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

Running title: Plantar resistance exercise for leg lymphoedema

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Abstract

Objectives. To assess if seated plantar resistance exercise programme using a StepIt pedal is a feasible intervention for control and improvement of leg lymphoedema symptoms.

Methods. A total of 26 leg lymphoedema patients, recruited in community setting, were randomised to either a standard care or adjuvant StepIt exercise programme arm for 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. Baseline characteristics for control and StepIt arm were comparative, bar a difference in lymphoedema chronicity (36 vs 16 months) and leg compression use (75% vs 43%). No discernible median change (Δ) in leg volume over 12-week trial period was observed in either group, with large variation between patients: for the control arm it measured Δ +16 ml (inter-quartile range 522 ml) and for the StepIt arm it was Δ +82 ml (223). Overall quality of life, measured with EQ-5D-5L survey, also remained largely stable over 12 weeks trial period. Four out of 14 StepIt arm participants experienced an adverse event where they discontinued use of the exercise pedal, and all were possibly linked to its use. Amongst the StepIt users, the majority of participants would only recommend the StepIt pedal 'a little' and they did not think it had improved their leg lymphoedema symptoms at all.

Conclusions: there is no indication from this study that seated plantar resistance exercise may improve leg lymphoedema symptoms for the assessed outcomes of leg volume and quality of life. The efficacy of the StepIt pedal may possibly depend on the degree of patient compliance with the exercise programme, which was relatively poor in this study (partly due to withdrawals due to adverse events). Any follow-up studies could use the outcome measures applied here, but would also benefit from radiographic measurement of underlying venous function, careful titration of exercise levels, and safety monitoring.

Effectiveness and acceptableness of an exercise regime using a portable device to improve leg lymphoedema, ISRCTN21615265, https://doi.org/10.1186/ISRCTN21615265

Background

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). It is caused by damage to the lymphatic system, whereby the impaired drainage raises proteins and solutes in the soft tissue, leading to fibrosis and hardening of the skin; complications may include cellulitis (Cox, 2006). The causes of oedema can be due to increased capillary pressure (from increased venous pressure) or capillary permeability, a decreased in plasma proteins or lymphatic destruction. Some associated diseases of oedema are heart failure, cancer treatment, hepatic failure, chronic venous insufficiency and diabetes (Rabe et al, 2018).

Mainstay treatment includes decongestive lymphatic therapy (DLT), a specialised medical massage (manual lymphatic drainage), coupled with compressive bandage and regular exercise. Exercise within this group may be of particular benefit, but is a causal nexus as lymphoedema tends to lead to less exercise and exercise programmes started by sedentary adults (around 50%) often stop within the first 6 months of involvement (Heinen et al 2007; Bogan et al, 2007). A case series noted exercise along with compression bandaging did significantly decrease leg volume (Rooney et al, 2018). 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 appropriate form of exercise needs to be employed to assist lymphoedema patients, a routine that is straightforward and ideally home-based to ensure compliance and to make it suitable for people with limited mobility, the frail and elderly.

This study investigates the use of a StepIt™ rocker pedal, a pedal that was originally designed to increase blood circulation through the leg when seated for longer periods and shown to reduce leg swelling in healthy volunteers (Bergqvist, 2009). The device also seems to promote wound healing in patients with venous leg ulcers (Jonker et al, 2019). This is the first time a study has utilised the StepIt™ pedal in patients with leg lymphoedema; its use may be suited to this group as it is used in a seated position, providing plantar flexion, exercising the calf muscle as if walking. The aim of this initial randomised, controlled, prospective feasibility study is to determine the acceptability and efficacy of the StepIt™ pedal as an adjuvant therapy for leg lymphoedema, with an additional outcome measure of leg volume and lymphoedema-related quality of life.

Methods

Study design

This concerned a multi-centre prospective randomised controlled feasibility trial, registered at and approved by National Research Ethics Service (reference 17/WA/0103), Health Research Authority (reference 222694) and International Standardised Clinical Trial Number registry (reference ISRCTN75319519) under the name PEDAL study (Plantar Exercise, DAily, for Lymphoedema). The study was carried out across 11 GP practices and the Hospice at Home (Carlisle and Lakeland) lymphoedema service clinics.

Eligible participants were those over 18 years old, with a diagnosis of primary or secondary lymphoedema (chronicity>3 months) in one or both legs, same type of compression therapy for at least 2 months and mental and linguistic capacity to participate. Additional exclusion criteria were currently receiving, or within six months of receiving chemotherapy or radiotherapy for cancer, surgery on lower limb within the last three months, surgery within the last month, a BMI >50, active infection in one or both legs treated with systematic antibiotics (or within one week of finishing antibiotics), inability to comply with the SepIt pedal exercise (including discomfort) or having commenced or changed dose of diuretic medication within the last two weeks. Patients provided written informed consent prior to participating and were randomised to either the control group (standard care) or the intervention group (standard care plus use of StepIt pedal); trial duration was 12 weeks and visits were at week 0, week 6 and week 12.

Procedures

The study used the StepIt rocker pedal, which is used in a seated position, activating the calf muscle, mimicking the walking movement and increasing the blood circulation (Bergqvist). Only patients who could utilise the device without difficulty and pain at the baseline screening/consent visit were enrolled in the study. The pedal has a non-adjustable resistance of circa 6 Kg, with no tempo recommended by the manufacturer. The StepIt exercise intervention has been described previously (Jonker et al, 2019). In brief, Intervention participants were encouraged to work at a minimum of 2 second downwards, 2 second upwards motion frequency, working in two short sessions per day that were ten minutes each. This means five minutes per leg, per session: one minute per leg then changeover, to allow rest of each leg in between exercise. Participants were reminded to comply with the regime and to not exceed it, the latter to standardise the intervention for all patients.

Outcomes

The primary objectives were to determine if patients could be recruited to the trial and eligibility criteria were suitable, plus attrition rates and adverse events. Furthermore, participant compliance with the StepIt exercise regime, the suitability of the exercise programme itself, and adequacy of the follow-up period in relation to clinical outcomes were assessed. Clinical outcome measures were volume of the index leg, determined only between 9.30am to 3.30pm (Brijker et al) and 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: $V = (1/3) * \pi * h * (r12 + r22 + (r1 * r2))$. In addition, ankle circumference was measured (Brodovicz et al, 2009) as well as the oedema severity

score (Nieman et al, 2013). Patient-reported outcomes concentrated on (lymphoedema-related) quality of life with EQ-5D-5L and LYMQOL-L scores (Herdman 2011; Keeley 2010).

Statistical analysis

Julious (2005) advises the use of 12 participants per treatment arm, and this approach was taken here; data was analysed on a per protocol basis. Statistical analyses were two-sided and a $P < 0.05$ was considered significant. Due to the non-normal distribution of leg volume data in particular, non-parametric statistical measures (such as the median) are reported. For the comparison of quality of life outcome ordinal data between and within groups, Mann-Whitney U-test was performed. Data was collated with Excel (Microsoft) and analysed using Statistical Package for the Social Sciences v24 (SPSS, IBM).

Results

Figure 1, CONSORT flowchart of PEDAL feasibility trial

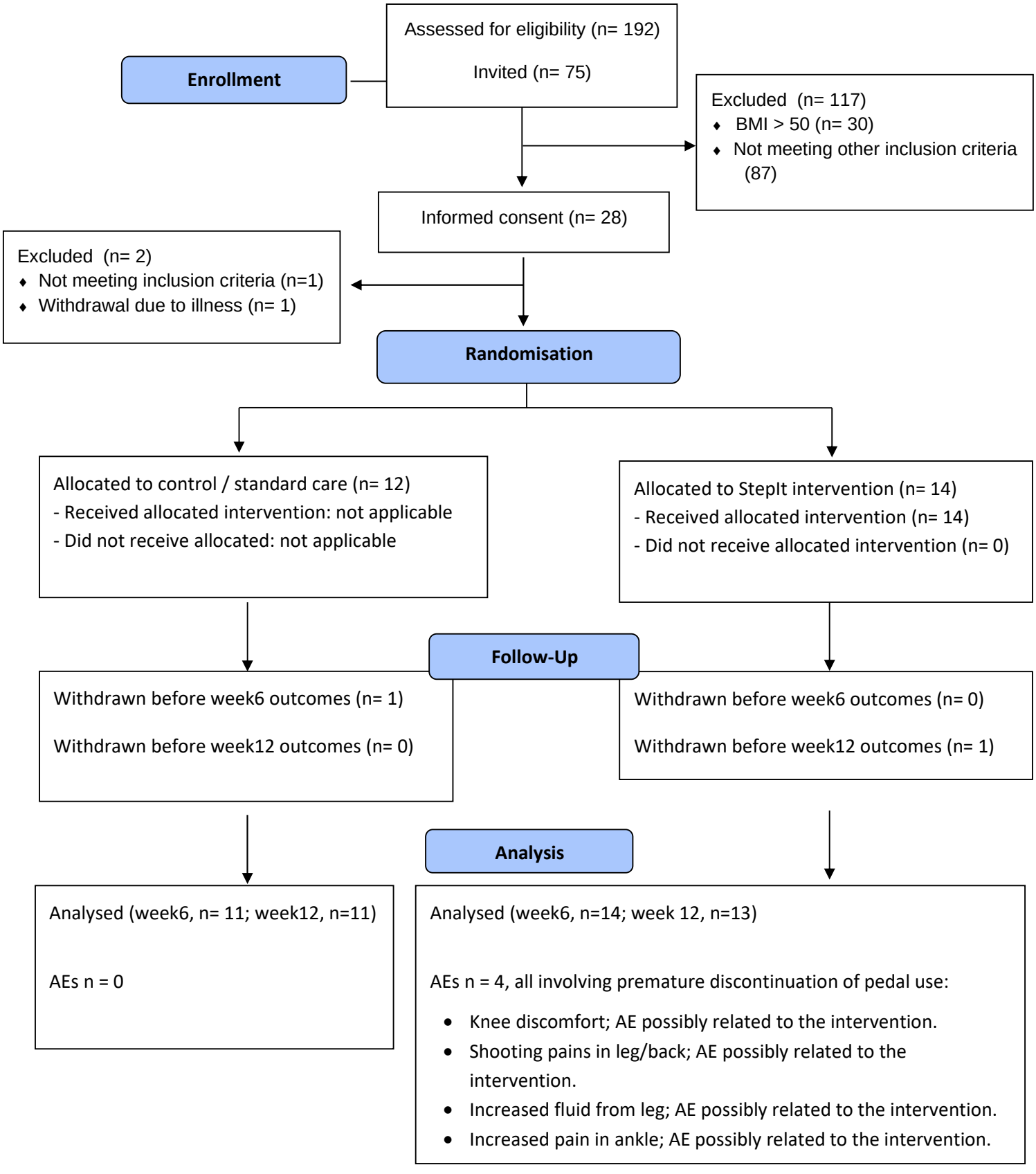

Table 1, Demographics and patient reported outcome measures at baseline

Variable	**Control arm [n = 12]**	**StepIt arm [n = 14]**
Age in yrs, mean (95% CI)	69 (58 to 79)	69 (62 to 76)
Sex, male / female	1 / 11	4 / 10
BMI in kg/m^2, mean (95% CI) , [n]	37 (34 to 41) [12]	35 (29 to 40) [12]
Smoking status, never / ex / current, [n]	8 / 4 / 0 [12]	6 / 6 / 1 [13]
Chronicity lymphoedema in months, mean (95% CI) , [n]	36 (12 to 61) [12]	19 (9 to 28) [13]
Leg hosiery or compression bandaging, yes / no, n	9 / 3	6 / 8
LYMQOL quality of life score, median (interquartile range, IQR)	15.66 (4)	14.79 (3)
VAS pain score, median (IQR)	4.5 (4)	4 (5)
EQ-5D-5L overall score, median (IQR)	0.68 (1)	0.61 (0)
Health score (from EQ5D-5L), median (IQR)	78 (41)	68 (30)

Table 2, Lymphoedema and health related outcomes over time

Variable	**Control arm [n]**	**StepIt arm [n]**
Leg volume at baseline, median ml (IQR), [n]	3008 (1526), [12]	2427 (1060), [14]
Delta leg volume , 6 weeks follow-up versus baseline , median (IQR), [n]	5 (267), [11]	23 (160), [14]
Delta leg volume , 12 weeks follow-up versus 6 weeks follow-up, median (IQR), [n]	-12 (215), [11]	-43 (293), [13]
Delta leg volume , 12 weeks follow-up versus baseline, median (IQR), [n]	16 (522), [11]	82 (223), [13]

Figure 1, Lower leg volume over time

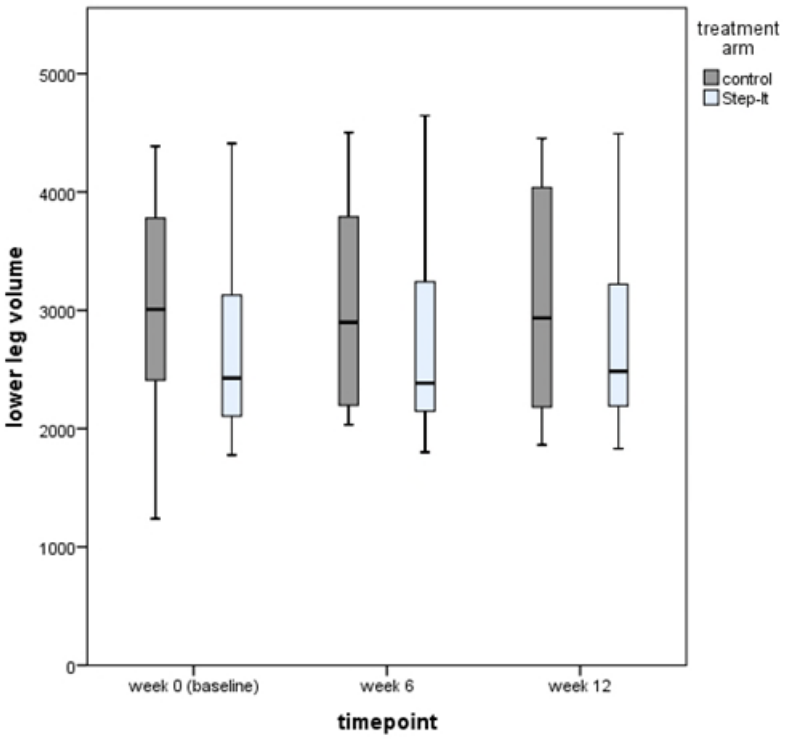

Figure 2, Self-reported quality of life (EQ5D-5L) over time

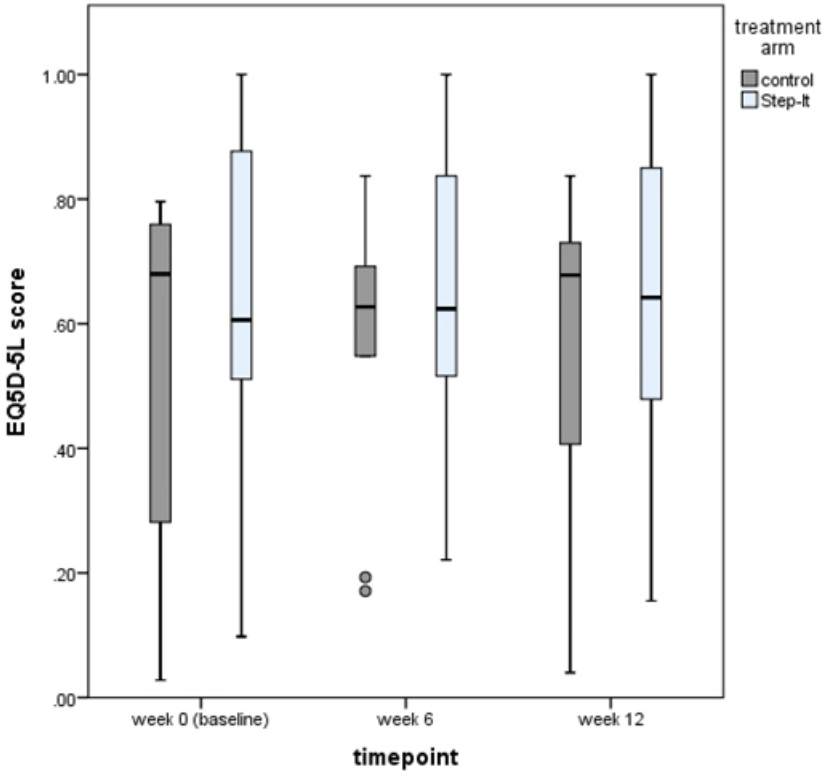

Figure 3, patient feedback on use of StepIt pedal

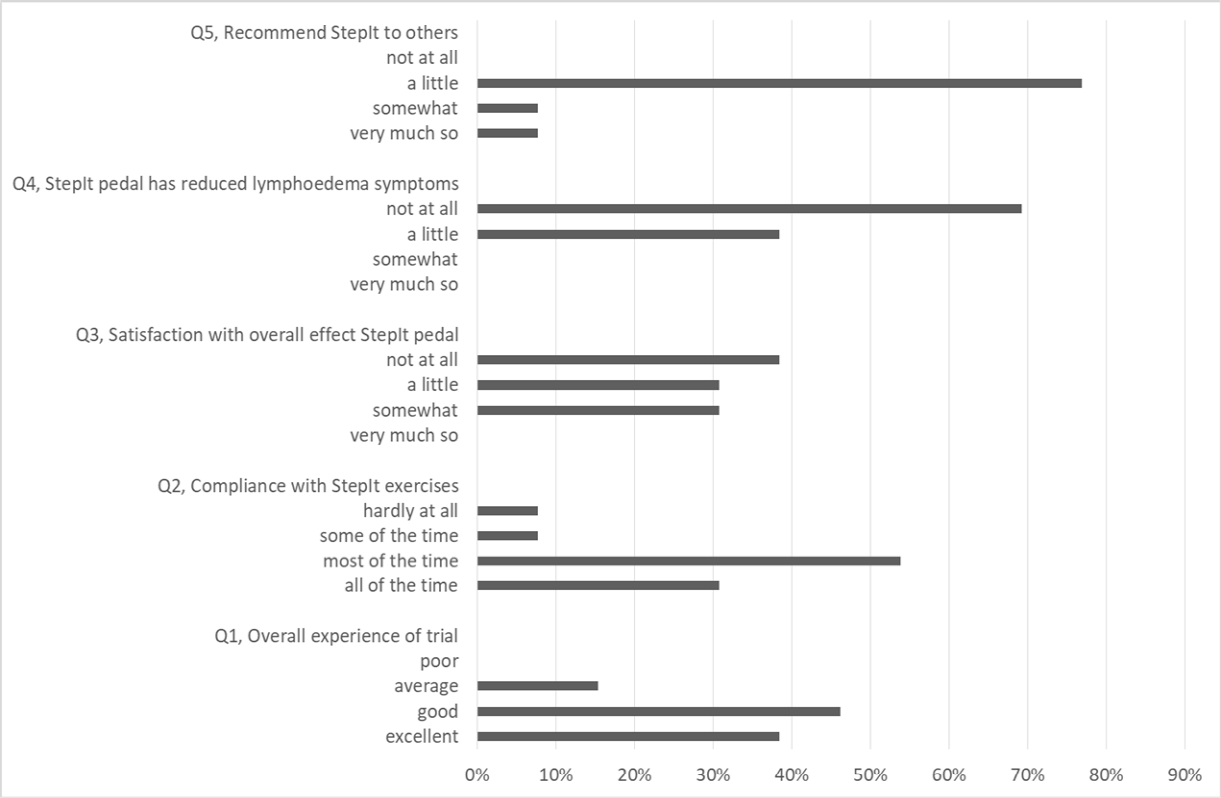

Table 3, Summary of trial feasibility findings

Methodological issues	**Findings & notes**
Appropriateness eligibility and randomisation criteria	Future studies should consider stratification for baseline lower leg volume of patients. There is variation in leg volume of up to a factor of two in this current sample. The underlying pathology causing the leg lymphoedema is poorly recorded in medical records, but can be used to further control the sample. A very high BMI is common in patients with diagnosis of leg lymphoedema; it should be considered if a BMI > 50 is an appropriate cut-off or whether it should be lower, to enable more precise leg volume measurement.
Were clinical staff willing to recruit and follow-up patients?	After initial positive start, recruitment rate from specialist leg lymhoedema services waned and bulk of recruitment was achieved through postal inviting of patients whose medical records were screened for eligibility.

Was recruitment successful?	Recruitment rate was initially slower than anticipated due to COVID19 pandemic; eventually, more than planned 24 patients were recruited (final accrual was 27 participants).
Patients willing to participate in, and complete the trial?	Out of 75 eligible patients approached, approximately one in three patients agreed to take part in the trial. Two withdrawals from the study (see Figure 1).
Was a median and inter-quartile range of the lower leg volume obtained?	Published method was successfully applied and formula used in Excel to calculate the lower leg volume. Time consuming exercise but feasible otherwise.
Intervention acceptable and complied with?	Majority of patients rated the trial experience good or excellent (see Figure 3). However, less than half of the Step-It intervention patients complied with the exercise regime all of the time. One patient struggled to fit the exercise in around other daily commitments. Twelve out of 14 patients would only recommended the Step-It exercise 'a little' to others.
Possible to calculate intervention costs?	Yes; each StepIt pedal would cost under £20 at full retail price.
Response rates to and suitability of clinical and patient-related outcome measures.	Since outcome measures were collated at a clinic appointment, response rates were acceptable for the outcome measures. Compliance with StepIt pedal is self-reported by patients, and a digital counter for measuring StepIt device use is desired. The outcome measures applied were all validated for leg lymphoedema. More challenging is to add measurements to check venous return function in the legs. Relatively high BMI in this patient population makes it harder to measure leg volume precisely.
Appropriate outcome identified for definitive trial?	No discernible difference in lower leg volume, or (lymphoedema-specific) quality of life, could be observed with the Step-It pedal exercise regime versus no intervention controls. These outcome measures are established tools used in leg lymphoedema trials and are probably suitable outcome measures. The challenge is whether daily calf muscle exercise, with eg Step-It pedal, is feasible for leg lymphoedema patients and if it has a positive effect on lymphoedema symptoms. Four adverse events amongst 14 StepIt participants, all with possible link to use of the pedal, is cause for careful monitoring if StepIt pedal is to be used in future in this patient population.

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