VLU healing.^[29] To determine if the range of movement was indeed severely impaired in the trial subjects, the plantarflexion and dorsiflexion angles were measured as part of the trial. Both average plantar and dorsiflexion motion were at the lower end of normal values of approximately 20-50° and 0-20° respectively,^[34] but the values for the StepIt cohort were not significantly different from those in the control cohort (Table 1) and similar to those reported in VLU patients by Klonizakis et al.^[17]

[Figure 2a and 2b here]

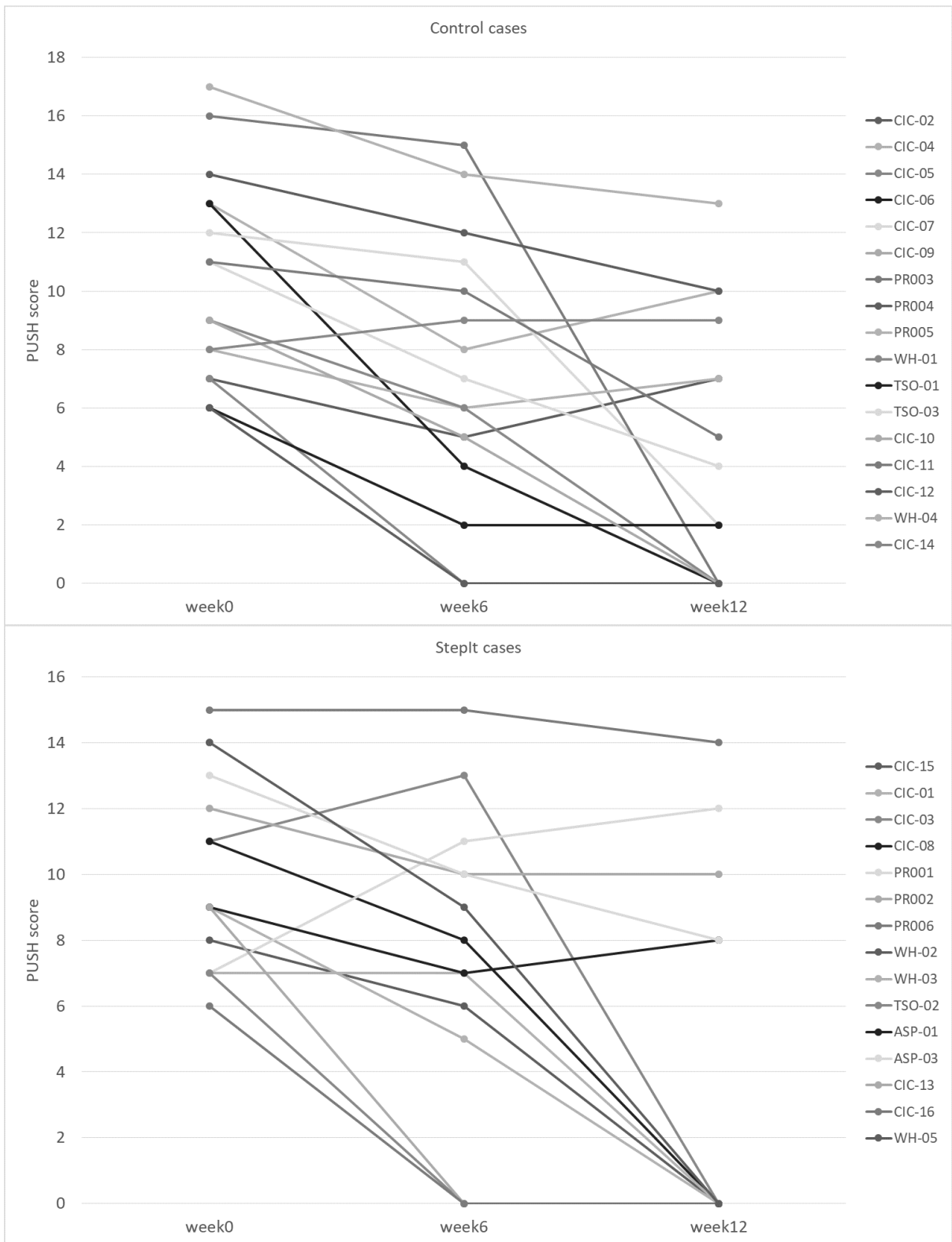


Table 1, Demographics and clinical parameters at baseline

Variable	Control arm [n]	Stepl arm [n]
Age in yrs, mean (95% CI)	77 (71 to 82) [17]	73 (69 to 78) [15]
Sex, male / female, n	5 / 12 [17]	7 / 8 [15]
BMI in kg/m ² , mean (95% CI)	30.1 (25.9 to 34.4) [14]	30.6 (26.8 to 34.5) [14]
Smoking status, never / ex / current, n	9 / 4 / 1 [14]	10 / 2 / 2 [14]
Plantarflexion motion (degrees), mean / 95% CI	21 (17 to 25) [17]	25 (19 to 31) [13]
Dorsiflexion motion (degrees), mean / 95% CI	14 (10 to 18) [17]	13 (7 to 20) [13]
Chronicity wound in weeks , mean (95% CI)	20 (0 to 41) [13]	42 (13 to 70) [11]
VLU quality of life, median (interquartile range, IQR)	65 (20) [17]	52.5 (29.5) [14]

Table 2, PUSH scores and wound sizes at different trial time points

	Week 0		Week 6		Week 12	
<i>Control n=17; Steplt n=15</i>	<i>Control</i>	<i>Steplt</i>	<i>Control</i>	<i>Steplt</i>	<i>Control</i>	<i>Steplt</i>
PUSH score, median (IQR)	11.0 (5.5)	9.0 (6)	7 (15)	8 (15)	2 (13)	0 (14)
p-value (control vs Steplt)*	0.88		0.78		0.45	
<i>Control n=13; Steplt n=12</i>	<i>Control</i>	<i>Steplt</i>	<i>Control</i>	<i>Steplt</i>	<i>Control</i>	<i>Steplt</i>
size cm ² , median (IQR)	4.39 (9.49)	3.76 (5.80)	1.3 (4.81)	2.3 (4.57)	0.12 (0.88)	0 (3.23)
p-value (control vs Steplt)*	1.00		0.79		0.73	

*Mann-Whitney U-test

Table 3, wound healed status

Wound status at week 12	Control [n=17]	Steplt [n=15]
Healed	7 (41%)	10 (67%)
Not healed	10 (59%)	5 (33%)
Fisher exact test, p-value = 0.18		

Pain levels improved for both control and SteplIt participants as they progressed through the trial; from a median 4 (out of 10 on visual analogue scale) at baseline to 2, and from 3 to 0 respectively. There was no significant difference between the two treatment arms at either baseline or at 12 weeks (p -values of 0.058 at baseline and 0.40 at 12-weeks [$n=14$ vs 13]). In terms of other patient-related outcome measures, there were issues with participants reporting back with the exercise diary and requests for text reminders were very limited. Nine out of fifteen returned their diary at follow-up appointments (60% compliance) and two opted to be sent text reminders on SteplIt use (13%). Of six diary responders who complied with the exercise programme > 80% of the trial days, four wounds were healed at 12 weeks; amongst the three other surveyed who complied to a lesser degree, none of the wounds had healed at week 12. The overall feedback given by participants who were randomised to the SteplIt arm was positive (see Figure 3); of the fifteen subjects in the SteplIt arm, fourteen (93%) provided feedback. The majority of participants would recommend the SteplIt pedal to others, and the overall experience of taking part in the trial was 'good' or 'excellent'. When stratified for wound status at week 12, those with healed VLU were more positive about the healing of their wound and the contribution that the SteplIt exercises may have had. Likewise, better self-reported compliance with the exercise regime appeared to correlate with better wound healing outcomes – the sample size being too small to test this statistically. Free-text feedback on SteplIt pedal exercise included two notes on it being boring, one stating that it was hard to fit in the day, and one explaining that compliance was sub-optimal due to other health issues.

Patient feedback on use of the SteplIt pedal was one of the findings as part of this feasibility trial. Table 4 summarises other methodological topics that were appraised and what has

been learned as a result of conducting the study. Various minor changes should allow future studies to be improved from a methodological point of view.

[Figure 3 here]

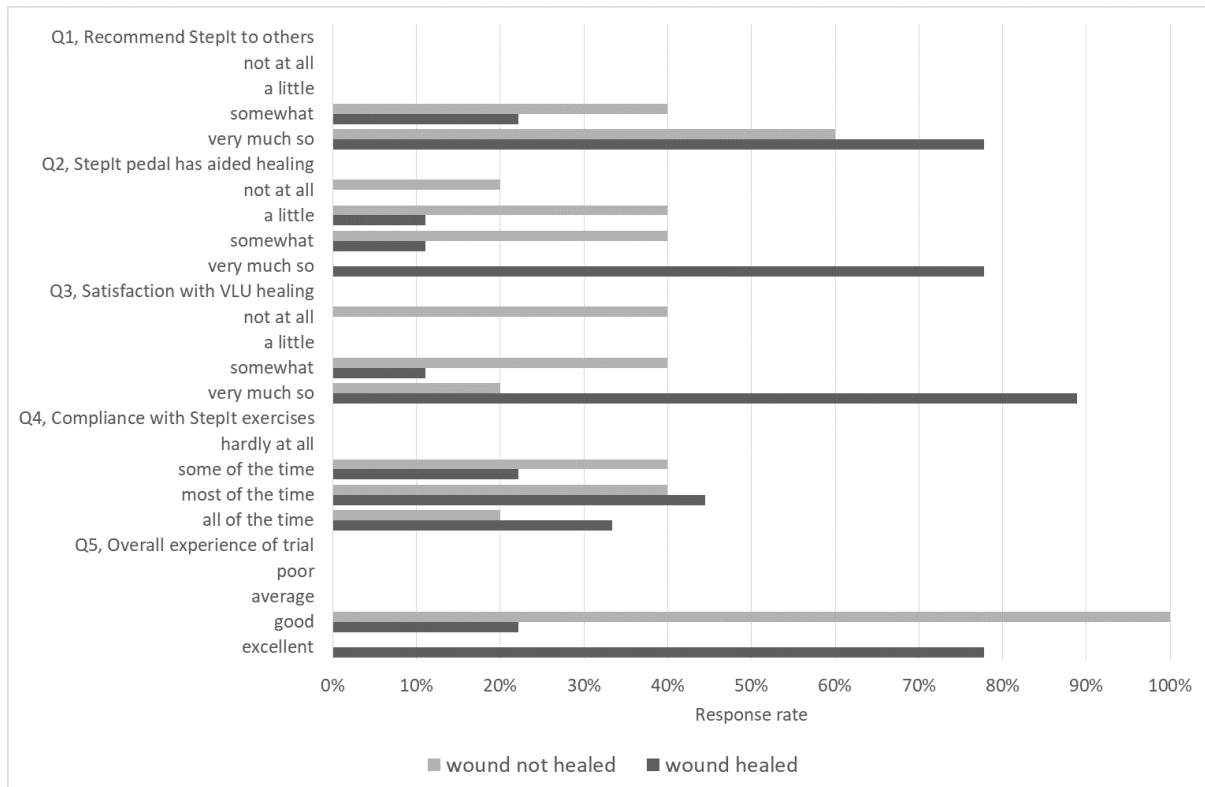


Table 4, Summary of trial feasibility findings

Methodological issues	Findings & notes
Appropriateness eligibility and randomisation criteria	Future studies should be more controlled, with minimum and maximum allowed VLU wound sizes applied, and stratification for wound chronicity in addition to wound size.
Were clinical staff willing to recruit and follow-up patients?	Positive experiences in GP practices and hospitals, whereas district nursing staff struggled to accommodate the clinical outcome measures (particularly wound size measurements with grid). Non-standardised care for VLU patients is challenging, with dermatology, tissue viability and vascular surgery departments all managing said patients.

Was recruitment successful?	Recruitment rate was slower than anticipated; 32 patients recruited in 17 month period, whereas aim was twelve months.
Patients willing to participate in, and complete the trial?	Out of 42 eligible patients approached, 10 either declined or failed to respond to an invite to take part in the trial. One participant lost to follow-up, otherwise all participants completed the trial (see Figure 1).
Was a mean and standard deviation (SD) of the wound size obtained?	At week 12, the mean (SD) was 0.54 cm ² (0.94) for the control arm and 8.62 cm ² (23.97) for the StepIt arm, see Table 2. Issue where VLU of one StepIt participant measured > 80cm ² (ie ten-fold the mean VLU size).
Intervention acceptable and complied with?	All patients rated the trial experience good or excellent (see Figure 3). Sixty percent of participants completed exercise diary, with 6 out of 9 responders claiming to be >80% compliant. In survey at end of trial, 10 out of 14 participants claimed to have been compliant 'most of the time' or 'all of the time'. One patient felt the exercise slightly boring, another struggled to fit it in around shift work.
Possible to calculate intervention costs?	Yes; each StepIt pedal would cost £15 at full retail price.
Response rates to and suitability of clinical and patient-related outcome measures.	No issues with response rates from participants, apart from for exercise diary. Digital counter for measuring StepIt device is desired. Clinical score such as Venous Clinical Severity Score would enhance information on patient status. It is desirable to replace wound tracing with digital measurement of wounds, provided this is logistically feasible.
Appropriate outcome identified for definitive trial?	If min-max VLU size at baseline is controlled for then status 'wound healed' at week 12 would be a feasible outcome measure. Time to heal should be appraised in follow-up study with more timepoints and longer follow-up period.

Discussion

Literature suggests that there is a relationship between VLU severity and calf muscle pump dysfunction.^[11, 12, 13] Therefore, the SteplIt pedal – which offers resisted plantar flexion movement exercise with the patient seated - was used as an exercise intervention in this prospective, pilot, randomised, controlled trial. Other studies have shown that patients are able and willing to do home-based exercise^[17,18] Unsupervised exercise would potentially be more economical than supervised exercise, as recommended by SIGN and used by others,^[16,17,32] but only if said unsupervised exercise is effective, and as effective as supervised exercise, and safe. With only one adverse event reported, and a reduction in pain observed, thus far the use of SteplIt does not appear to be associated with wound deterioration or be a source of discomfort. Nonetheless, the SteplIt pedal will have to be used by many more patients – and possibly for longer periods – to establish its exact safety profile. Since VLU patients cite fear of harm due to exercise, the seated approach with the SteplIt pedal may suit this patient population.^[33] The recommended daily number of 600 plantarflexion steps ‘prescribed’ in the current study is considerably less than the 6,500 average number of regular steps reputedly taken by older adults.^[34] However, we hypothesized that VLU patients will on average not come close to the reported numbers for the general public and that a too strenuous or lengthy regime could potentially lead to non-compliance and withdrawal. On average, trial participants had a slight impairment in ankle movement at the start of the study. Although the sample was too small to draw conclusions, it appears that some limitation in ankle movement should not necessarily preclude patients from using a plantarflexion resistance exercise device. Davies and colleagues^[31] reported an improvement in ankle range after a 24-week plantar resistance exercise programme; testing any change in ankle range of motion was not an objective in this study, but may be tested in the future in a larger cohort using SteplIt.

This present study had some recognised limitations, some of which could potentially be addressed in a larger trial. The researchers were not blinded either to the subjects' intervention, and ideally a person blinded to this would be used to obtain research outcome data including patient-reported outcome measures. This could potentially reduce any bias, e.g. when measuring the VLU wound. Introducing a true sham treatment for participants in the control arm would be hard to achieve – even non-resistance plantar flexion will likely train the calf muscles to some degree. However, the primary outcome measure, size of the VLU is a quantitative outcome measure which is less prone to bias than for example a patient reported outcome measure or a clinician reported outcome measure. There was a reliance on patient-reported compliance to the StepIt exercise regime. The addition of a counter to the pedal itself or a pedometer on the ankle may give more quantitative evidence on the amount of exercise that is done by each participant. This is of particular interest since – judging from our very limited sample - better compliance to the programme may possibly result in better healing outcomes. Thus far only one exercise regime has been trialled; further research may include trialling different regimes, eg variable days of the week that exercise is performed and/or time spent doing the exercise. One study objective was to determine if this kind of research can successfully take place in different care settings; in contrast to a hospital setting, it was more challenging to obtain all data in a community setting and this affected sample numbers for some variables that were evaluated.

VLUs in the StepIt cohort were more chronic than in the control cohort; despite this being a known risk factor for delayed healing,^[35] there was still a trend for wounds in the StepIt cohort to heal faster by week 12. Future research could include a longer trial period of

around 18-26 weeks, to determine if more wounds heal by that time point and if long-term use of the StepIt pedal is feasible in view of some reporting that the exercise is slightly boring. Furthermore, a long-term wound status follow-up point should inform if plantar flexion exercise with the StepIt pedal can reduce the risk of VLU recurrence and need for surgical intervention since over 50% of patients will experience a recurrence within a year.^[36]

In summary, the results from this feasibility study add to the current evidence that exercise by a VLU patient at home can promote wound healing. Furthermore, this patient population is receptive to exercise and can be programme compliant – in this study 11/14 (78%) reported to comply most or all of the time, which is similar to compliance rates observed in a different (supervised) exercise trial.^[17] As with other studies, a larger trial, focusing on healing as well as more long-term clinical outcomes is indicated to allow more definitive conclusions to be drawn.

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Figure titles for figures not included:

Figure 2a, VLU healing trajectory for control cohort

Figure 2b, VLU healing trajectory for SteplIt cohort

Figure 3, patient feedback on use of SteplIt pedal