Statistical Analysis Plan (SAP)

A Multicentre Randomised Controlled Study: Does **N**euromuscular **E**lectrical **S**timulation Improve the Absolute Walking Distance in Patients with **I**ntermittent **C**laudication (NESIC) compared to best available treatment?

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1. Abbreviations

ABPI	Ankle Brachial Pressure Index
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
AWD	Absolute Walking Distance
BMI	Body Mass Index
BMT	Best Medical Therapy
CACE	Complier Average Causal Effect
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
DMEC	Data Monitoring and Ethics Committee
DU	Duplex Ultrasound
EA	Exercise Advice
eCRF	Electronic Case Report Form
EME	Efficacy and Mechanism Evaluation
EQ-5D-5L	EuroQoL five dimensions questionnaire (EuroQoL 5D – 5L) on five-levels scale
GMP	Good Manufacturing Practice
HRA	Health Research Authority
IC	Intermittent Claudication
ICD	Initial Claudication Distance
ICMJE	International Committee of Medical Journal Editors
ICQ	Intermittent Claudication Questionnaire
ICTU	Imperial Clinical Trials Unit
IPC	Intermittent Pneumatic Compression
IQR	Inter-quartile range
ITT	Intent to Treat
LAET	Local Available Exercise Therapy
LDF	Laser Doppler Flowmetry
MCS	Mental Component Score
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMES	Neuromuscular Electrical Stimulation
PAD	Peripheral Arterial Disease
PCS	Physical Component Score
PCS	Physical components score
PP	Per Protocol
QA	Quality Assurance
QALY	Quality-adjusted-life-year
QC	Quality Control
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SET	Supervised Exercise Therapy
SF-36	Short Form Health Survey 36-items

SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAMV	Time Averaged Mean Velocity
TMG	Trial Management Group
TSC	Trial Steering Committee
USADE	Unanticipated Serious Adverse Device Effect
VF	Volume Flow

2. Introduction

Peripheral arterial disease (PAD) generates a significant global health burden with over 202 million individuals suffering from a manifestation of this disease worldwide [1]. The impact of this burden is highly important as patients suffering from PAD are more likely to suffer co-morbid conditions related to underlying atherosclerotic disease processes [2].

Intermittent claudication (IC) is the commonest manifestation of PAD, presenting as pain in the lower limbs on exertion, which settles after a period of rest. National guidelines from the National Institute for Health and Care Excellence (NICE) [3] recommend that all patients suffering from IC should receive first line treatment of best medical therapy (BMT), which include exercise advice to control cardiovascular risk factors, and supervised exercise therapy (SET). SET involves a number of lower limb related physical activities that are undertaken for a set period and duration under the supervision of a healthcare professional.

There is a strong evidence base in favour of using SET, contributing to the NICE recommended first line therapy strategy in all IC patients. Despite these benefits, SET remains underutilised in the UK. The main reasons for this have been attributed to a lack of funding, staff and infrastructure. Where SET was available, compliance was a major concern. The reasons cited for lack of compliance include patient difficulties with travelling to the SET class, travel expenditure and time. Therefore, the actual standard of care in the majority of the UK and Ireland is best medical therapy and exercise advice only.

The proposed study is vital to robustly identify the potential contribution of a clinical change. The study compares the NMES (Neuromuscular Electrical Stimulation) to the current gold standard recommended practice of SET and to the actual standard of care offered in the majority of the UK and Ireland, which is BMT (including exercise advice). It is anticipated that compliance with NMES is likely to be better than SET as NMES devices can be used in the patient's own environment, at a time convenient to them and for a variable duration. This flexibility is in contrast to the scheduled and unlimited duration associated with a SET program schedule.

Another aspect to the study is evaluating the potential underlying mechanism by which NMES may improve lower limb IC symptoms. A number of studies evaluating IPC (Intermittent Pneumatic Compression) have shown functional and symptomatic benefit in patients suffering from IC [4]. Potential mechanisms include enhanced activation of the calf muscle pump increasing the venoarterial pressure gradient, thereby increasing the blood flow in the lower limbs. The drawbacks of IPC are that it is expensive and uses bulky equipment, the treatment takes substantial time (3-4 hours daily) and there is patient discomfort due to the pressure required to increase venous return. Lower limb NMES may mimic the effect of IPC by causing sufficient calf contraction to activate the calf muscle pump. Although haemodynamic assessment has shown significant increases in lower limb arterial blood flow measured by ultrasonography in healthy individuals that were using the Revitive IX device, further haemodynamic assessment in a robust clinical trial of NMES in IC patients will help advance our understanding and assist in developing future technology to optimise the use of this mechanism for patient benefit.

This study will enable robust research to determine definitive clinical efficacy, mechanistic evaluation and cost effectiveness of a novel intervention that will significantly impact care provision and outcomes for patients with PAD.

3. Study Objectives

The objective of the study is to assess the benefit of using a neuromuscular electrical stimulation device as an adjunct to the local standard care available at the study sites compared to local standard care alone.

The device is expected to increase the walking distance in patients with intermittent claudication, and to have an adjuvant benefit on the same when provided in addition to supervised exercise programmes. It is also expected to cause a reduction in pain symptoms and reduced likelihood of major intervention in late stage PAD.

3.1 Primary Objectives

The primary research objective is to assess the clinical efficacy of a NMES device as an adjunct to the local standard care available at the study sites in improving walking distance in patients with IC. The clinical efficacy will primarily be measured by a change in the Absolute Walking Distance (AWD) over the study protocol period, as measured by a standardised treadmill test.

3.2 Secondary Objectives

Secondary outcomes, including validated Quality of Life (QoL) questionnaires and compliance data, will assist in modelling for economic evaluation of this intervention compared to standard treatment practice. This will be used to assess cost effectiveness. The health economic assessment will be done by Dr Epstein and thus is not covered in this SAP.

Analysis will also be carried out to understand the underlying mechanisms of change in clinical and subjective outcomes. This will take the form of lower limb gross and superficial haemodynamic assessment. These assessments will be undertaken using Duplex Ultrasonography (DU) and Laser Doppler Flowmetry (LDF), respectively.

4. Study End Points

4.1 Primary Endpoint

Absolute walking distance (AWD) measured by standardised treadmill testing at 3 months (the end of the intervention period).

4.2 Secondary Endpoints

- Initial claudication distance (ICD)
- Quality of life (QoL): Intermittent Claudication Questionnaire (ICQ), EuroQoL 5D – 5L (EQ-5D-5L), Short Form 36 (SF-36)
- Haemodynamic assessment: Duplex ultrasonography, Laser Doppler Flowmetry (LDF), Ankle Brachial Pressure Index (ABPI)
- Health economic assessment
- Compliance with interventions
- Device experience questionnaire

5. General Considerations

5.1 Study Design

The NESIC trial is a pragmatic, multicentre two-arm randomised controlled study stratified by centre. There are 11 participating centres in England, distributed according to local therapy provision between SET and exercise advice only. Initially 5 SET centres and 6 exercise only centres recruited to the trial until all the SET sample of patients was recruited, subsequently 3 SET centres (Imperial, Bristol and Hull) also recruited patients for the exercise only group. Subject to any patient specific restrictions, all participants will receive the best medical therapy (BMT), which include exercise advice, and if the patient has cardiovascular risk factors, then they will aim to control this, e.g. smoking cessation, hypertensive medication and controlling diet.

5.2 Treatment

5.2.1 Supervised Exercise Therapy (SET)

The Supervised Exercise Therapy program (SET) is carried out under the supervision of a healthcare professional and entails a circuit of lower limb specific exercises for a minimum of 30 minutes per week. The Supervised Exercise Therapy program (SET) is not standardized among the centres. The number of SET sessions varies from

8 to 36, depending on the number of SET sessions per week and the number of months it is practiced for. Attendance is recorded via patient diaries (See Appendix 1 for more information).

5.2.2 Neuromuscular Electrical Stimulation Device (NMES)

The Neuromuscular Electrical Stimulation device (NMES) is recommended to the patient to be used once a day for 30 minutes, 7 days a week, for 12 weeks (84 days). The time of the day that the device is used is left up to the patient and usage is recorded via patient diaries.

5.2.3 Exercises Advice (EA)

The participants will be given standard advice on exercise as per local guidelines. The recommended minutes per week varies between centres. In general, it is recommended to perform at least 30 minutes of physical exercise 3 - 5 times per week. (A set of specific exercises is provided for each patient). Participants will be provided with a diary to note the frequency and duration of their exercise activity.

5.3 Treatment Groups

Subjects will be randomised to one of 2 treatments: the inclusion of the NMES device together with the local available exercise therapy (NMES+LAET) versus just the local available exercise therapy (LAET). Depending on the type of centre, local available exercise therapy will consist of Supervised Exercise Therapy (SET) and Exercise Advise (EA) in SET centres or exercise advice alone in non-SET centres.

Table 1 Summary of Treatment groups

Type of centre	Treatment
SET Centre	Control 1: Best Medical Therapy (BMT) + Exercise Advise (EA) + Supervised Exercise Therapy (SET) Treatment 1: Best Medical Therapy (BMT) +Exercise Advise (EA) + Supervised Exercise Therapy (SET) + Neuromuscular electrical stimulation (NMES)
Non-SET Centre	Control 2: Best Medical Therapy (BMT) + Exercise Advise (EA) Treatment 2: Best Medical Therapy (BMT) + Exercise Advise (EA) + Neuromuscular electrical stimulation (NMES)

- Treatment duration: 3 months of device use
- Follow-Up duration: 12 months (follow-up visits at 3, 6, and 12 months).

5.4 Study Population

This study is open to all patients at the participating NHS sites with a diagnosis of IC and who meet all inclusion and exclusion criteria. The 11 sites have been selected with respect to their ability to provide SET. The protocol includes a list of the recruiting centres and specifies whether the centre provides SET, or only provides exercise advice (EA).

5.5 Eligibility Criteria

The patients participating in the study must meet the following inclusion and exclusion criteria:

5.5.1 Inclusion Criteria

- Capacity to provide informed consent
- Aged 18 or above
- Positive Edinburgh Claudication Questionnaire
- ABPI <0.9 or positive stress test (fall in ankle pressure >30mmHg, 40 secs post 1 min treadmill at 10% gradient, 4 km/h).

5.5.2 Exclusion Criteria

- Severe IC requiring invasive intervention as determined by the treating clinician
- Critical limb Ischaemia as defined by the European Consensus Document
- Co-morbid disease prohibiting walking on a treadmill or taking part in supervised exercise therapy.
- Popliteal Entrapment Syndrome
- Commenced vascular symptom specific medication in previous 6 months e.g. naftidrofuryl oxalate, cilostazol
- Pregnancy Participants must be of non-childbearing potential* OR using adequate contraception for the duration of the study period and have a negative urine pregnancy test result
- Any implanted electronic, cardiac or defibrillator device
- Acute Deep Vein Thrombosis
- Broken or bleeding skin including leg ulceration
- Peripheral neuropathy
- Recent lower limb injury or lower back pain.
- Able to walk longer than 15 minutes on the study treadmill assessment **
- Already using a NMES device†
- Have attended supervised Exercise therapy classes in the previous 6 months†

*Defined as those who have no uterus, ligation of the fallopian tubes, or permanent cessation of ovarian function due to ovarian failure or surgical removal of the ovaries. A woman is also presumed to be infertile due to natural causes if she has been amenorrhoeic for greater than 12 months and has an FSH greater than 40 IU/L.

**This criterion was initially classified as a screening failure in post-randomisation because it was not documented as exclusion criteria in the protocol. An amendment to the protocol to include this as an exclusion criteria was submitted on 16th September 2019. REC/HRA approval was granted on 18th October 2019.

†These criteria were not initially part of the exclusion criteria but were checked prior to randomisation and so were excluded. An amendment to the protocol was submitted on 16TH September 2019. REC/HRA approval was granted on 18th October 2019.

With permission of the participant the reasons for non-inclusion will be logged anonymously along with a minimum data set of age, sex and ABPI and reasons for exclusion. The anonymized pre-screening logs will be transferred to the Trial Coordinating Centre for the purposes of monitoring recruitment. Written informed consent will be obtained before the subject is enrolled in the study.

5.6 Blinding

This study is unblinded.

5.7 Sample Size

Assuming that the mean AWD in the control group is 200m at 3 months [5] and a common equal standard deviation of 120m [6], without considering the dropout rate, it is estimated that a sample size of 172 participants (86 per group) will have 90% power with a two-sided alpha = 0.05 to detect a difference of 60m in the mean absolute walking distance at 3 months between the intervention and the control group.

Assuming a 10% dropout rate, the sample size required for this study is 192 participants; 96 in each arm.

5.8 Schedule of Time and Events

The actual study commenced recruitment on 21st March 2018 and was expected to recruit for 15 months but was extended to finish on 31st March 2020 (granted by REC/HRA). However recruitment was temporarily paused on 20th March 2020 due to COVID-19. The last follow up will end one year after the recruitment of the last patient. The summary table of Visit Schedule and the summary of Treatment time are displayed in Section 5.8.1 and Section 5.8.2 respectively.

5.8.1 Summary of Visit Schedule

	Screening	Baseline*	Treatment Phase	[6]Follow-up (months) [+]		
Visit	**1**	**2**		**3**	**4**	**5**
			0 - 3 months	**3 months**	**6 months**	**12 months**
Informed consent	x					
Pregnancy Test[1]	x					
Ankle Brachial Pressure index (ABPI) / positive stress test	x			x	x	x
Edinburgh Claudication Questionnaire	x					
Medical History	x					
Drug history	x			x	x	x
Peripheral pulse examination	x			x	x	x
Other exclusion criteria	x					
Randomisation		x				
Demography		x				
Vital Signs		x				
Quality of life questionnaires: EQ-5D-5L /SF-36 /ICQ		x		x	x	x
Treadmill test (ICD/ AWD)[2]		x		x	x	x
Duplex Ultrasonography		x[2]		x[2]		
Laser Doppler Flowmetry		x[2]		x[2]	x	x
NMES training[3]		x				
SET booking[4]		x				
Compliance Diary (SET[5]/device/EA)		x		x		
Resources use diary		x	x	x		
Weekly text messages			x			
Data logger		x	x			
Device experience questionnaire				x		
Safety reporting			x	x	x	x

Baseline and screening visit occur on the same day if both the researcher and participant agree that informed consent has been adequately considered with time to ask questions

[1]women of childbearing potential a required to take a urine pregnancy test

[2]At rest and during device use in device arm

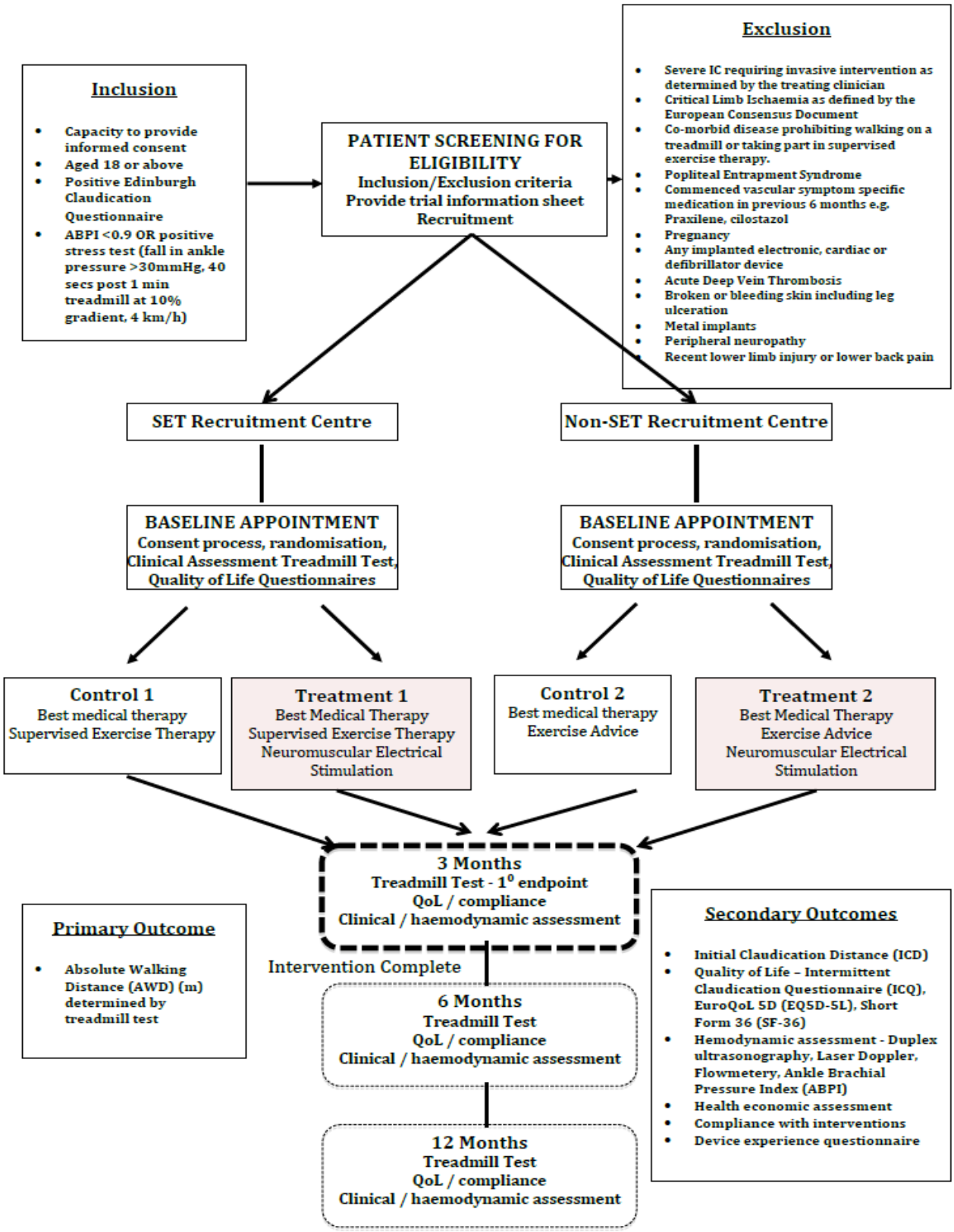
[3]NMES treatment groups only

[4]SET centres only

[5]For first 3 months (treatment period) or for whole duration they are completing SET classes (whichever is longer)

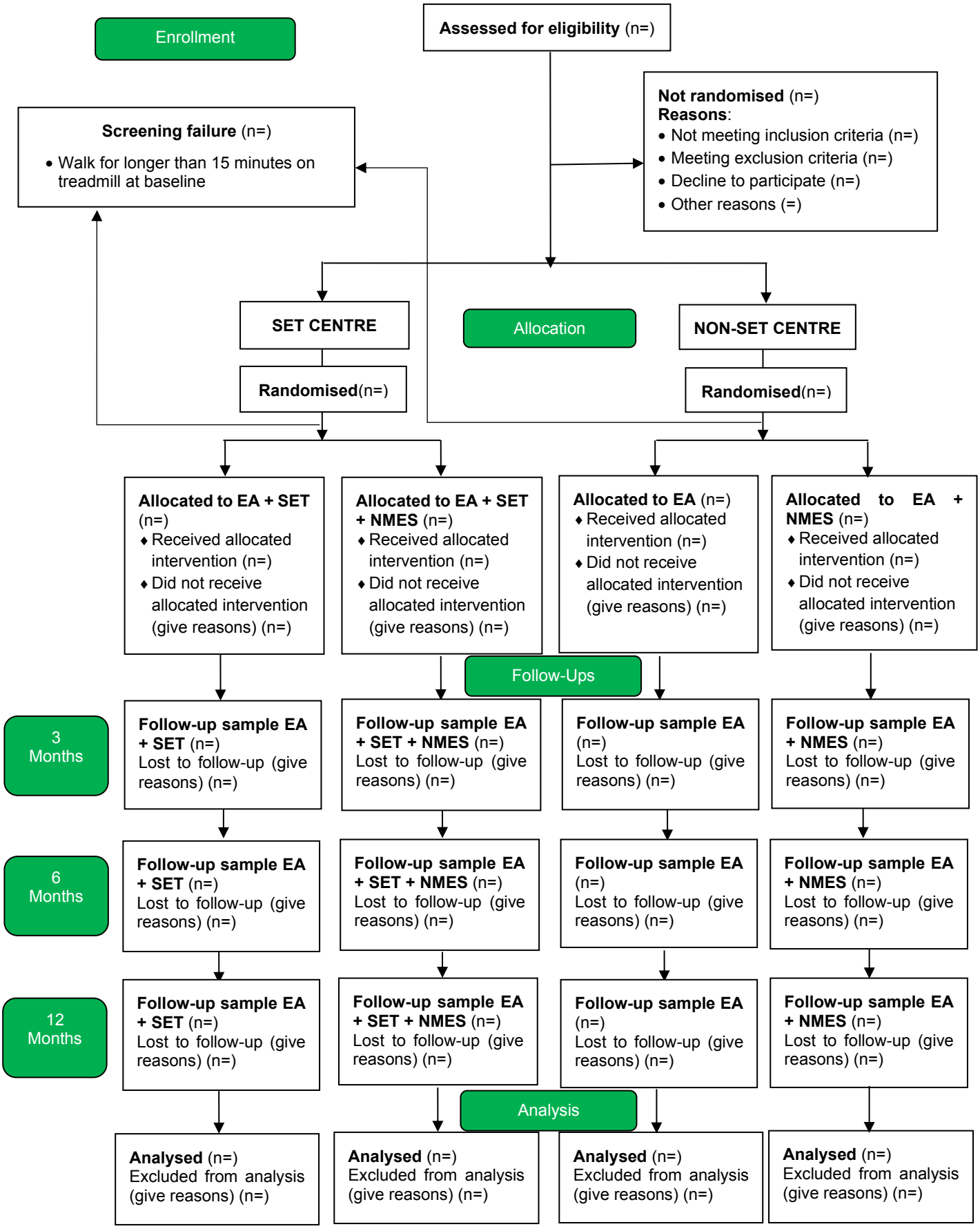
[6] The follow up information may be collected remotely (i.e. over the telephone completely or in combination with postal questionnaires) in the event that the participant is unable to attend the appointment in the clinic or the site is unable to accommodate the onsite visit due to COVID-19.

5.8.2 Summary of Treatment Plan



Details about patient enrolment, follow-up and inclusion in analysis is provided in the CONSORT diagram below.

5.8.3 Patient Flow CONSORT diagram



5.9 Randomization

Once eligibility has been confirmed, subjects will be randomised to one of the two arms of the study and assigned a pseudononymised study number unique to each individual enrolled in the trial.

Randomisation will take place via the InForm system (the electronic case report form database for the study), which will be programmed with a randomisation schedule provided by an independent statistician. Randomisation will be blocked with random block sizes and stratified by centre.

SET CENTRE randomisation:

- Control 1: EA + SET
- Treatment 1: EA + SET + NMES

Non-SET CENTRE randomisation:

- Control 2: EA
- Treatment 2: EA + NMES

6. Analysis Sets

Definition of Primary Analysis

The primary analysis will estimate the difference in the absolute walking distance at 3 months (AWD3M) between the two treatment groups NMES + local available exercise therapy (NMES+EA or NMES+EA+SET) vs. local available exercise therapy (EA or EA+SET).

There are two populations of interest: the intention to treat (ITT) population for efficacy and the per-protocol (PP) population for efficacy.

6.1 Intent-to-Treat Population

This population includes all patients, with eligibility confirmed at screening that were randomised regardless of treatment adherence. The follow-up period for these patients will be 12 months in total (with primary endpoint measured at 3 months). This analysis set will exclude all those who specifically asked to be withdrawn and their data not to be used for the trial.

If there is a difference in SET uptake, measured by number of attended SET classes over the centre specific prescribed attendance target, between the groups (NMES+SET+EA vs SET+EA), then we will conduct an appropriate analysis using CACE methods that do take into consideration non-compliance.

6.2 Per protocol Population

In SET centres the per-protocol population includes all randomized patients who participated in some or all the centre prescribed SET classes as defined in the protocol.

Participants who in SET centres did not attend any centre specific SET class are excluded.

For all centres (offering SET or not), participants who withdraw from the study before the primary outcome measurement at 3 months is carried out or withdraw from the study and explicitly decide to not allow use of the primary outcome data already collected will be excluded from this analysis set.

The per-protocol analyses will be carried out for the primary and secondary endpoints.

6.3 Subgroup Analysis

Subgroup analysis will investigate the effect of the intervention among NMES+SET+EA, NMES+EA, SET+EA, EA. We will estimate the treatment effect in the following subgroups comparisons:

- Subgroup analysis 1: Treatment effect in SET sites vs non-SET sites (NMES+SET+EA & SET+EA vs NMES+EA & EA).
- Subgroup analysis 2: Treatment effect of NMES in the SET sites (NMES+SET+EA vs SET+EA)
- Subgroup analysis 3: Treatment effect of NMES in the non-SET sites (NMES+EA vs EA)
- Subgroup analysis 4: Investigate if the treatment effect of (NMES+EA) has a similar effect as (SET+EA)
- Subgroup analysis 5: Determine if (NMES+SET+EA) is more effective than (NMES+EA)

The subgroup analyses will be on an ITT basis and only for the primary outcome measure at 3 months.

7. Variables for Analysis

7.1 Baseline Demographic Variables

The patient baseline and demographic characteristic data will be collected, on all patients, once a written consent is obtained. The information collected includes:

- Age
- Gender
- Ethnicity
- Working Status
- Performance limited due to IC
- Lifestyle (Smoking and alcohol consumption).
- Medical History
- Pregnancy
- Concomitant medication
- Pulse
- Blood Pressure
- Body Mass Index (BMI)
- Treadmill test results

7.2 Derived Variables

The following variables will be calculated using specific formulas or by using special software (see Appendix 2 - 13.2).

- Intermittent Claudication Questionnaire (ICQ) score
- Short Form 36 (SF-36) scores. There are two possible ways to obtain these scores.

Section scores

- Physical function score
- Role-Physical score
- Body pain score
- General Health score
- Vitality score
- Social functioning score
- Role-Emotional score
- Mental Health score

Summary scores

- Physical components score (PCS)
- Mental component score (MCS)

- Compliance Classification

We have classified a participant as "compliant" if they have done at least 75% of the recommended target minutes for Device use, at least 75% of the recommended EA minutes performing exercises and attend at least 50% of SET sessions by the end of the treatment period. Then compliance can be dichotomised, coding "Yes, complied" if the patient complied with the recommended threshold treatment and "No" if patient did not comply. This classification is obtained by combining the compliance classification of the three instruments used to collect compliance information from each intervention (Device, SET and EA). Procedures for these classifications are outlined in Appendix 3 section 13.3).

For each treatment group, a patient is considered compliant if they are compliant for all of their assigned treatments. Therefore, for each of the treatment groups compliance is defined as follows:

- EA: compliant if done 75% or more of recommended level of EA (75% of minutes performing exercises recommended by centre)
- EA + SET: compliant if done 75% or more of recommended level of EA and attended 50% or more SET sessions held by centre.
- EA + NMES: compliant if done 75% or more of recommended level of EA and done 75% or more of recommended level of NMES usage
- EA + SET + NMES: compliant if done 75% or more of recommended level of EA, attended 50% or more SET sessions held by centre and done 75% or more of recommended level of NMES usage

These variables, excluding compliance classification, will be summarized at follow up time periods by treatment group using the ITT analysis set. Compliance classification will be summarised at the end of the intervention period. Summaries of continuous variables will be presented as mean and standard deviations if normally distributed, and as mean and inter-quartile ranges for skewed data. Categorical variables will be presented as frequencies and percentages.

7.3 Primary Endpoint variable

Absolute walking distances (AWD) at baseline, 3, 6 and 12 months (measured in metres).

For participants who walked more than 15 minutes on the treadmill during any follow up, their AWD will be censored at 790 metres. It was communicated directly to the sites that 790 metres will be used as a censored value.

In cases that the AWD is recorded when the patient walked more than 15 minutes during the study assessment (at baseline) the patient will be removed from the analysis.

In cases that the AWD is recorded at 3, 6 or 12 months with a value equal to or greater than 790 metres the value will then be censored at 790m.

7.4 Secondary Endpoint variables

- Initial claudication distance (ICD) at baseline, 3, 6 and 12 months.
  For participants that walked more than 15 minutes, their ICD will be censored at 15 minutes. The ICD at this point will be recoded as 790 metres (same procedure used to censor cases in AWD will be applied for the ICD)
- The proportion of patients who improved AWD at each time point by
  60 metres or more from baseline
  100 metres or more from baseline
- The proportion of who improved ICD at each time point by
  60 metres or more from baseline
  100 metres or more from baseline
- Quality of life scores measured at baseline, 3, 6 and 12 months
  - Recorded ICQ Health score (calculated using the formula in Appendix 2 - Section 13.2.1)
  - Recorded EQ-5D-5L Health state score [7]

- Short Form 36 (SF-36) scores (Using Health Outcome Scoring Software 4.0 see section 13.2.2) [8]

Section scores

Recorded Physical function score
Recorded Role-Physical score
Recorded Body pain score
Recorded General Health score
Recorded Vitality score
Recorded Social functioning score
Recorded Role-Emotional score
Recorded Mental Health score

Summary scores

Physical components score (PCS)
Mental component score (MCS)

- Haemodynamic assessment:
  - Mean values of the readings taken for the Duplex ultrasonography measure at baseline and 3 months. In the control group, only resting values will be undertaken over a 3-minute period. The intervention group will have these parameters measured at rest, at 15 and 30-minutes into device use and then at 1 and 5 minutes after device cessation [9].
    - Mean Volume Flow (VF, cc/min) for one leg (Right or Left) for each patient.
    - Mean Time average Mean Velocity (TAMV, cm/s) for one leg (right or left)
  - Mean values of the readings (before use, during use and after use for the Device group and at rest for the Control group) taken for the Laser Doppler Flowmetry (LDF) measure at baseline,3,6 and 12 months
    - Mean Blood flux for one leg (Left or Right)
  - Ankle Brachial Pressure Index (ABPI) measure at baseline,3,6 and 12 months for the Left and Right Ankle

- Compliance with interventions. All compliance measures below will be summarized from each participant's personalized diary.

Supervised Exercise Therapy (SET) measured weekly from baseline to treatment, the duration of which will vary from 2 months to 6 months depending on local policy (see Appendix 3).

Total number of weeks of exercise (summarized from each participant's personalised diary).
Number of therapy sessions attended each week
Total minutes of exercise at home each week

Device - Neuromuscular Electrical Stimulation (NMES) measured daily from baseline to 3 months

Number of minutes of the NMES device use for each day
Intensity setting of the NMES device for each day's use
Some devices have a data logger that will record usage each time. Information will be recorded and uploaded at the 3 months follow up.

Exercise Advice (EA) measured weekly from baseline at 3 months

Recorded number of weeks of exercise reported in diary
Recorded total minutes of exercise at home per week

- Device experience questionnaire

A simple device use questionnaire will be administered by device users to report their subjective experience with the device. The questionnaire contains 6 questions:

- Overall, how easy did you find the device to use?
- Do you think the device helped to lessen the pain?
- Do you think you can walk further?
- Did you use the device as instructed?
- Do you think you could have used the device more often than you did?

- Did you use the device beyond the 3 months treatment?

- Compliance Classification for each of SET, NMES and EA.

7.5 Safety Variables

Adverse Event (AE). An AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons whether or not related to the investigational medical device.

Adverse Device Effect (ADE). An ADE is an adverse event related to the use of an investigational medical device resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device and/or the result of a use error or intentional misuse.

To assess patient and study safety the following variables of AE/ADE will be analysed:

- Severity of Adverse Events
- Relationship to device
- Outcome
- SAE classification
- Site

Serious Adverse Events (SAE). A Serious Adverse Event (SAE) is defined as any adverse event that has:

a) Led to a death
b) Led to a serious deterioration in health that either:
i) Resulted in a life-threatening illness or injury, or
ii) Resulted in a permanent impairment of a body structure or a body function, or
iii) Required in-patient hospitalisation or prolongation of existing hospitalisation, or
iv) Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
c) Led to foetal distress, foetal death or a congenital abnormality or birth defect.

These includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.

Serious Adverse Device Effect (SADE). A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune. SADEs can be classified into either Anticipated Serious Adverse Device Effects (ASADE) or Unanticipated Serious Adverse Device Effects (USADE).

To assess patient and study safety the following variables of SAE/SADE will be analysed:

- Reasons
- Severity of Adverse Events
- Outcome
- Causal Relationship to device
- Action taken
- Site

Protocol deviation and violations

- Protocol Deviation or Violation
- Any Protocol Deviation or Violation by Site
- Type of Protocol Deviation

Concomitant medication

8. Statistical Methodology

The planned analyses for all the endpoints are summarised in Table 2 below.

Table 2 Endpoints and related planned Statistical Analysis Summary

	End Point	Model
Continuous	Absolute walking distance (AWD) measured by treadmill testing at 3 months (censored at 15 mins and the distance reached to this point is 790 metres) ** Proportion of patients whose absolute walking distance at 3 months improved by 60 metres or more from baseline Proportion of patients whose absolute walking distance at 3 months improved by 100 metres or more from baseline	Tobit Regression for Absolute walking distance (AWD) at three months with AWD at baseline, treatment indicator, centre and group (SET vs non-SET) as covariates. Chi-square test at 3 months Chi-square test at 3 months
	Absolute walking distance (AWD) measured at 3, 6, and 12 months. This variable is censored at 15 mins and the distance reached to this point is 790 metres.	Multilevel Tobit model, treating patient as a random effect (repeated measurement) to investigate the relationship between AWD and covariates: AWD baseline measurement Treatment Time Time*Treatment interaction, Centre Group (SET vs non-SET) Age Gender BMI Smoking status
	The proportion of patients who improved AWD at each time point by • 60 metres or more from baseline • 100 metres or more from baseline	Table of proportion of AWD improvements by treatment and by visit.
Continuous	Initial claudication distance (ICD) measured at 3, 6 and 12 months. This variable is censored at 15 mins and the distance reached to this point is 790 metres.	Multilevel Tobit model Linear mixed-effects model, treating patient as a random effect (repeated measurement) to investigate the relationship between ICD and covariates: ICD baseline measurement Treatment Time Time*Treatment interaction Centre Group (SET vs non-SET) Age Gender BMI
	The proportion of patients who improved ICD at each time point by • 60 metres or more from baseline • 100 metres or more from baseline	Table of proportion of ICD improvements by treatment and by visit.

	Quality of Life (QoL)	
	ICQ health score (calculated using the formulas in Appendix 2 measured at 3, 6 and 12 months	Plot of mean ICQ health score change over time by treatment arm (mean and SD). ANCOVA model for ICQ health score on treatment group indicator, controlling for ICD baseline measurement.
	EQ-5D-5L health score measured at 3, 6 and 12 months	Plot of mean EQ-5D-5L health score changes over time by treatment arm (mean and SD). ANCOVA model for EQ-5D-5L health score on treatment group indicator, controlling for EQ-5D-5L baseline measurement.
	SF36-scores (obtained using software Appendix 2) measured at 3, 6 and 12 months Section scores Physical function score Role-Physical score Body pain score General Health score Vitality score Social functioning score Role-Emotional score Mental Health score Summary scores Physical component scores (PCS) Mental component scores (MCS)	Plot of mean SF36-scores change over time by treatment arm (mean and SD). Separate ANCOVA models for SF36 scores on treatment group indicator, controlling for the baseline measurement of the outcome being analysed.
	Haemodynamic Assessment^{T}	
	Duplex ultrasonography measure at baseline and 3 months • Mean Volume Flow (VF, cc/min) for one leg (either Right or Left) for each patient • Mean Time average Mean Velocity (TAMV, cm/s) one leg (Left or Right) 2 models	Separate Linear regression models for the Duplex ultrasonography measurements (MVF and MTAMV), using as covariates: Specific baseline measurement Treatment Time Time*Treatment interaction Centre Group (SET vs non-SET) Age Gender BMI
	Laser Doppler Flowmetry (LDF) measure at baseline,3,6 and 12 months • Mean Blood flux for one leg (Left or Right)	Separate ANCOVA models for the variables of Laser Doppler Flowmetry (LDF) on treatment group indicator, controlling the baseline measurement of the outcome being analysed.
	Ankle Brachial Pressure Index (ABPI) measure at baseline,3,6 and 12 months ABPI for the Left Ankle ABPI for the Right Ankle	Separate ANCOVA models for the variables of Ankle Brachial Pressure Index (ABPI) on treatment group indicator, controlling the baseline measurement of the outcome being analysed.

	Compliance with interventions	
Continuous	Supervised Exercise Therapy (SET) measured weekly from baseline to 3 months (recorded in participant's personalised diary**)** • Total number of weeks of exercise • Number of therapy sessions attended each week • Total minutes of exercise at home each week	Summary in a table by treatment group. -Mean (SD) -Median (IQR)
	Neuromuscular electrical stimulation measured daily from baseline to at 3 months (recorded in participant's personalised diary) • Number of minutes of the NMES device use for each day • Intensity setting of the NMES device for each day's use	Summary in a table by treatment group. -Mean (SD) -Median (IQR)
	Exercise Advice (EA) measured weekly from baseline to 3 months (recorded in participant's personalised diary) • Recorded number of weeks of exercise reported in diary • Recorded total minutes of exercise at home per week	Summary in a table by treatment group. -Mean (SD) -Median (IQR)
Categorical	Device experience questionnaire(6 questions on patient experience using the devices)	Table of summary statistics
	Compliance	Table of proportion of compliance by treatment.
	Subgroup Analysis Summary	
Continuous	Estimate the treatment effect in the SET vs the non-SET groups, at 3 months Subgroup analysis 1: SET vs non-SET groups (NMES+SET+EA & SET+EA **vs** NMES+EA & EA). Proportion of patients whose absolute walking distance at 3 months improved by 60 metres or more from baseline Proportions of patients whose absolute walking distance at 3 months improved by 100 metres or more from baseline	Tobit Regression for absolute walking distance at 3 months with AWD at baseline , Treatment, Centre and Group as covariates. Chi-square test at 3 months Chi-square test at 3 months
	Estimate the treatment effect of NMES in the SET and non-SET groups, at 3 months Subgroup analysis 2: NMES in the SET (NMES+SET+EA **vs** SET+EA) Subgroup analysis 3: NMES in the non-SET (NMES+EA **vs** EA) For both subgroups we will calculate:	Tobit Regression for absolute walking distance at 3 months with AWD at baseline ,Treatment, Centre and Group as covariates.

	• Proportion of patients whose absolute walking distance at 3 months improved by 60 metres or more from baseline	Chi-square test at 3 months
	• Proportions of patients whose absolute walking distance at 3 months improved by 100 metres or more from baseline	Chi-square test at 3 months
	Investigate if NMES+EA has similar effect as SET+EA, at 3 months Subgroup analysis 4: NMES+EA **vs** SET +EA Proportion of patients whose absolute walking distance at 3 months improved by 60 metres or more from baseline Proportions of patients whose absolute walking distance at 3 months improved by 100 metres or more from baseline	Tobit Regression for absolute walking distance at 3 months with AWD at baseline, Treatment, Centre and Group as covariates. Chi-square test at 3 months Chi-square test at 3 months
	To determine if NMES+SET+EA is more effective than NMES+EA, at 3 months. Subgroup analysis 5: NMES+SET+EA **vs** NMES+EA Proportion of patients whose absolute walking distance at 3 months improved by 60 metres or more from baseline Proportions of patients whose absolute walking distance at 3 months improved by 100 metres or more from baseline	Tobit Regression for absolute walking distance at 3 months with AWD at baseline, Treatment, Centre and Group as covariates. Chi-square test at 3 months Chi-square test at 3 months

**Primary outcome

[T] Mechanistic outcome

Summaries of continuous variables will be presented as mean and standard deviations if normally distributed, and as medians and inter-quartile ranges for skewed data. Categorical variables will be presented as frequencies and percentages in the form of summary tables.

All statistical tests will be two-tailed with a 5% significance level.

8.1 Baseline Demographics

Patient characteristics will be summarized by treatment. Refer to the table of baseline characteristics (tables 6 -12, Section 8.9.3)

8.2 Primary End Point Analysis

The primary endpoint is the absolute walking distance (AWD) measured by treadmill test at 3 months.

The measured absolute walking distance, by treatment group and time point, will be presented for all patients within the ITT population in a summary table (Table 16, Section 8.9.5).

The primary analysis will estimate the difference in the absolute walking distance at 3 months between the two treatment groups (NMES + local available exercise therapy vs. local available exercise therapy only) by using a

Tobit regression model to address the cut-off point of 15 min (where the distance reached to this point will be censored at 790 metres). The model will include the measurements of AWD baseline, treatment indicator, centre indicator and group indicator as covariates. The results of the Tobit regression model will be reported (see Table 17, Section 8.9.5).

As a secondary analysis of the primary endpoint, we will estimate the difference between the groups in the proportion of patients that increased the absolute walking distance at 3 months by 60 metres or more from baseline using a chi-square test (Table 18). This analysis will be repeated for the proportion of patients that increases the AWD at 3 months by 100 metres or more (Table 19).

A summary table of proportion of patients who increased the AWD both by more than 60 and by more than 100 metres by treatment and by visit will be presented (Table 20 and Table 21)

A Multilevel Tobit model will be used to investigate the difference in absolute walking distance between the two treatment groups at 3, 6 and 12 months adjusting for the following independent baseline covariates:

- AWD baseline measurement
- Treatment
- Time
- Time*Treatment interaction,
- Centre
- Group (SET vs non-SET)
- Age
- Gender
- BMI
- Smoking Status

The results of the Multilevel Tobit model will be presented (Table 22, Section 8.9.5)

8.3 Secondary End Points Analysis

8.3.1 Continuous Secondary End Point Analysis

The continuous variables of initial claudication distance (ICD), measured at baseline, 3, 6, and 12 months will be analysed using a Multilevel Tobit model fitted to the censored ICD measurements. The Multilevel Tobit models will be performed to investigate the effect of the treatment indicator on the changes over time (3, 6, and 12 months), treating patient as a random effect, while the baseline measurement of the continuous ICD variable , treatment, time, interaction of time*treatment, centre, group (SET vs non-SET), age, gender and BMI will be treated as covariates. Results of the Multilevel Tobit model will be presented (see Table 24 Section 8.9.6.1).

A summary table of proportion of patients who increased the ICD both by more than 60 and by more than 100 metres by treatment and by visit will be presented (Table 25 and Table 26)

The secondary end points concerned with quality of life scores (QoL) measured at baseline, 3, 6 and 12 months, will be analysed using separate ANCOVA models for each outcome variable. The measurements of quality of life are the Intermittent Claudication Questionnaire (ICQ), EuroQoL 5D 5L (EQ-5D-5L) and the SF-36.

The ANCOVA models of each of the QoL scores will be performed to investigate changes in QoL over time and to assess the difference between the two treatment groups, while controlling for the baseline measurement of the QoL score being analysed. Results of the ANCOVA models will be presented in tables (see Section 8.9.6.2).

All individual scores for ICQ, EuroQoL 5D 5L and the SF-36 will be presented as Plots. Plots of the mean QoL scores will be used to illustrate changes over time by treatment arm (Figure 1-3, Section 8.10).

Duplex ultrasonography (DU) measurements (Mean Volume Flow and Mean Time Average Mean Velocity) from the Haemodynamic assessment will be analysed using separate linear regression models. The linear regression models will be used to compare the Mean Volume Flow (VF) and Mean Time Average Mean Velocity (TAMV)

for one leg (either the left or right) at 3 months, between the intervention group and the control group, using the baseline value of the specific measurement, the treatment indicator variable, centre, group (SET vs non-SET), age, gender and BMI as covariates. Results of these regression models will be presented in tables (see Section 8.9.6.3).

Laser Doppler Flowmetry (LDF), Duplex ultrasonography (DU) measurements, (Mean Volume Flow and Mean Time Average Mean Velocity) and Ankle Brachial Pressure Index (ABPI) for Left and Right Ankle from the Haemodynamic assessment will be analysed using separated Analysis of Covariance (ANCOVA) models.

Analysis of Covariance (ANCOVA) models for the Haemodynamic assessment for both Laser Doppler Flowmetry (LDF) and Ankle Brachial Pressure Index (ABPI) will be analysed, on treatment group indicator, controlling for the baseline measurement of the outcome assessment being analysed. They will be used to explore changes over time and assess the difference between the two treatment groups. Result of these ANCOVA models will be presented in tables (see Section 8.9.6.3).

The information collected with regards to compliance will be summarized by treatment. The information will be displayed in 3 different tables, one for each intervention: Exercise Advice (EA) compliance, Supervised Exercise Treatment (SET) compliance and the Neuromuscular Electrical Stimulation device (NMES) compliance. (Section 8.9.6.4).

8.3.2 Categorical End Point Analysis

The device experience questionnaire for people who used the device will be summarized using descriptive statistics by treatment.

For the compliance classification a table of proportion of compliance by treatment will be presented.

8.4 Subgroup Analysis

The subgroups are described in section 6.3. Summary statistics for the subgroups are presented (Section 8.9.7.1 and Section 8.9.7.2).

Subgroup analysis will investigate the effect of the intervention among subgroups. The subgroup effects will be based on the interaction between subgroup and treatment through a set of Tobit regression models. Tobit Regression will be used to evaluate the difference in absolute walking distance at 3 months between treatment groups. The Tobit model will include the AWD baseline measurement, a treatment indicator, a centre indicator and a group indicator (SET vs non-SET) as covariates . The results of the Tobit regression model will be reported (see Section 8.9.7.3).

In addition, as secondary analysis we will estimate both the difference between the proportion of patients whose absolute walking distance at 3 months improved by 60 metres or more from baseline and the difference between the proportion of patients whose absolute walking distance at 3 months improved by 100 metres or more from baseline using a chi-square test.

The secondary analysis will be repeated for each one of the subgroups.

All subgroup analyses will be presented in a Forest plot for comparison (see Figure 5).

8.5 Safety Analysis

All safety variables will be summarized by treatment in the form of frequency tables for categorical variables or descriptive statistics for continuous variables. The tables will be produced using all randomized patients.

A list of all Protocol Deviations, Concomitant Medications, Adverse Events and Serious Adverse Events will be produced (see Section 8.9.8).

8.6 Missing Data

Before starting the data analysis, the level and pattern of the missing data in the baseline variables and outcomes will be established by forming appropriate tables. The likely causes of any missingness will be summarised.

8.6.1 Missing AWD Data

A summary table containing the reasons for missing primary outcome data and the relationship to the treatment will be presented.

Missing data are expected for some patients at the follow up visits at 3, 6 and 12 months as trial related patient assessment was suspended following NIHR guidance to individual trusts in response to the COVID-19 pandemic. For this reason, the missing primary outcome data will be assumed to be missing at random and multiple imputation will be used. If, when the missing data are analysed, they present another pattern other than missing at random, we will explore other methods of imputation.

This will be done only if more than 5% of the primary end point data are missing.

A sensitivity analysis on the primary endpoint, comparing both complete cases and imputed cases analysis, will be performed to assess the impact of any bias due to missing data. The estimated treatment effect and 95% confidence interval for each analysis will be presented, with the statistical significance summarised by the corresponding p-value.

8.6.2 Missing Data for other secondary outcomes

Missing data for the secondary endpoints QoL (Intermittent Claudication Questionnaire (ICQ) [10], EuroQoL 5D 5L (EQ-5D-5L), and Short form 36 (SF-36)) and the Laser Doppler Flowmetry (LDF) will be imputed.

8.6.2.1 Quality of Life (QoL)

Missing data are expected for some patients at the 3, 6 and 12 months follow up visits as trial related patient assessment was suspended following NIHR guidance to individual trusts in response to the COVID-19 pandemic. [11] For this reason, we will assume that the missing pattern of the data is missing at random and chained equations (a multiple imputation method for imputing the missing scores) will be used. When the missing data are analysed, if they present another pattern other than missing at random, we will explore other methods of imputation.

8.6.2.2 Laser Doppler Flowmetry (LDF)

Multiple imputation, under the 'missing at random' assumption, will be undertaken for all participants who have missing values in the Laser Doppler Flowmetry outcome. If when the missing data is analysed and it presents another pattern other than missing at random, we will explore other methods of imputation. This will be done only if 10% or more of data is missing.

8.6.2.3 Sensitivity of Secondary Outcomes Analysis to Missing Data

A sensitivity analysis on the secondary outcomes, both complete cases and imputed cases, will be performed to assess the impact of any bias due to missing data. The estimated treatment effect and 95% confidence interval for each analysis will be presented, with the statistical significance summarised by the corresponding p-value.

8.7 Interim Analysis

No formal interim analysis is planned for this trial.

8.8 Sensitivity Analysis

We will carry out sensitivity analyses as detailed below.

8.8.1 Compliance

For the primary and secondary endpoints, we will assess the impact of compliance by performing a subgroup analysis on the compliers population using the compliance definition in section 8.9.6.4. The estimated treatment effect and 95% confidence interval for each analysis will be presented, with the statistical significance summarized by the corresponding p-value.

8.8.2 Sensitivity to Alternative Data collection (due to COVID-19)

Meyer [12] lists recommendations on how to address issues related to study objectives, inference, and statistical analysis for trials conducted during the COVID-19 Pandemic. From the assessment list suggested only missing data and the impact of alternative ways of collecting data are the factors that could have an impact on the NESIC trial. The missingness of data has been discussed already in section 8.6.

To protect the safety and wellbeing of patients, the NESIC trial submitted an amendment on the protocol to allow the follow up data to be done remotely (i.e., over the telephone completely or in combination with postal questionnaire) during the pandemic period. For issues of alternative methods of data collection, Meyer recommends performing a sensitivity analysis to judge whether these alternative ways to collect data are exchangeable.

To assess whether this alternative way to collect follow up data has had an impact on the trial a sensitivity analysis on the secondary outcome of QoL will be performed, comparing all cases and cases where the data that were collected in other ways than originally stipulated in the Protocol have been removed. The estimated treatment effect and 95% confidence interval for each analysis will be presented, with the statistical significance summarised by the corresponding p-value.

8.9 Tables to present

8.9.1 Subject Disposition

Table 3 Subject Disposition

	Center1	Center2	Center3	.....	.....	Total
Screened Randomised **Treatment[1]: NMES + EA and NMES+EA+SET** **Control[2]: EA and EA+SET** Withdrawn Reason for withdrawal Completed						

8.9.2 Protocol Deviations

Table 4 Listing of all Protocol Deviations

Site	Subject ID	Type	Details of Deviation	Treatment	Start Date	End Date

Table 5 Number of protocol deviations by centre and category

Type of Deviation	Center1	Center2	Center3	.....	Total
Patient was incorrectly included in the trial (did not meet all the inclusion and exclusion criteria)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
. .					
Patient pregnancy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Total					

Table 6 Summary of Protocol Deviation of randomised patients (ITT) by treatment

Variables N(%)	Treatment[1]: NMES + EA and NMES+EA+SET N=(XX)	Control[2]: EA and EA+SET N=(XX)	Total N=(XX)
Protocol Deviation or Violation			
Protocol Deviation	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Protocol Violation	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Type of Protocol Deviation			
Device administration	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Sampling	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit outside window	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other, please give details	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other			
Break in SET classes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Classes did not commence within 2 weeks of randomisation	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Device not in use	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Height and Weight not recorded	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Non-SET class patient (we are a SET centre)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Peripheral pulses not assessed	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Received wrong treatment - patient bought own device	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Problems with attendance to SEP class	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Treadmill not increased as per protocol could only increase to a maximum of 7.5% and not 8%	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Incomplete data measurement at baseline	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Any Protocol Deviation or Violation by site			
Cambridge University Hospital	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Dorset County Hospital	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Hull and East Yorkshire Hospitals	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Imperial College Healthcare	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Newcastle Upon Tyne Hospitals	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
North Bristol	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Nottingham University Hospitals	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Royal Bournemouth & Christchurch Hospital	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
St George's University Hospitals	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Taunton & Somerset	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
University Hospital Southampton	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

[1] Treatment: NMES + Local Available Exercise Therapy (NMES+EA and NMES+EA+SET)

[2] Control: Local Available Exercise Therapy (EA and EA+SET)

8.9.3 Baseline Characteristics

Table 7 Summary of baseline characteristics of randomised patients (ITT) by treatment

Variable	Treatment[1]: NMES + EA and NMES+EA+SET N=(XX)	Control[2]: EA and EA+SET N=(XX)	Total N=(XX)
Age			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Sex N(%)			
Female	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Male	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Ethnicity N(%)			
Asian	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Black	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Mixed	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
White	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Work status N(%)			
Higher managerial and professional occupations	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Intermediate occupations (e.g. clerical, sales, service)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lower managerial and professional occupations	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lower supervisory and technical occupations	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Never worked or long-term unemployed	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Routine occupations	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Semi-routine occupations	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Small employers and own account workers	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Retired N(%)			
No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Performance limited due to IC (N%)			
A little	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
A lot	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not at all	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

[1] Treatment: NMES + Local Available Exercise Therapy (NMES+EA and NMES+EA+SET)

[2] Control: Local Available Exercise Therapy (EA and EA+SET)

Table 8 Summary of Medical History of randomised patients (ITT) by treatment

Medical History N(%)	Treatment[1]: NMES + EA and NMES+EA+SET N=(XX)	Control[2]: EA and EA+SET N=(XX)	Total N=(XX)
Childbearing potential*			
No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Hypertension			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Stroke			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Heart attack			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
High cholesterol			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Angina			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Diabetes			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Bypass revascularisation			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Angio revascularisation			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Data presented as frequency (percentage) for categorical variables

*Female population only

[1]Treatment: NMES + Local Available Exercise Therapy (NMES+EA and NMES+EA+SET)

[2]Control: Local Available Exercise Therapy (EA and EA+SET)

Table 9 Summary of Medication list of randomised patients (ITT) by treatment

Concomitant Medications N(%)	Treatment[1]: NMES + EA and NMES+EA+SET N=(XX)	Control[2]: EA and EA+SET N=(XX)	Total N=(XX)
Antiplatelets			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Currently taking glycoprotein IIb IIIa antagonists			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lipid modification therapy			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Anticoagulant			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Antihypertensives			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other Medications			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

[1] Treatment: NMES + Local Available Exercise Therapy (NMES+EA and NMES+EA+SET)

[2] Control: Local Available Exercise Therapy (EA and EA+SET)

Table 10 Summary of Vital Signs of randomised patients (ITT) by treatment

Vital Signs	Treatment[1]: NMES + EA and NMES+EA+SET N=(XX)	Control[2]: EA and EA+SET N=(XX)	Total N=(XX)
Height			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Weight			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Pulse			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Systolic - Blood Pressure			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Diastolic - Blood Pressure			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
BMI			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)

[1] Treatment: NMES + Local Available Exercise Therapy (NMES+EA and NMES+EA+SET)

[2] Control: Local Available Exercise Therapy (EA and EA+SET)

Table 11 Summary of Lifestyle History of randomised patients (ITT) by treatment

Lifestyle History	Treatment[1]: NMES + EA and NMES+EA+SET N=(XX)	Control[2]: EA and EA+SET N=(XX)	Total N=(XX)
Smoking status of subject N(%)			
Current smoker	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Former smoker	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Never	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Current smoker (av. cigarettes/pipes per day			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Former smoker (av. cigarettes/pipes per day)			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Electronic cigarettes N(%)			
No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Electronic cigarettes - Usage			
High user	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Low user	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate user	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Participant consume alcohol N(%)			
Current drinker	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Current drinker (Number of units per week)			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)

[1] Treatment: NMES + Local Available Exercise Therapy (NMES+EA and NMES+EA+SET)

[2] Control: Local Available Exercise Therapy (EA and EA+SET)

Table 12 Summary of Treadmill test of randomised patients (ITT) by treatment

Treadmill Test	Treatment[1]: NMES + EA and NMES+EA+SET N=(XX)	Control[2]: EA and EA+SET N=(XX)	Total N=(XX)
Did the patient complete the treadmill test N(%)			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Patients subjective initial walking distance estimate			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Patients subjective absolute walking distance estimate			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Treadmill speed			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Incline			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Initial Claudication Distance ICD			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Absolute Walking Distance AWD			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)

[1] Treatment: NMES + Local Available Exercise Therapy (NMES+EA and NMES+EA+SET)

[2] Control: Local Available Exercise Therapy (EA and EA+SET)

8.9.4 Derived Variables

Table 13 Summary of ICQ and EQ-5D-5L - Quality of Life scores of randomised patients (ITT) by treatment

QoL	Specific Score, mean(SD)	Treatment[1]: NMES + EA and NMES+EA+SET N=(XX)	Control[2]: EA and EA+SET N=(XX)	Total N=(XX)
ICQ*	**ICQ health score**			
	Baseline	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 weeks	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	6 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
EQ-5D-5L	**Health state score**			
	Baseline	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 weeks	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	6 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)

*The scores of ICQ where obtained using the procedure described in Appendix 2

[1] Treatment: NMES + Local Available Exercise Therapy (NMES+EA and NMES+EA+SET)

[2] Control: Local Available Exercise Therapy (EA and EA+SET)

Table 14 Summary SF-36 of Quality of Life scores of randomised patients (ITT) by treatment

QoL	Specific Score, mean (SD)	Treatment[1]: NMES + EA and NMES+EA+SET N=(XX)	Control[2]: EA and EA+SET N=(XX)	Total N=(XX)
SF-36**	**Section Score**			
	Physical function			
	Baseline	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 weeks	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	6 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	Role-Physical			
	Baseline	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 weeks	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	6 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	Body pain			
	Baseline	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 weeks	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	6 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	General Health			
	Baseline	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 weeks	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	6 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	Vitality			
	Baseline	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 weeks	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	6 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	Social functioning			
	Baseline	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 weeks	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	6 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	Role-Emotional			
	Baseline	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 weeks	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	6 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	Mental Health			
	Baseline	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 weeks	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	6 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	Component Score			
	Physical component score (PCS)			
	Baseline	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 weeks	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	6 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	Mental component score (MCS)			
	Baseline	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 weeks	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	6 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
	12 months	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)

[1] Treatment: NMES + Local Available Exercise Therapy (NMES+EA and NMES+EA+SET)

[2] Control: Local Available Exercise Therapy (EA and EA+SET)

**The SF-36 scores where obtained using the procedure described in Appendix 2

Table 15 Summary of Compliance classification of randomised patients (ITT) by treatment

Classification	Treatment[1]: NMES + EA and NMES+EA+SET N=(XX)	Control[2]: EA and EA+SET N=(XX)	Total N=(XX)
Compliance	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Non-Compliance	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

[1] Treatment: NMES + Local Available Exercise Therapy (NMES+EA and NMES+EA+SET)

[2] Control: Local Available Exercise Therapy (EA and EA+SET)

8.9.5 Primary End Point Analysis

The primary end point will be analysed for the ITT population and PP population.

Table 16 Summary of Absolute Walking Distance (AWD) by visit point and Treatment

Visit	Treatment	N	Mean	SD	Median	Min	Max
Baseline							
	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX.XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX.XX	XX	XX
3 moths							
	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX.XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX.XX	XX	XX
6 months							
	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX.XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX.XX	XX	XX
12 months							
	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX.XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX.XX	XX	XX

Table 17 Tobit Regression Model for AWD at 3 months

Variable	Coefficient	SE	t	P>|t|	Confidence interval	
AWD(Baseline)	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Treatment	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Centre	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Group	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
_cons	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
/sigma	XX.XX	XX.XX			X.XX	X.XX
Obs. Summary:	XX left-censored observations					
	XX uncensored observations					
	XX right-censored observations at (..) dependent variable					

Tobi Regression Model: AWD at 3 months = intercept + AWD (baseline) + Treatment +Centre + Group + residual error. Treatment=NMES + local available Exercise therapy vs. local available Exercise therapy only (1,0), Group= Set or non-SET group (1,0) and Centre=centre identifier.

Table 18 Chi square test of Improvement of >60 m in AWD at three months between treatment groups

Improvement of >60 m in the AWD at 3 months	NMES + Local available Exercise therapy N=(XX)	Local available Exercises therapy N=(XX)	Total N=(XX)
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 19 Chi square test of Improvement of >100 m in AWD at three months between treatment groups. Same display as Table 18, but for improvement of >100 m in AWD

Table 20 Summary of Proportion of Patients that improved AWD by more than 60 m by visit and by treatment

Visit	Improvement of >60 m in the AWD	NMES + Local available Exercise therapy N=(XX)	Local available Exercises therapy N=(XX)	Total N=(XX)
Baseline	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
3 months	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
6 months	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
12 months	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 21 Summary of Proportion of Patients that improved AWD by more than 100 m by visit and by treatment. Same display as Table 20, but for improvement of AWD by more than 100 m

Table 22 Output of Multilevel Tobit model to assess the effects of baseline characteristics for AWD at 3,6, and 12 months

Fixed Part	Coefficient	SE	z	P>|z|	95% Confidence interval	
AWD(Baseline)	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Treatment	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Time	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Treatment *Time	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Centre	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Group	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Age	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Gender	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
BMI	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Smoking status	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
_cons	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX

Random part	Estimate	SE	95% Confidence interval	
Between variance	XX.XX	XX.XX	X.XX	X.XX
Within variance	XX.XX	XX.XX	X.XX	X.XX

Number of obs = XX, Uncensored = XX, Left-censored= XX, Right-censored = XX

Multilevel Tobit model: Absolute Walking distance (3,6 and 12 months) = intercept + AWD(Baseline) + Treatment + Time + Treatment *Time + Centre + Group + Age +Gender +BMI +Smoking Status + residual error. Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0), time= variable indicator, one for each follow up period (3 months, 6 months, 12 months) or treat it as time variable, Treatment*time: Interaction term between treatment and time, Centre=centre identifier, Group= Set or non-SET group (1,0) and Baseline characteristics= Age, gender, BMI, Smoking status.

8.9.6 Secondary End Points Analysis

The secondary end points will be analysed for the ITT population and PP population.

8.9.6.1 **Initial Claudication Distance (ICD)**

Table 23 Summary of Initial Claudication Distance (ICD) by visit point and Treatment

Visit	Treatment	N	Mean	SD	Median	Min	Max
Baseline							
	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
3 moths							
	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
6 months							
	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
12 months							
	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX	XX	XX

[1] Treatment: NMES + Local Available Exercise Therapy (NMES+EA and NMES+EA+SET)

[2] Control: Local Available Exercise Therapy (EA and EA+SET)

Table 24 Output of Multilevel Tobit model for Initial Claudication Distance (ICD)

Fixed Part	Coefficient	SE	z	P>|z|	95% Confidence interval	
ICD(Baseline)	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Treatment	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Time	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Treatment *Time	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Centre	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Group	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Age	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Gender	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
BMI	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
_cons	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX

Random part	Estimate	SE	95% Confidence interval	
Between variance	XX.XX	XX.XX	X.XX	X.XX
Within variance	XX.XX	XX.XX	X.XX	X.XX

Number of obs = XX, Uncensored = XX, Left-censored= XX, Right-censored = XX

Mixed-Effect model: Initial Claudication Distance (ICD) at 3,6 and 12 months = intercept + ICD(Baseline) + Treatment + Time + Treatment *Time + Centre + Group + Age +Gender +BMI + residual error. Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0), time= variable indicator, one for each follow up period (3 months, 6 months, 12 months) or treat it as time variable. Treatment*Time: Interaction term between treatment and time, Centre=centre identifier, Group= Set or non-SET group (1,0) and Baseline characteristics= Age, gender, BMI, Smoking status.

Table 25 Summary of Proportion of Patients that improved ICD by more than 60 m by visit and by treatment

Visit	Improvement of >60 m in the ICD	NMES + Local available Exercise therapy N=(XX)	Local available Exercises therapy N=(XX)	Total N=(XX)
Baseline	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
3 months	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
6 months	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
12 months	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 26 Summary of Proportion of Patients that improved ICD by more than 100 m by visit and by treatment. Same display as Table 25, but for the Proportion of Patients that improved ICD by more than 100 m

8.9.6.2 **Quality of Life scores**

See Table 13 and 14 for Summary of Quality of life scores by time point and treatment.

Table 27 Output of ANCOVA model for changes in Intermittent Claudication score (ICQ-score) from baseline to follow up periods (3,6 and 12 months)

Source	Partial SS	df	MS	F	Prob>F
Model	XX.XX	XX.XX	X.XX	X.XXX	X.XX
Treatment group indicator	XX.XX	XX.XX	X.XX	X.XXX	X.XX
Baseline measurement	XX.XX	XX.XX	X.XX	X.XXX	X.XX
Residual	XX.XX	XX.XX	X.XX		
Total	XX.XX	XX.XX	XX.XX		
R squared =XX.XX	Adjusted R squared = XX.XX			Root MSE = XX.XX	

ANCOVA model: Initial Claudication Distance (ICD) at 3,6 and 12 months = intercept + treatment group indicator + ICD(Baseline). Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0)

Table 28 Output of ANCOVA model for changes in Quality of life (EQ-5D-5L score) between baseline and follow up periods (3,6 and 12 months). Same display as Table 27, but for the Quality of life (EQ-5D-5L score). ANCOVA model: Quality of life (EQ-5D-5L score) at 3,6 and 12 months = intercept + treatment group indicator + EQ-5D-5L score (Baseline). Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0).

Table 29 Output of ANCOVA model for changes in Quality of life (SF-36-score) - Physical function score. between baseline and follow up periods (3,6 and 12 months). Same display as Table 27, but for the Physical function score from the SF-36 questionnaire. ANCOVA model: Physical function score (SF-36-score) at 3,6 and 12 months = intercept + treatment group indicator + Physical function (Baseline). Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0).

Table 30 Output of ANCOVA model for changes in Quality of life (SF-36-score) – Role Physical score. between baseline and follow up periods (3,6 and 12 months). Same display as Table 27, but for Role Physical score from the SF-36 questionnaire. ANCOVA model: Role Physical score (SF-36-score) at 3,6 and 12 months = intercept + treatment group indicator + Role Physical score (Baseline). Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0).

Table 31 Output of ANCOVA model for changes in Quality of life (SF-36-score) – Body Pain score between baseline and follow up periods (3,6 and 12 months). Same display as Table 27, but for the Body Pain score from the SF-36 questionnaire. ANCOVA model: Body Pain score (SF-36-score) at 3,6 and 12 months = intercept

+ treatment group indicator + Body Pain score (Baseline). Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0).

Table 32 Output of ANCOVA model for changes in Quality of life (SF-36-score) – General Health score between baseline and follow up periods (3,6 and 12 months). Same display as Table 27, but for the General Health score from the SF-36 questionnaire. ANCOVA model: General Health score (SF-36-score) at 3,6 and 12 months = intercept + treatment group indicator + General Health score (Baseline). Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0).

Table 33 Output of ANCOVA model for changes in Quality of life (SF-36-score) – Vitality score between baseline and follow up periods (3,6 and 12 months). Same display as Table 27, but for the Vitality score from the SF-36 questionnaire. ANCOVA model: Vitality score (SF-36-score) at 3,6 and 12 months = intercept + treatment group indicator + Vitality score (Baseline). Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0).

Table 34 Output of ANCOVA model for changes in Quality of life (SF-36-score) – Social functioning score between baseline and follow up periods (3,6 and 12 months). Same display as Table 27, but for the Social functioning score from the SF-36 questionnaire. ANCOVA model: Social functioning score (SF-36-score) at 3,6 and 12 months = intercept + treatment group indicator + Social functioning score (Baseline). Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0).

Table 35 Output of ANCOVA model for changes in Quality of life (SF-36-score) – Role-Emotional score between baseline and follow up periods (3,6 and 12 months). Same display as Table 27, but for the Role Emotional score from the SF-36 questionnaire. ANCOVA model: Role-Emotional score (SF-36-score) at 3,6 and 12 months = intercept + treatment group indicator + Role-Emotional score (Baseline). Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0).

Table 36 Output of ANCOVA model for changes in Quality of life (SF-36-score) – Mental Health score between baseline and follow up periods (3,6 and 12 months). Same display as Table 27, but for the Mental Health score from the SF-36 questionnaire. ANCOVA model: Mental Health score (SF-36-score) at 3,6 and 12 months = intercept + treatment group indicator + Mental Health score (Baseline). Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0).

Table 37 Output of ANCOVA model for changes in Quality of life (SF-36-score) – Physical Component score between baseline and follow up periods (3,6 and 12 months). Same display as Table 27, but for the Physical Component score from the SF-36 questionnaire. ANCOVA model: Physical Component score (SF-36-score) at 3,6 and 12 months = intercept + treatment group indicator + Physical Component score (Baseline). Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0).

Table 38 Output of ANCOVA model for changes in Quality of life (SF-36-score) – Mental Component score between baseline and follow up periods (3,6 and 12 months). Same display as Table 27, but for the Mental Component score from the SF-36 questionnaire. ANCOVA model: Mental Component score (SF-36-score) at 3,6 and 12 months = intercept + treatment group indicator + Mental Component score (Baseline). Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0).

8.9.6.3 **Haemodynamic Assessment**

Table 39 Summary of Duplex ultrasonography (Mean Volume flow – measured in one leg) by Time and Treatment

Time	Treatment	N	Mean	SD	Median	Min	Max
Baseline	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
3 months	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX	XX	XX

The average value of the 5 readings taken from the Volume Flow for the measured in one leg by patient in the Device group is presented in the table.

[1] Treatment: NMES + Local Available Exercise Therapy (NMES+EA and NMES+EA+SET)

[2] Control: Local Available Exercise Therapy (EA and EA+SET)

Table 40 Output of Linear Regression Model for Duplex ultrasonography (Mean Volume flow – measured in one leg) at 3 months

Variable	Coefficient	SE	t	P>|t|	Confidence interval	
Mean-DU - VF(Baseline)	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Treatment	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Centre	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Group	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Age	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Gender	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
BMI	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
_cons	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
R-square = X.XX	**Adj R-Squared=X.XX**		**Prob>F=X.XX**			

Linear regression model: Mean DU -Volume flow (VF) measured in one leg at 3 months = intercept + Mean-VF (Baseline) + Treatment + Centre + Type + Age + Gender + BMI + residual error. Treatment=NMES + local available Exercise therapy vs. local available Exercise therapy only (1,0), Group= Set or Non-SET group (1,0), Centre=centre identifier.

Table 41 Summary of Duplex ultrasonography (Mean Time Average Mean Velocity – measured in one leg) by Visit and Treatment. Same display as Table 39, but for Duplex ultrasonography (Time average mean velocity – measured in one leg).

Table 42 Output of Linear Regression Model for Duplex ultrasonography (Mean Time average mean velocity – measured in one leg) at 3 months. Same display as Table 40, but for Duplex ultrasonography (Mean Time average mean velocity – measured in one leg). Linear regression model: DU – Mean Time average mean velocity (TAMV) measured in one leg at 3 months = intercept + TAMV(Baseline) + Treatment + Centre + Group + Age + Gender + BMI + residual error. Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0), Centre=Centre identifier, Group= Set or non-SET group (1,0) and Baseline characteristics= Age, gender, BMI, Smoking status .

Table 43 Summary of Laser Doppler Flowmetry (Mean Blood Flux – measured in one leg) by Time and Treatment

Time	Treatment	N	Mean	SD	Median	Min	Max
Baseline	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
3 months	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
6 months	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
12 months	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX	XX	XX

Note: The average of the 3 reading in the Device group is presented in the table

Table 44 Output of ANCOVA model for changes in Laser Doppler Flowmetry (Mean Blood Flux – measured in one leg) between baseline and follow up periods (3,6 and 12 months). Same display as Table 27, but for the Laser Doppler Flowmetry (LDF) -Mean Blood Flux on one leg. ANCOVA model: Laser Doppler Flowmetry (LDF) - Mean Blood Flux in one leg at 3,6,12 months = intercept + treatment group indicator + Mean Blood Flux (Baseline). Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0)**.**

Table 45 Summary of Right Ankle Brachial Pressure Index (ABPI) by Visit and Treatment

Visit	Treatment	N	Mean	SD	Median	Min	Max
Baseline							
	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
3 moths							
	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
6 months							
	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
12 months							
	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX	XX	XX

Table 46 Output of ANCOVA model for changes in Right Ankle Brachial Pressure Index (ABPI) between baseline and follow up periods (3,6 and 12 months). Same display as Table 27, but for the Right Ankle Brachial Pressure Index (ABPI). ANCOVA model: Right Ankle Brachial Pressure Index (ABPI) 3,6,12 months = intercept + treatment group indicator + Right Ankle Index (Baseline). Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0).

Table 47 Summary of Left Ankle Brachial Pressure Index (ABPI) by visit point and Treatment. Same display as Table 45, but for the Left Ankle Brachial Pressure Index (ABPI).

Table 48 Output of ANCOVA model for changes in Left Ankle Brachial Pressure Index (ABPI) between baseline and follow up periods (3,6 and 12 months). Same display as Table 27, but for the Left Ankle Brachial Pressure Index (ABPI). ANCOVA model: Left Ankle Brachial Pressure Index (ABPI) 3,6,12 months = intercept +

treatment group indicator + Left Ankle Index (Baseline). Treatment=NMES + local available exercise therapy vs. local available exercise therapy only (1,0).

8.9.6.4 **Compliance**

Table 49 Supervise Exercise Therapy (SET) compliance information randomised patients (ITT) by treatment

Exercise Advice - Set Centre	Treatment[1]: NMES + EA and NMES+EA+SET N=(XX)	Control[2]: EA and EA+SET N=(XX)	Total N=(XX)
Total of week recording exercises at home			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Total number of Therapy sessions by persons			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Total minutes of exercise at home at week			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Total minutes of therapy exercise (SET)			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)

Table 50 Neuromuscular Electric Stimulation -compliance information randomised patients (ITT) by treatment

Device Use Diary	Treatment[1]: NMES + EA and NMES+EA+SET N=(XX)	Control[2]: EA and EA+SET N=(XX)	Total N=(XX)
Total of days using the devices			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Total time on (NMES)			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Average - Intensity Setting			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)

Table 51 Exercise Advice (EA) -compliance information randomised patients (ITT) by treatment

Exercise Advice - Non-Set Centre	Treatment[1]: NMES + EA and NMES+EA+SET N=(XX)	Control[2]: EA and EA+SET N=(XX)	Total N=(XX)
Total weeks of exercises reported			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Total minutes of exercised at home			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Average minutes of exercise at home at week			
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)

Table 52 Summary table of Device use questionnaire

Variable	Value
N	**N = (XX)**
Overall, how easy did you find the device to use	
1 Very easy	XX (XX.X%)
2	XX (XX.X%)
3	XX (XX.X%)
4	XX (XX.X%)
5 Very difficult	XX (XX.X%)
Do you think the device helped to lessen the pain in your legs	
1-Yes, a lot	XX (XX.X%)
2	XX (XX.X%)
3	XX (XX.X%)
4	XX (XX.X%)
5-Not at all	XX (XX.X%)
Do you think you can walk further	
Yes	XX (XX.X%)
No	XX (XX.X%)
No change	XX (XX.X%)
Did you use the device as instructed	
Yes	XX (XX.X%)
No	XX (XX.X%)
Do you think you could have used the device more often than you did?	
Yes	XX (XX.X%)
No	XX (XX.X%)
Did you use the device beyond the 3 months treatment	
1-Yes, a lot	XX (XX.X%)
2	XX (XX.X%)
3	XX (XX.X%)
4	XX (XX.X%)
5-Not at all	XX (XX.X%)

8.9.7 Subgroup

8.9.7.1 Baseline characteristics by Subgroups

Table 53 Summary of baseline characteristics of randomised patients (ITT) by Subgroups

Variable	EA N=(XX)	EA+NMES N=(XX)	EA+SET N=(XX)	EA+SET+NMES N=(XX)	Total N=(XX)
Age					
mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)
median (IQR)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Sex N(%)					
Female	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Male	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Ethnicity N(%)					
Asian	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Black	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Mixed	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
White	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Work status N(%)					
Higher managerial and professional occupations	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Intermediate occupations (e.g. clerical, sales, service)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lower managerial and professional occupations	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lower supervisory and technical occupations	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Never worked or long-term unemployed	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Routine occupations	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Semi-routine occupations	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Small employers and own account workers	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Retired N(%)					
No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Performance limited due to IC (N%)					
A little	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
A lot	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not at all	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 54 Summary of Medical History of randomised patients (ITT) by Subgroups

Table 55 Summary of Medication list of randomised patients (ITT) by Subgroups

Table 56 Summary of Vital Signs of randomised patients (ITT) by Subgroups

Table 57 Summary of Lifestyle History of randomised patients (ITT) by Subgroups

Table 58 Summary of Treadmill test of randomised patients (ITT) by Subgroups

8.9.7.2 Derivative variables by Subgroups

Table 59 Summary of ICQ and EQ5D-5L Quality of Life scores of randomised patients (ITT) by Subgroups

Table 60 Summary SF-36 of Quality of Life scores of randomised patients (ITT) by Subgroups

Table 61 Summary of Compliance of randomised patients (ITT) by Subgroups

8.9.7.3 Subgroups Analysis

Table 62 Summary of AWD by Visit and for SET vs Non-SET (subgroup1)

Visit	Subgroup	N	Mean	SD	Median	Min	Max
Baseline							
	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
3 moths							
	Treatment[1]: NMES + EA and NMES+EA+SET	XX	XX.XX	XX.XX	XX	XX	XX
	Control[2]: EA and EA+SET	XX	XX.XX	XX.XX	XX	XX	XX

[1] Treatment: NMES + Local Available Exercise Therapy (NMES+EA and NMES+EA+SET)
[2] Control: Local Available Exercise Therapy (EA and EA+SET)

Table 63 Output of Tobit Regression Model to assess the effects of SET vs non-SET (subgroup1) for AWD at 3 months

Variable	Coefficient	SE	t	P>|t|	Confidence interval	
AWD(Baseline)	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Treatment	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Centre	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
Group	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
_cons	XX.XX	XX.XX	X.XX	X.XXX	X.XX	X.XX
/sigma	XX.XX	XX.XX			X.XX	X.XX
Obs. Summary:	XX left-censored observations					
	XX uncensored observations					
	XX right-censored observations at (…) dependent variable					

Tobit Regression Model: AWD at 3 months = intercept + AWD (baseline)+ Treatment + Centre + Group + residual error.
Treatment=NMES + local available Exercise therapy vs. local available Exercise therapy only (1,0), Centre=Centre identifier and Group= Set or non-SET group (1,0).

Table 64 Chi square test of Improvement of >60 m in AWD at three months between SET and Non-SET (subgroup1)

Improvement of >60 m in the AWD at 3 months	NMES + Local available exercise therapy N=(XX)	Local available exercises therapy N=(XX)	Total N=(XX)
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 65 Chi square test of Improvement of >100 m in AWD at three months between SET and Non-SET (subgroup1). Same display as Table 64, but for improvement of >100 m in AWD and subgroup1.

Table 66 Summary of AWD by Visit and for NMES+SET+EA vs SET+EA (subgroup2). Same display as Table 62, but for subgroup2.

Table 67 Output of Tobit Regression Model to assess the effects of NMES+SET + EA vs SET+ EA (subgroup2) for AWD at 3 months. Same display as Table 63, but for subgroup2. Tobit Regression Model: AWD at 3 months = intercept + AWD (baseline)+ Treatment + Centre + Group + residual error. Treatment=NMES + local available Exercise therapy vs. local available Exercise therapy only (1,0), Centre=Centre identifier and Group= Set or non-SET group (1,0). Subgroup2: NMES+SET+EA vs SET+EA.

Table 68 Chi square test of Improvement of >60 m in AWD at three months between NMES+SET + EA and SET+ EA (subgroup2). Same display as Table 64, but for improvement of >100 m in AWD and subgroup2.

Table 69 Chi square test of Improvement of >100 m in AWD at three months between NMES+SET + EA and SET+ EA (subgroup2). Same display as Table 64, but for improvement of >100 m in AWD and subgroup2.

Table 70 Summary of AWD by Visit and for NMES+EA vs EA (subgroup3). Same display as Table 62, but for subgroup3.

Table 71 Output of Tobit regression model to assess the effects of NMES+EA vs EA (subgroup3) for AWD at 3 months. Same display as Table 63, but for subgroup3. Tobit Regression Model: AWD at 3 months = intercept + AWD (baseline)+ Treatment + Centre+ Group + residual error. Treatment=NMES + local available Exercise therapy vs. local available Exercise therapy only (1,0), Centre=Centre identifier and Group= Set or non-SET group (1,0). Subgroup3: NMES in the non-SET (NMES+EA vs EA).

Table 72 Chi square test of Improvement of >60 m in AWD at three months between NMES+EA and EA (subgroup3). Same display as Table 64, but for improvement of >60 m in AWD and subgroup3.

Table 73 Chi square test of Improvement of >100 m in AWD at three months between NMES+EA and EA (subgroup3). Same display as Table 64, but for improvement of >100 m in AWD and subgroup3.

Table 74 Summary of AWD by Visit and for NMES+EA vs SET+EA (subgroup4). Same display as Table 62, but for subgroup4.

Table 75 Output of Tobit regression model to assess the effects of NMES+EA vs SET+EA (subgroup4) for AWD3M. Same display as Table 63, but for subgroup4 Tobit Regression Model: AWD at 3 months = intercept + AWD (baseline)+ Treatment + Centre+ Group + residual error. Treatment=NMES + local available Exercise therapy vs. local available Exercise therapy only (1,0), Centre=Centre identifier and Group= Set or non-SET group (1,0). Subgroup4: NMES+EA vs SET +EA.

Table 76 Chi square test of Improvement of >60 m in AWD at three months between NMES+EA and SET+EA (subgroup4). Same display as Table 64, but for improvement of >60 m in AWD and subgroup4.

Table 77 Chi square test of Improvement of >100 m in AWD at three months between NMES+EA and SET+EA (subgroup4). Same display as Table 64, but for improvement of >100 m in AWD and subgroup4.

Table 78 Summary of AWD by Visit and for NMES+SET+EA vs NMES+EA (subgroup5). Same display as Table 62, but for subgroup5.

Table 79 Output of Tobit regression model to assess the effects of NMES+SET+EA vs NMES+EA (subgroup5) for AWD3M. Same display as Table 63, but for subgroup5. Tobit Regression Model: AWD at 3 months = intercept + AWD (baseline)+ Treatment + Centre+ Group + residual error. Treatment=NMES + local available Exercise therapy vs. local available Exercise therapy only (1,0), Centre=Centre identifier and Group= Set or non-SET group (1,0). Subgroup5: NMES+SET+EA vs NMES+EA.

Table 80 Chi square test of Improvement of >60 m in AWD at three months between NMES+SET+EA and NMES+EA (subgroup5). Same display as Table 64, but for improvement of >60 m in AWD and subgroup5.

Table 81 Chi square test of Improvement of >100 m in AWD at three months between NMES+SET+EA and NMES+EA (subgroup5). Same display as Table 64, but for improvement of >100 m in AWD and subgroup5.

8.9.8 Safety Analysis

Table 82 Summary of Adverse Events by treatment

Variable N (%)	Treatment[1]: NMES + EA and NMES+EA+SET N=(XX)	Control[2]: EA and EA+SET N=(XX)	Total N=(XX)
Severity			
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Life threatening or disabling	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Fatal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Relationship Study device			
Definitely	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Probably	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Possibly	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Unlikely	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not assessable	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Site name			
Cambridge University Hospital	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Dorset County Hospital	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Hull and East Yorkshire Hospitals	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Imperial College Healthcare	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Newcastle Upon Tyne Hospitals	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
North Bristol	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Nottingham University Hospitals	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Royal Bournemouth & Christchurch Hospital	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
St George's University Hospitals	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Taunton & Somerset	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
University Hospital Southampton	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

[1] Treatment: NMES + Local Available Exercise Therapy (NMES+EA and NMES+EA+SET)

[2] Control: Local Available Exercise Therapy (EA and EA+SET)

Table 83 Summary of Serious Adverse Events by treatment

Variable N(%)	Treatment[1]: NMES + EA and NMES+EA+SET N=(XX)	Control[2]: EA and EA+SET N=(XX)	Total N=(XX)
Severity			
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Life threatening or disabling	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Fatal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Outcome			
Recovered	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Recovering/Improving	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not recovered	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Fatal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not assessable	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Causal Relationship to device			
Definitely	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Probably	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Possibly	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Unlikely	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not assessable	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Site Name			
Cambridge University Hospital	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Dorset County Hospital	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Hull and East Yorkshire Hospitals	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Imperial College Healthcare	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Newcastle Upon Tyne Hospitals	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
North Bristol	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Nottingham University Hospitals	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Royal Bournemouth & Christchurch Hospital	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
St George's University Hospitals	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Taunton & Somerset	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
University Hospital Southampton	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

[1] Treatment: NMES + Local Available Exercise Therapy (NMES+EA and NMES+EA+SET)

[2] Control: Local Available Exercise Therapy (EA and EA+SET)

Table 84 List of all Adverse Events

Subject id	Site Name	Adverse Event Description	Frequency	Severity	Relationship Study device	Treatment of Event	Outcome	SAE Classification	Reason	Treatment

Table 85 List of all Serious Adverse Events

Same display as Table 84, but for SAEs.

Table 86 Summary of Concomitant Medications

Same display as Table 83, but for Concomitant Medications.

Table 87 List of all Concomitant Medications

Same display as Table 84, but for Concomitant Medications.

8.10 Figures to present

Figure 1 Time trend of EQ5D: Health Score;
Figure 3 Time trend of SF-36 in the treatments (all the scores)
Figure 4 Time trend of ICQ score in the treatments
Figure 5 Forest Plot of all Sub-Groups Analysis

9. Data Monitoring and Ethics Committee (DMEC)

In line with current NIHR recommendations a Data Monitoring Committee (DMC) will be convened and will include as a minimum a clinician with experience in the relevant area and an expert trial statistician.

The role of the DMC is to monitor patient safety and treatment efficacy data. Details of membership, responsibilities and frequency of meetings will be conducted as per the EME research governance guidelines and are defined in a separate DMC Charter. A DMC meeting will be held prior to the first patient's first visit, following completion of an internal pilot study and will then be held one month prior to each TSC meeting.

The independent Data Monitoring Committee (DMC) meeting will be scheduled yearly, with possible reviews every 6 months.

10. Acknowledgements

11. Amendments to Version 1.0

12. References

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13. Appendices

13.1 Appendix 1- Treatments

13.1.1 Supervised Exercise Program (SET)

The supervised exercise program (SET) is not standardised among the centres. The table below shows the differences, both in the frequency of sessions as well as total length of the program.

Table A1. Overview of the Program Information by Centre (target SET per centre)

SET Centre	Number of sessions per week (target)	Program duration by months	Total number of sessions
*Imperial College Healthcare	1	6	24
North Bristol	2	3	24
Hull and East Yorkshire Hospitals	3	3	36
University Hospital Southampton	1	2	8
Dorset County Hospital	1	2	8
Royal Bournemouth & Christchurch Hospital	1	3	12

*Imperial SET classes typically last 6 months so extra classes beyond 3 months will be entered under unscheduled visit

13.1.2 Neuromuscular electrical stimulation device (NMES)

The table below shows the summary of the recommended uses of NMES

Table A2 Overview of the Neuromuscular electrical stimulation device (NMES)

Minutes for session	Sessions per week	Number of weeks	Total of sessions	Total minutes
30	7	12	84	2520

13.1.3 Exercise Advice (EA)

The Exercise Advice (EA) is not standardised among the centres. The table below shows an example of recommended guidelines.

Table A3 Overview of the Exercise Advice (EA)

Centre	Weeks	Instructions	Min of exercise per week[2]	Total min
Imperial College Healthcare	12	3 times a week	90	1080
University Hospital Southampton	12	3 - 5 times a week	90 - 150	1080 - 1800
Royal Bournemouth & Christchurch Hospital	12	5 times a week	150	1800
Taunton & Somerset	12	3 times a week	90	1080
Cambridge University Hospital	12	5 times a week	150	1800
Dorset County Hospital	12	3 times a week	90	1080
Hull and East Yorkshire Hospitals[1]	12			
Newcastle Upon Tyne Hospital	12	3 times a week	90	1080
North Bristol	12	3 times a week	90	1080
Nottingham University Hospital	12	7 times a week	210	2520

[1]Patients are advised on the type of exercise but with no specification as to duration and frequency of exercise.

[2]The minimum of exercise per week was estimated assuming the advice patients were given to exercise at least 30 minutes per session.

13.2 Appendix 2 - Formulas for Derived Variables

13.2.1 Intermittent Claudication Score (IC)

The IC score will be calculated using the answers provided by the patients recorded according to the Intermittent Claudication Questionnaire. This information is collected at baseline, 3 ,6 and 12 months.

The Individual Intermittent Claudication Score is obtained by adding all the points assigned in each question and scaling to 100 (where the maximum score of 80 is represented as 100). [13]

Table A4 The intermittent Claudication Questionnaire – Question scores

Answers for question 1	Score	Answers for questions 2 -8	Score
None, I had no leg pain	0	Not limited at all	0
Very mild	1	A little limited	1.25
Mild	2	Moderately limited	2.5
Severe	3	Very limited	3.75
Moderate	4	Totally limited	5
Very severe	5		
Answers for question 9	**Score**	**Answers for questions 10-16**	**Score**
Not at all	0	None of the time	0
Less than once a week	1.25	A little of the time	1.25
Once a day	2.5	Some of the time	2.5
2 to 3 times a day	3.75	Most of the time	3.75
More than 3 times a day	5	All of the time	5

13.2.2 The Short Form 36 Score (SF-36)

The SF-36 will be scored using SF-36 Health Survey Manual for physical health and mental health dimensions, and all eight scales.

13.3 Appendix 3 - Compliance Classification

13.3.1 EA Compliance Measurement

The Imperial College Healthcare guidelines suggest that people with intermittent claudication should aim to exercise at least 3 times a week for a minimum of 30 minutes (90 min/wk). We measure a patient as being compliant if they have done 75% or more of this recommended amount by the end of the 12 weeks (810 minutes).

Table A5 Exercise Advice Compliance Measurement

Centre	Weeks	Instructions	Min of exercise per week[2]	Total min	75% of min
Imperial College Healthcare	12	3 times a week	90	1080	810
University Hospital Southampton	12	3 - 5 times a week	90 - 150	1080 - 1800	810
Royal Bournemouth & Christchurch Hospital	12	5 times a week	150	1800	1350
Taunton & Somerset	12	3 times a week	90	1080	810
Cambridge University Hospital	12	5 times a week	150	1800	1350
Dorset County Hospital	12	3 times a week	90	1080	810
Hull and East Yorkshire Hospitals[1]	12				
Newcastle Upon Tyne Hospital	12	3 times a week	90	1080	810
North Bristol	12	3 times a week	90	1080	810
Nottingham University Hospital	12	7 times a week	210	2520	1890

[1]Patients are advised on the type of exercise but with no specification as to duration and frequency of exercise.

[2]The minimum of exercise per week was estimated assuming the advice patients were given to exercise at least 30 minutes per session.

13.3.2 SET Compliance Measurement

For SET, we know how many sessions per week each centre recommends, how many weeks they run the SET for (see table below) as well as how many sessions are attended by each patient. We measure a patient as being compliant if they have done 50% or more of the amount recommended by the centre by the end of the period the centre runs the SET (see table below).

Table A6 Supervised Exercise Therapy Compliance Measurement

Centre	Sessions per week	Months	total session	50%
*Imperial College Healthcare	1	6	24	12
North Bristol	2	3	24	12
Hull and East Yorkshire Hospitals	3	3	36	18
University Hospital Southampton	1	2	8	4
Dorset County Hospital	1	2	8	4
Royal Bournemouth & Christchurch Hospital	1	3	12	6

*Imperial SET classes typically last 6 months so extra classes beyond 3 months are entered under unscheduled visit

13.3.3 NMES Compliance Measurement

For NMES, we know that the patients are recommended to use the device for 30 minutes a day for 12 weeks, for a total of 2520 minutes. Therefore, we will classify a patient as a complier if they use the NMES device at least 75% of the recommended time for 12 weeks.

Table A7 NMES Compliance Measurement

Minutes for session	Sessions per week	Number of weeks	Total of sessions	Total minutes	75% of min
30	7	12	84	2520	1890