

BMJ Open manuscript- LF-EMS in advanced CHF

1 **Randomised feasibility trial into the effects of low frequency electrical muscle**
2 **stimulation in advanced heart failure patients**

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11 **Abstract**

12 **Objectives:** Low Frequency Electrical Muscle Stimulation (LF-EMS) may have the
13 potential to reduce breathlessness and increase exercise capacity in the chronic
14 heart failure population who struggle to adhere to conventional exercise. The study's
15 aim was to establish if a randomised controlled trial of LF-EMS was feasible.

16 **Design and setting:** Double blind (participants, outcome assessors), randomised
17 study in a secondary care outpatient cardiac rehabilitation program.

18 **Participants:** Severe heart failure patients (New York Heart Association class III-IV)
19 with left ventricular ejection fraction <40% documented by echocardiography were
20 eligible.

21 **Interventions:** Participants were randomised(remotely by computer) to 8 weeks (5 x
22 60 mins per week) of either LF-EMS intervention (4Hz, continuous, n=30) or SHAM
23 placebo (skin level stimulation only, n=30) of the quadriceps and hamstrings
24 muscles. Participants used the LF-EMS straps at home and were supervised weekly

25 **Outcome measures:** Recruitment, adherence and tolerability to the intervention
26 were measured during the trial as well as physiological outcomes (primary outcome:
27 6 minute walk, secondary outcomes: quadriceps strength, quality of life and physical
28 activity).

29 **Results:** Sixty of 171 eligible participants (35.08%) were recruited to the trial. 12
30 (20%) of the 60 patients (4 LF-EMS, 8 SHAM) withdrew. Forty one patients (68.3 %),
31 adhered to the protocol for at least 70% of the sessions. The physiological measures
32 indicated no significant differences between groups in 6 minute walk
33 distance,(P=0.13) and quality of life, (P=0.55) although both outcomes improved
34 more with LF-EMS.

35 **Conclusion:** Severe heart failure patients can be recruited to and tolerate LF-EMS
36 studies. A larger Randomised Controlled Trial (RCT) in the advanced heart failure
37 population is technically feasible, although adherence to follow-up would be
38 challenging. The preliminary improvements in exercise capacity and quality of life
39 were minimal and this should be considered if planning a larger trial.

40 **Trial registration number: ISRCTN16749049**

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42 **Strengths and Limitations**

- 43 1. To our knowledge, this was the first study to evaluate the design of a study into
44 LF-EMS in advanced (NYHA III-IV) heart failure patients
- 45 2. Analysis of recruitment, retention and adherence in this hard to reach group
46 contributes useful knowledge to the heart failure literature on how practical
47 exercise interventions could be implemented.
- 48 3. This study was a real-world feasibility study. Advanced heart failure patients
49 were recruited when deemed eligible by experienced clinicians based on
50 available information. This approach can be subjective and lead to variability in
51 disease severity in our sample. However this is in keeping with the pragmatic
52 aim of our trial and provides external validity to our findings.
- 53 4. This study had a small sample size, and was not powered or designed to
54 assess the effects of LF-EMS in advanced heart failure. The findings should
55 therefore be considered preliminary.

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57 **Introduction**

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59 Chronic Heart Failure (CHF) affects approximately 26 million people worldwide, ¹
60 and is associated with a poor prognosis; 30- 40% of patients diagnosed with heart
61 failure die within a year. ² Patients in New York Heart Association (NYHA) class
62 III/IV are unable to perform the simplest daily activities, become depressed and have
63 a poor quality of life.³

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65 Regular aerobic exercise reduces breathlessness and muscle dysfunction for
66 individuals with CHF whilst improving exercise capacity.^{4,5,6} According to the
67 ExTraMATCH meta-analysis,⁷ exercise training leads to a 35% relative reduction in
68 mortality, similar to the effects of beta-blockers⁸ and ACE inhibitors.⁹ However,
69 those with advanced CHF are often so limited that they are unable to gain the holistic
benefits of exercise.^{4,7}

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71 Electrical Muscle Stimulation (EMS) may provide an alternative rehabilitative
72 therapy for this group. In patients with mild to moderate CHF, EMS can improve
73 muscle strength of the legs, exercise capacity and quality of life. ^{10,11,12} Low
74 frequency (4-5Hz) electrical muscle stimulation (LF-EMS) produces shivering-like
75 sub-tetanic muscle contractions that can stimulate an aerobic response equivalent to
76 51% of maximal oxygen uptake.¹³ Therapeutic levels of aerobic exercise can thus be
77 achieved passively by LF-EMS,¹⁴ and it has been shown to be comfortable and well
78 tolerated in healthy individuals and those with mild to moderate CHF. ^{15,16} However,
79 the impact of LF-EMS in advanced heart failure (NYHA class III/IV) patients is
80 currently unknown. As advanced heart failure patients have shown poor uptake and
81 adherence to intervention studies,¹⁷ a preliminary study was needed to determine the
82 feasibility of LF-EMS in this patient cohort prior to the development of a large-scale
definitive trial.

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84 Based upon recommendations for good practice in the design of pilot and
85 feasibility studies ¹⁸ this study was undertaken with the following aims: To (a) test the
86 robustness of the study protocol for a potential future trial, (b) estimate rates of
87 recruitment, consent and retention, (c) determine the tolerability of the LF-EMS
88 intervention and the effectiveness of the sham placebo in the NYHA III/IV CHF
89 population, and (d) gain initial estimates of the efficacy of LF-EMS for all potential
90 primary outcomes. This can be used for sample size calculations in future
substantive trials.

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92 **Methods**

93 **Experimental Design**

94 This feasibility study used a double blind parallel group randomised control
95 design. Participants were randomised to either LF-EMS or 'sham' placebo for a
96 period of eight weeks and blinded to group allocation. Outcomes were assessed at
97 baseline (pre randomisation), eight weeks and 20 weeks follow-up.

98 **Recruitment and screening**

99 Between October 2013 and March 2015, University Hospital Coventry and
100 Warwickshire, (UHCW) Hospital NHS Trust heart failure clinics lists were screened
101 for patients fulfilling the eligibility criteria for the study. Sixty eligible participants were
102 recruited. The study conformed to the Declaration of Helsinki and was approved by
103 the local NHS Ethics Committee. All participants provided written informed consent.

104 **Randomisation**

105 The trial statistician, in conjunction with Warwick Clinical Trials Unit generated
106 the randomisation sequence remotely (by computer) using permuted block
107 randomisation. Group allocation was concealed from outcomes assessors and
108 participants.

109 **Participants**

110 Male and female adults, >18 years old, with stable CHF, documented by
111 echocardiography of left ventricular systolic dysfunction (ejection fraction < 40%)
112 were eligible for the study. All participants had New York Heart Association (NYHA)
113 functional class III-IV symptoms as judged by an experienced heart failure
114 cardiologist. Participants were required to be medically stable, defined as the
115 absence of hospital admission or alterations in medical therapy within the preceding
116 two weeks. Exclusion criteria for safety and practical reasons were: (1) presence of
117 implantable cardiac devices, (2) serious cardiac arrhythmias, (3) neurological
118 disorders or previous stroke significant enough to limit exercise, (4) orthopaedic
119 problems that prevented walking, (5) neuromuscular disease, (6) dementia or (7) a
120 mid-thigh circumference of more than 50cm (due to the size of the LF-EMS straps).

121 **LF-EMS Stimulation**

122 The LF-EMS equipment (Biomedical Research Limited, Galway, Ireland)
123 consisted of a pair of neoprene straps containing built-in adhesive gel electrodes.
124 The equipment is CE marked under the European Medical Device Directive. The
125 stimulator current waveform was designed to produce rhythmical contractions in the
126 leg muscle groups occurring at a pulse frequency of 4-5Hz (pulse width: 620µs).
127 The maximum peak output pulse current used was 140mA.

128 **LF-EMS intervention**

129 Participants used the LF-EMS or sham placebo for one hour, five times a
130 week, for eight consecutive weeks. Of the five hourly sessions per week, four were

131 completed unsupervised in the participant's own home. The remaining session was
132 conducted in a cardiac rehabilitation outpatient setting under the supervision of an
133 exercise physiologist. The LF-EMS technology was retrospectively interrogated (i.e.
134 at the weekly supervised sessions) to report date, frequency, duration and
135 stimulation intensity.

136 **'Sham' Placebo intervention**

137 In the sham arm of the study, participants were provided with identical straps
138 and electrodes. In contrast to the LF-EMS group the controller was programmed to
139 deliver a very low level of stimulation (Frequency: 99Hz, pulse width: 150µs,
140 maximum current amplitude: 7.3mA). This provided sensory input to the skin surface
141 but little or no muscle activation. Participants in the sham group had the same
142 induction, supervision and follow-up as the intervention arm.

143 **Outcome Measures**

144 **Feasibility criteria**

145 In relation to the design of pilot and feasibility studies, Thabane et al,¹⁹
146 recommends stipulating criteria for success '*a priori*'. The feasibility criteria were:

- 147 1. *Recruitment rate* – At least 40% of eligible participants recruited to the trial
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- 149 2. *Retention* – no more than 33% of participants drop out during the intervention
150 period.
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- 152 3. *Adherence* – 66% of participants tolerate the intervention and adhere to the
153 protocol for ≥70% of the intervention period.
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- 155 4. *Placebo efficacy*- Participants would be able to guess their group allocation
156 no more often than would be expected by chance.
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158 **Primary outcome**

159 **Six Minute Walk Test (6MWT).**

160 The 6MWT was conducted in accordance with the American Thoracic Society
161 (ATS) guidelines.²⁰ Participants were instructed to walk as far as possible in six
162 minutes along a 30m, flat, obstacle free corridor, turning 180 degrees at the end of
163 every 30m. Standardised instructions and verbal encouragement were given.

164 **Secondary outcomes**

165 **Isometric muscle strength**

166 A hand held dynamometer (MicroFET2 Torque/Force indicator, Hoggan
167 Health Industries, Utah, US) validated for assessing functional leg strength in elderly
168 populations was used.²¹ Participants sat in an elevated chair and were instructed to

169 maximally extend the knee while the assessor provided an equal and opposite
170 resistive force, against the lower shin. Mean force generated was measured in
171 Newtons.

172 **Quality of Life: Minnesota Living with Heart Failure Questionnaire (MLHFQ)**

173 The MLWHF questionnaire is a disease validated questionnaire,²² that has
174 been extensively used in heart failure studies. Questionnaire scores range from 0 to
175 105, with higher scores reflecting lower Quality of life. Participants were asked to
176 answer each question based on their perception of health in the week previous to
177 testing.

178 **Physical Activity levels**

179 Physical activity levels were measured by the Bodymedia© SenseWear Pro3
180 Armband. The multi-plane accelerometer was worn continuously for the seven days
181 prior to testing to determine Total Energy Expenditure (TEE) per 24hr period was
182 used as the main indicator of physical activity.

183 **LF-EMS acceptability questionnaire**

184 At the end of the trial participants were given a brief questionnaire used in previous
185 LF-EMS studies,^{13,14} to collect feedback on the acceptability of using LF-EMS
186 regularly. Questions used the likert scale and covered ease of use, comfort,
187 tolerability and overall satisfaction.

188 **Safety: Blood test**

189 Venous blood samples were taken at baseline, four weeks and eight weeks to
190 assess creatine kinase (CK), urea, and electrolytes. Participants would discontinue
191 the trial if levels exceeded the upper limit of normal reference ranges

192 **Data analysis**

193 Data analyses for the feasibility objectives of this study were descriptive,
194 based on the pre-determined levels specified above. Confidence intervals (set at
195 95%) were calculated for all secondary outcome measures in both groups and paired
196 two-sample t-test conducted for between group comparisons. Intent-to-treat (ITT)
197 analysis was employed in this study as is recommended for clinical trials.²⁴

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200 **Results**

201 **Feasibility criteria outcomes**

202 *Recruitment*

203 There were 171 eligible participants identified in the Coventry and
204 Warwickshire area from November 2013 - April 2015. Sixty of 171 eligible
205 participants (35.08%) were recruited to the trial. Participants were randomised and
206 started on the trial during this period and were followed up until data collection
207 finished in August 2015. Participant characteristics are presented in Table 1.

208

209 Table 1. Baseline demographic and clinical characteristics of the LF-EMS and sham
 210 placebo groups. Data presented as mean \pm SD or absolute number and percent.

211	Demographics	LF-EMS (n=30)	Sham (n=30)
212	n Male	20 (66%)	22 (73%)
213	Age (yrs)	66.5 \pm 7.8	66.8 \pm 13.5
214	Body Mass Index (kg/m ²)	30.1 \pm 4.9	27.8 \pm 4.8
215	Comorbidities		
216	Prev MI/PCI/CABG	17 (56%)	11 (36%)
217	Diabetes	12 (40%)	10 (33%)
218	COPD	9 (30%)	8 (26%)
219	AF	20 (66%)	16 (53%)
220	Hypertension	13 (43%)	10 (33%)
221	CKD	5 (16%)	13 (43%)
222	Clinical		
223	NT-pro-BNP (pg/mL)	3086 \pm 3746	2046 \pm 2545
224	Creatinine (μ mol/L)	108 \pm 49	113 \pm 39
225	LVEF %	39 \pm 11*	22 \pm 12**
226	BP _{sys} (mmHg)	118 \pm 16	126 \pm 17
227	BP _{dia} (mmHg)	69 \pm 9	74 \pm 14
228	NYHA III	24 (80%)	22 (73%)
229	NYHA IV	6 (20%)	8 (26%)
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231 NT-pro-BNP (pg/mL), N-terminal pro B-type natriuretic peptide; LVEF; left ventricular
 232 ejection fraction; BP_{sys} (mmHg), systolic blood pressure; BP_{dia} (mmHg), diastolic
 233 blood pressure; NYHA, New York Heart association; MI, myocardial infarction; PCI,
 234 percutaneous coronary intervention; CABG, coronary artery bypass graft surgery;
 235 COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; CKD, chronic
 236 kidney disease;

237 *n=10. Ejection fraction could not be accurately assessed in all patients due to poor
 238 body habitus/atrial fibrillation. An experienced cardiac sonographer made an 'eyeball'
 239 assessment of poor left ventricular function for all other participants

240 **n=5. See previous comments.

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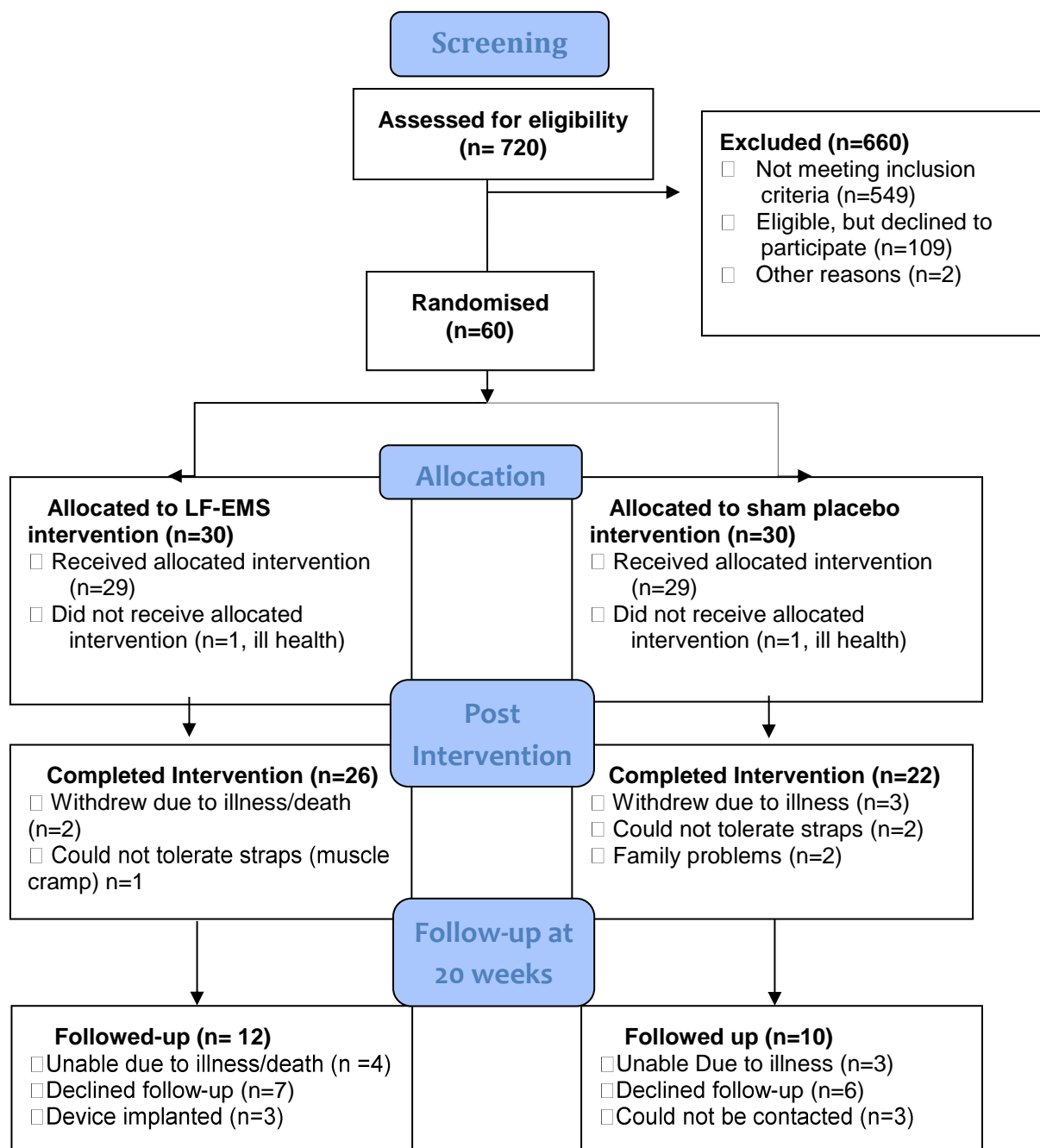
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244 *Retention*

245 Twelve of the 60 participants (4 LF-EMS, 8 sham) (20%) withdrew and did not
246 finish the intervention period (See Fig 1). Of these, only three found the intervention
247 intolerable (1 LF-EMS, 2 sham). Other reasons for dropout were: deterioration in
248 health (n= 6) family problems (n=2) and implantation of a cardioverter defibrillator
249 (ICD) (n=1). Only 22 (45%) of those completing the intervention period returned for
250 follow-up testing at 20 weeks. Reasons for non-follow-up were: deterioration in
251 health (n=9), excluded due to implantation of cardiac resynchronisation therapy
252 device (n=2), declined to take part without further explanation (n=13), and could not
253 be contacted after repeated attempts (n= 3).

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275 Figure 1. Flow diagram of a single centre blinded parallel group randomised
276 feasibility trial of electrical muscle stimulation versus sham placebo in severe heart
277 failure patients.

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282 *Adherence*

283 Forty one (85.4 %) of the 48 participants (22-LF-EMS, 19-SHAM) who
284 completed the intervention period (68.3% of the total sample) adhered to the strict
285 protocol for the majority (>70%) of the eight weeks. Interrogation of the LF-EMS
286 controllers revealed that participants in the LF-EMS group became more tolerant to
287 the intervention; mean stimulation intensity increased from 57.79mA (95%CI: 51.16
288 to 64.42) during week 1 of the study to 84.86mA (95%CI: 75.44 to 94.28) by week 8,
289 an improvement of 46.5%.

290 *'Sham' Placebo*

291 The sham placebo for the study appeared to be convincing as only 61% of
292 participants guessed their treatment group correctly. The 95% confidence interval
293 for the proportion of participants guessing correctly was (46% to 74%) and thus not
294 significantly different from 50% which would be expected by chance. Furthermore,
295 participants demonstrated an inclination to guess that they were randomised to LF-
296 EMS regardless of group allocation.

297 *Safety*

298 No abnormalities were detected in CK, urea or electrolytes taken before,
299 during or after the study. Likewise, no adverse events due to the intervention were
300 recorded in either group.

301 *Primary outcome- 6-minute walk test*

302 Non-significant improvements after LF-EMS (8 week time point) and sham groups
303 were observed in 6 MWD with a mean increase from baseline of 24m (P=0.13)in the
304 LF-EMS group (Table 2.)

305 *Secondary outcomes*

306 Table 2 shows the mean values of the secondary outcome measures at each
307 time point. There were no significant differences between groups in the change from
308 baseline for any of the secondary outcome variables (Table 3). There was a non-
309 significant improvement in quality of life in both groups.

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313 Table 2: Outcome measurements – Time point averages and 95% confidence
 314 intervals (CI)

Outcome	Time point	LF-EMS	Sham
Mean 6 MWD (metres) [95% CI]	Baseline	283 [237 – 328]	290 [243 – 337]
	(<i>n</i>)	29	29
	8 weeks	312 [262 – 362]	318 [270 – 365]
	(<i>n</i>)	26	22
	20 weeks	257 [173 – 342]	226 [126 – 325]
	(<i>n</i>)	12	10
(Mean leg strength (newtons) [95% CI]	Baseline	234.3 [196.5 – 272.]	297.5 [253 – 342]
	(<i>n</i>)	29	29
	8 weeks	224.9 [187.5 – 262.3]	321 [267.8 – 374.3]
	(<i>n</i>)	25	22
	20 weeks	181.6 [131.7 – 231.5]	207.1 [148.6 – 265.7]
	(<i>n</i>)	11	10
Mean QoL (score) [95% CI]	Baseline	53.1 [42.7 – 63.5]	50 [40 – 60.1]
	(<i>n</i>)	28	29
	8 weeks	43.9 [34.2 – 53.5]	43.1 [30.9 – 55.3]
	(<i>n</i>)	25	22
	20 weeks	51.7 [31.6 – 71.8]	37.0 [16.9 – 57]
	(<i>n</i>)	12	10
Mean TEE (joules) [95% CI]	Baseline	63,438 [56,170 – 70,705]	65,371 [59,675 – 71,067]
	(<i>n</i>)	25	27
	8 weeks	59,783 [51,094 – 68,471]	59,687 [50,630 – 68,745]
	(<i>n</i>)	19	17
	20 weeks	61,878 [53,345 – 70,410]	63,541 [55,795 – 71,287]
	(<i>n</i>)	7	6

315 6 MWD, 6 minute walk distance, QoL, quality of life; TEE, Total Energy Expenditure

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317 Table 3: -Changes from baseline averages and 95% confidence intervals (CI)

Outcome	Time point	LF-EMS	Sham	p-value
Mean 6 MWD (metres) [95% CI]	Baseline to 8 weeks	24 [9 – 40]	9 [-4 – 22]	0.1366
	(n)	26	22	
[95% CI]	Baseline to 20 weeks	0 [-32 – 31]	-26.30 [-63 – 11]	0.2409
	(n)	12	10	
(Mean leg strength (newtons) [95% CI]	Baseline to 8 weeks	-9.2 [-28.9 – 10.5]	6.0 [-19.3 – 31.4]	0.3244
	(n)	25	22	
[95% CI]	Baseline to 20 weeks	-43.4 [-78.7 – -8.2]	-74.1 [-116.3 – -31.9]	0.2223
	(n)	11	10	
Mean QoL (score) [95% CI]	Baseline to 8 weeks	-7.6 [-15.5 – 0.3]	-4.7 [-10.5 – 1.0]	0.5505
	(n)	25	22	
[95% CI]	Baseline to 20 weeks	1.5 [-12.5 – 15.7]	-14.0 [-34 – 6]	0.1610
	(n)	12	10	
Mean TEE (joules) [95% CI]	Baseline to 8 weeks	-4635 [-3963 – 4692]	-8168 [-14,342 – -1995]	0.5108
	(n)	19	17	
[95% CI]	Baseline to 20 weeks	1686 [-6435 – 9809]	4177 [-7695 – 16,050]	0.6634
	(n)	7	6	

318 6 MWD, 6 minute walk distance; QoL, quality of life; TEE, Total Energy Expenditure

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322 **Acceptability questionairre**

323 Participants responses to the LF-EMS acceptability questionairre
 324 are summarised in table 4. The mean response to putting on the straps was 2 ('quite
 325 easy') and the overall mean satisfaction of participants with the intervention was 6
 326 out of 10. Mean responses to comfort, sensation, tolerabilty and continued use of LF-
 327 EMS were between 3 (medium) and 4 (quite hard/unpleasant).
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329 Table 4. Mean responses to acceptability questionairre and standard deviations

Question	Mean response
1. I found putting on the straps (1-easy, 5-hard)	2.0 (± 1.17)
2. At the highest intensity I found the comfort level (1-acceptable, 5-unacceptable)	3.5 (± 1.19)
3. Overall I found the sensation (1-pleasant, 5-unpleasant)	3.3 (± 1.13)
4. I found putting on the LF-EMS for an hour (1-easy, 5-hard)	3.1 (± 1.08)
5. I think I would find staying on a LF-EMS training routine (1-easy, 5-hard)	3.4 (± 1.29)
6. Overall satisfaction with LF-EMS as a way of improving your fitness (1-none,10 extremely satisfied)	6.0 (± 1.94)

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331 **Sample size calculation**

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 333 The point estimate from the study and the upper CI limit of this estimate were
 334 calculated. The upper CI limit was used for the sample size calculation. For
 335 detecting the observed difference of 13.4 metres in this study a sample size of 240
 336 patients per group would be required. However, a recent study²⁵ suggested that the
 337 minimal clinically important difference for 6MWD is 36 metres in mild-moderate CHF
 338 patients. The clinical benefit of the effect size in this study should be considered
 339 before proceeding with a larger trial

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342 **Discussion**

343 The predetermined criteria for proceeding to a larger trial were achieved for dropout
344 (20%), adherence (68.3%) and sham placebo efficacy (61.53% participants guessed
345 correctly). However, only 35.06% of eligible patients were recruited, below the target
346 of 40%. Initial outcome measures revealed no significant difference between
347 intervention and placebo groups, although there was a non-significant improvement
348 in 6MWD and quality of life after LF-EMS.

349

350 **Feasibility outcomes**

351 *Recruitment*

352 Percentage uptake (35.06%) of eligible patients in the study was below the
353 predetermined criteria of 40%. This is similar to the poor uptake of conventional
354 cardiac rehabilitation (CR) nationally in the UK: less than 40% of eligible heart failure
355 patients accessed CR in the most recent National Audit of Cardiac Rehabilitation.²⁶

356 *Retention/adherence/tolerance*

357 One strength of this study is the good level of adherence (68.3%) and
358 retention (80%) compared with other clinical studies; In the HF-ACTION trial,²⁷ only
359 40% of patients in the exercise group (n=1159) reported adherence to recommended
360 training volumes after three months. This may have been because of the ease of
361 independent use at home of LF-EMS, in combination with the weekly supervised
362 sessions with an exercise physiologist. The patients recruited in the present trial
363 were more debilitated yet they engaged more with LF-EMS than those in the HF-
364 ACTION trial,²⁷ suggesting that LF-EMS maybe more acceptable to this population
365 than conventional exercise.

366 The dropout at 3 months follow-up was lower than expected due to ill health,
367 device implantation and apathy, and would be challenging to overcome in a larger
368 trial. Strategies to combat dropout could include combining assessment with clinical
369 patient appointments to ensure compliance or arranging home visits for some
370 assessments.

371 Feedback from the acceptability questionnaires may also be useful in
372 curtailing dropout in a larger trial: the LF-EMS group generally thought that wearing
373 the straps for an hour was 'medium' to 'quite hard/unpleasant'. Continued use of a
374 LF-EMS was deemed challenging also so it is possible that a reduced frequency of
375 LF-EMS whilst still maintaining a sufficient dose e.g. 3 x 1 hr a week may enhance
376 long term adherence.

377 Tolerance to the LF-EMS intervention improved during the study. Mean
378 current intensity increased by 46% from week one to week eight. This tolerance
379 effect is in keeping with an earlier study by Crognale, et al,¹³ that showed a 20%
380 increase in healthy active adults. The active adults tolerated higher absolute
381 stimulation levels than in this study, both before and after habituation, suggesting
382 that advanced CHF patients are subjectively less tolerant to LF-EMS than a healthy

383 population. In addition, the user feedback collected seems to support this view.
384 Vivodtzev and colleagues,²⁸ examined factors determining tolerance of EMS in
385 pulmonary patients. The study reported that lower tolerance to EMS was associated
386 with greater severity of condition, fat free mass and inflammatory response. It is
387 possible that the same is true in the CHF population but more research is needed to
388 confirm this.

389 Outcome Measures

390 Baseline 6MWD was higher in our study sample than in other advanced heart failure
391 studies.²⁹ This may have been due to high variability because of a few outliers in
392 each group. This reflects the subjective nature of the NYHA classification system.
393 However, signs and symptoms of advanced heart failure were primarily the eligibility
394 criteria for this study and not 6MWD. In addition, the ≤ 300 -m distance cutoff (below
395 which our baseline mean falls) is often cited, as prognostically important and
396 reflective of advanced disease in many investigations.^{30,31,32} The non-significant
397 improvements in exercise capacity as measured by 6 minute walk were smaller than
398 those in a meta-analysis of EMS in heart failure patients by Smart, Dieberg and
399 Gialluria.¹⁰ These authors reported a combined improvement in 6MWD of 46.9m vs
400 usual care or placebo, compared to the effect size of 13.2m in this study. However,
401 patients in this study were more symptomatic than those included in the meta-
402 analysis,¹⁰ and thus had a lower baseline exercise capacity (286m vs 342m.)
403 Nevertheless the mean relative increase (5%) in walk distance of participants in the
404 LF-EMS group is within the measurement error associated with this test,³³ and
405 probably should not be considered clinically significant.²⁵ The extrapolation from
406 these results that severe CHF patients are beyond help from EMS maybe premature;
407 a longer training period maybe required to show meaningful changes in exercise
408 capacity, particularly as some participants took longer to tolerate meaningful EMS
409 intensities than others.

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411 Quality of life (MLHFQ) improved in both groups after the intervention. This may, in
412 part, relate to the psychosocial benefits of engaging with researchers regularly in the
413 cardiac rehabilitation facility.³⁴ The placebo effect of both interventions and its
414 influence on patients' perception of well-being should not be underestimated.

415 Based on previous research by Banerjee et al,^{15,16} and numerous high
416 frequency EMS studies,^{35,36,12} improvement in leg strength after use of LF-EMS was
417 expected. The current trial however, showed no significant change in muscle
418 strength. Muscle wasting, prevalent in many advanced heart failure patients,³⁷ could
419 explain this observation. The chronic impairment of muscle tissue caused by heart
420 failure affects the muscle and skin nerve receptors and hence contractility of the
421 weakened muscle.³⁸ Participants with more functional leg muscles therefore, may
422 have received greater stimulus to muscle tissue that others did for the same level of
423 current intensity. This suggests that LF-EMS may not be effective for all advanced
424 CHF patients.

425 Limitations

426 The sample for this study was small as is recommended for feasibility
427 studies¹⁹ and this limits the external validity of our findings. Participants were
428 deemed eligible for the study based on the judgment of experienced heart failure

429 clinicians using available knowledge. This may have led to greater variability in
430 disease severity/limitation than was intended. The current amplitude (mA) stimulus
431 intensity that participants chose to use was a limitation to the study design.
432 Participants were instructed to adhere to the 'maximum tolerable intensity' during LF-
433 EMS sessions. Due to considerable individual differences in the subjective
434 perception of discomfort associated with EMS, It is therefore likely that there was
435 variability in the intensity that individuals received

436 **Conclusion**

437 As some of the predetermined feasibility criteria were met in this trial, a larger
438 study into the effects of LF-EMS on advanced heart failure patients could be
439 undertaken. However this 'difficult to engage with' patient group would be very
440 challenging to recruit and follow-up in sufficient numbers to provide definitive data on
441 its efficacy. The improvements seen in this study in 6MWD, and quality of life
442 measures, were not statistically significant. Leg strength and physical activity levels
443 showed no significant change. A longer intervention period than 8 weeks could be
444 considered, to give participants more time to adjust to the intervention. More
445 investigation is required to determine which CHF patients are unresponsive to LF-
446 EMS due to severe muscle dysfunction.

447 A larger trial may be feasible with this difficult population: however, it is
448 unlikely that the non-significant improvement in exercise capacity and quality of life
449 found in this pilot study justifies a larger pragmatic trial.

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462 **Author contributions**

463 SE, GM and PB contributed to the conception of the work. SE, GM, PB, SS, HJ, RS,
464 and TH contributed to the design of the work. SE and GM contributed to the
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466 analysis, or interpretation of data for the work. SE and GM drafted the manuscript.
467 PB, SS, HJ, RS, and TH critically revised the manuscript. All gave final approval and
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473 The Author(s) declare(s) that there is no conflict of interest

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481 **Data sharing statement**

482 All available data can be obtained by contacting the corresponding author:

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