The effect of an eight-week treatment program using a novel foot neuromuscular electrical stimulator on physical function, leg pain, leg symptoms and leg blood flow in community dwelling older adults: a randomized sham-controlled trial

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Trial Registration No: ISRCTN10576209

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Statistical Analysis Plan

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LIST OF ABBREVIATIONS

ANCOVA	Analysis of Covariance
BOCF	Baseline Observation Carried Forward
CI	Confidence Interval
COPM	Canadian Occupational Performance Measure
CRF	Case Report Form
ITT	Intent to Treat
MCID	Minimal Clinically Important Difference
MITT	Modified Intent to Treat
n	Number of patients
NMES	Neuromuscular Electrical Muscle Stimulator
NRS	Numerical Rating Scale
PP	Per Protocol
SAP	Statistical Analysis Plan
SD	Standard Deviation

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the Community study protocol version 4.0 dated 12 July 2022.

The SAP will be finalised prior to the database lock and statistical analysis.

The statistical analysis will be performed using SAS version 9.4 or higher.

2 STUDY OBJECTIVES AND DESIGN

2.1 Study Design

2.1.1 Primary objective

To evaluate the efficacy of a non-invasive foot Neuromuscular Electrical Muscle Stimulator (NMES) administered using Revitive Medic© Program 1 over 8-weeks compared with Revitive sham.

2.1.2 Secondary objective

To evaluate the efficacy of a non-invasive foot Neuromuscular Electrical Muscle Stimulator (NMES) administered using Revitive© Program 2 over 8-weeks compared with Revitive sham.

2.2 Study Design

This is a single centre, single blind, placebo-controlled (sham group), interventional study. The participants are randomised to one of three groups using a computer-generated block randomisation (IBM SPSS Statistics, Version 23). The allocation is blinded from the participants. Each group receiving a different type of NMES.

Group 1: Revitive Sham (Sham).

Group 2: NMES using Revitive Medic© Program 1 (Program 1).

Group 3: NMES using Revitive© Program 2 (Program 2).

Each participant is instructed to self-administer the foot stimulator using Revitive Medic© for 30 minutes twice daily (2 x 30 min sessions) for eight weeks. The treatment will be administered in sitting position with the participants placing the soles of their feet on the rubberised foot plates. The machine is timed to run for 30 minutes continuously. The user can increase or decrease the intensity of treatment with a remote control. During the study all participants will continue with their normal life, activities, medications, and diet with no restrictions.

2.3 Visit Structure

There are three assessment visits: pre-intervention (week 0), post-intervention (Week 8) and follow-up (Week 12).

2.4 Sample Size

At the time of protocol development, neither the anticipated effect of the Sham nor the effect of Program 1 and Program 2 interventions on the primary outcome (the Canadian occupational performance measure) was well understood. To inform response rates and to provide baseline data for a sample size calculation, an internal pilot study was conducted with the first 10 participants from each of the three groups (30 participants in total). Based on multiple publications, an improvement of '2' points in the COPM performance score for an individual participant was considered a 'minimally clinically important difference (MCID)', and therefore set as the threshold required for a participant to be considered a 'responder'. From the internal pilot study, the responder rate was calculated for the Sham, and based on this, an absolute risk difference was defined for determining what the responder rate in the two test interventions (Programs 1 and 2) needed to be to demonstrate a treatment benefit. The difference in responder rates was then used to calculate the total sample size required for the study. The 30 participants from the internal pilot will be included in the final analysis, as they followed the same protocol as the remaining participants will follow. No hypothesis test for stopping for futility or efficacy was conducted at the end of the internal pilot, and so inflation of Type I or Type II errors is considered negligible.

Based on the proportion of responders obtained from the internal pilot, an absolute difference of 30% in the proportion of participants that meet the COPM performance responder definition (improvement by '2' points) between Sham and Program 1 and 2 interventions was considered necessary to demonstrate a clinically meaningful difference for either test device. To control the Type I error, a single primary endpoint was chosen, namely Sham versus Program 1. The comparison between Sham and Program 2 interventions was taken as the secondary endpoint. A sequential testing procedure is being employed such that the secondary end point can only be formally assessed if the primary endpoint achieves statistical significance ($p < 0.05$). Basing the calculation on this design it was determined that 39 participants will be needed in each of the three intervention groups to show an absolute difference of 30% in the proportion of responders between Sham intervention and Program 1 and 2 interventions at 80% power and two-sided 5% significance. For the purposes of the power calculation, the statistical test to compare the groups was a Pearson Chi-square test at the two-sided significance level ($p < 0.05$).

Formulating the chosen sample size in terms of the continuous outcome of change from baseline in COPM-P, a study with 39 participants per group has 80% power to show an effect size (difference in means / pooled standard deviation) of 0.643, which is considered a medium to large effect size.

3 STUDY POPULATIONS

Data from this trial will be summarised and analysed for the intent to treat (ITT) population as the primary population for analysis. The analyses based on the modified intent to treat (MITT) and Per Protocol (PP) populations will be considered as secondary.

The ITT population will include all enrolled and eligible participants who are randomised and use their assigned device at least once. The ITT population will be used for summarising demographics, device compliance and all efficacy parameters.

The MITT population will include all enrolled and eligible participants who are randomised and use their assigned device at least once, and for whom the condition being assessed was present at baseline. There will be a separate MITT population defined for COPM, symptom score and leg pain since this will depend on the baseline scores for each parameter. The MITT will be used for summarising COPM, symptom score and leg pain. In cases where the ITT and MITT populations are identical, only the ITT analysis will be presented.

The PP population will include participants from the ITT population who have been compliant with their assigned device, defined as missing no more than 28 treatment sessions. Participants who provide no information on how many treatment sessions they have missed will be excluded from the PP population. The PP population will be used for summarising COPM, symptom score and leg pain.

4 DEFINITIONS AND DERIVED VARIABLES

Study Day: Day 0 will be defined as the date of the baseline assessment. Positive study days will be counted forward from Day 0.

Baseline: For all parameters, the baseline measurement will be the value determined on Day 0 (prior to first use of the device) or if not available, then the last value observed before Day 0.

Change: Change from baseline at a particular post-baseline time point will be calculated as the value at the post-baseline time point minus the baseline value.

5 EFFICACY PARAMETERS

5.1 Primary Endpoint

- Canadian Occupational Performance Measure Performance score (COPM-P), change from baseline to Week 8. Comparison between Program 1 and Sham.

5.2 Secondary Endpoints

- COPM-P, change from baseline to Week 8. Comparison between Program 2 and Sham.

- Canadian Occupational Performance Measure Satisfaction score (COPM-S), change from baseline to Week 8. Comparison between Program 1 and Sham, and Program 2 and Sham.

- COPM-P and COPM-S, change from baseline to Week 12. Comparison between Program 1 and Sham, and Program 2 and Sham.

- Leg pain, change from baseline to Week 8 and Week 12. Comparison between Program 1 and Sham, and Program 2 and Sham.

- Deep leg blood volume and intensity, change from baseline to during use. Comparison between Program 1 and Program 2 combined versus ShamSymptom score, change from baseline to Week 8 and Week 12 in the overall symptom score and each item (heaviness, tiredness, aching and cramps). Comparison between Program 1 and Sham, and Program 2 and Sham.

6 SAFETY PARAMETERS

No safety data will be reported as part of the statistical analysis defined in the SAP. Safety and adverse events will be reported in the clinical trial publication as part of standard reporting.

7 STATISTICAL METHODOLOGY

7.1 Statistical and Analytical Issues

7.1.1 Data Included in Tables and Listings

Data for all patients who entered the study will be included in the data listings. All data recorded in the database will be listed. Summary tables will be based on the ITT, MITT and PP populations.

7.1.2 Statistical Methods

All summaries and listings of data will be produced using SAS Version 9.4. Continuous variables will be summarised using non-missing counts (n), mean, standard deviation (SD), median, minimum, and maximum. In the presentation of summary statistics, the following rules will be applied, unless stated otherwise. Minimum and maximum will be presented to the same number of decimal places as the raw data, mean and median will be presented to one more decimal place than the raw data, and SD will be presented to two more decimal places than the raw data.

Categorical variables will be summarised as counts and percentages of patients with non-missing data in particular analysis populations. For calculation of percentages by time-point, the denominator will be the number of participants with data collected. Percentages will be presented to one decimal place. When a frequency is equal to zero, the percentage will not be displayed.

In cases where a parameter has a missing value, a row for ‘Missing’ will be added to the corresponding summary table.

For all parameters, at each time-point, only participants with both a baseline and the corresponding post-baseline assessment will be included in the calculation of change from baseline. Percentage change from baseline will be calculated as

100 X (Post-baseline – Baseline)/Baseline

In cases where baseline value is 0, the percentage change will be set to missing.

Data will be presented graphically, where appropriate, using line graphs and bar charts.

7.1.3 Handling of Dropouts and Missing Data

Participants who discontinue the study will only have data collected up to the point of discontinuation. For participants who do not have an assessment at either Week 8 or Week 12 due to either withdrawing from the study or not undertaking the assessment, the value will be left as missing for calculation and presentation of summary statistics. For statistical analysis, multiple imputation will be used to handle missing data from study visits not attended. It will be assumed that the data are missing at random (MAR). If the pattern of missing data is non-monotone, then partial imputation will firstly be carried out (just enough to get the monotone missing data pattern) using the MCMC method. Once the data exhibit a monotone missing data pattern, the monotone regression method will be used to impute the remaining missing data. The regression model will include terms for treatment and the observed values at visits prior to the missing value. For each endpoint, 20 imputed datasets will be created and analysed, and the results will then be pooled using the MIANALYZE procedure in SAS. A sensitivity analysis will be performed whereby missing data will be replaced by the value recorded at baseline (Baseline Observation Carried Forward, BOCF).

7.1.4 Pooling

Since all patients are recruited from one study site, pooling of sites is not applicable.

7.2 Patient Characteristics

7.2.1 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarised descriptively for the ITT population, by treatment group and for all participants:

Age, height, weight and body mass index (BMI) using summary statistics. Gender as a frequency table (N and %).

7.2.2 Compliance with NMES device

Compliance will be summarised descriptively as the number of sessions missed during the eight-week programme, by treatment group.

7.3 Efficacy Analysis

7.3.1 COPM-P

The COPM-P score is a measure of each participants self-evaluation towards their current performance and will be recorded by the assessor at each visit (baseline, Week 8 and Week 12). At each visit, summary statistics (n, mean, SD, median, minimum, and maximum) for the COPM-P score will be presented. Summary statistics will also be presented for the change from baseline and percentage change from baseline to each visit. Analysis of covariance (ANCOVA) with change from baseline as the dependent variable, and treatment group and baseline COPM-P as the independent variables will be used to compare Program 1 with Sham and Program 2 with Sham, at both Week 8 (end of treatment) and Week 12 (end of follow-up). Least square means for each group, treatment differences, 95% confidence intervals (CI) and p-values between each test group versus sham will be calculated. Model assumptions will be checked and if departures from Normality are evident, a Wilcoxon rank sum test and associated 95% CI using the Hodges Lehmann estimator will be used to compare groups.

Stating the primary efficacy objective as a null (H0) and alternative (H1) hypothesis:

H0: Change in COPM-P score in the participants randomized to receive NMES using Revitive Medic© Program 1 is equal to change in COPM-P score in the participants randomized to receive Revitive sham.

vs.

H1: Change in COPM-P score in the participants randomized to receive NMES using Revitive Medic© Program 1 is not equal to change in COPM-P score in the participants randomized to receive Revitive sham.

The best possible score for COMP-P is 10 points. Any participant who has a score of 10 at baseline will be excluded from the MITT analysis since the condition of interest is absent in these participants. Gains of at least 2 points on the COPM are considered clinically important (Minimal Clinically Important Difference, MCID) (Law et al, 2014). Using this threshold, participants will be classified as either a responder (change in COPM-P≥2) or non-responder (change in COPM-P<2) at Week 8 and Week 12. Participants who do not have an assessment at a visit will be categorised as responders or non-responders according to their value obtained via the multiple imputation. For the sensitivity analysis using BOCF they will be classified a non-responder (non-responder imputation) at that visit. The percentage of responders at each time point will be summarised by treatment group. Logistic regression with baseline COPM-P as a covariate and treatment group as a classification variable will be used to compare the percentage of responders in each test group versus the sham group. The treatment effect will be estimated as an odds ratio (test/sham), with a 95% CI and associated p-value. An odds ratio greater than 1 will indicate a better outcome in the test group. The responder analysis will be performed for the ITT, MITT, PP and

also the subset of participants who have a baseline score of 8 or less (since participants with a baseline score >8 do not have the ability to meet the MCID).

Stating the responder analysis as a null (H0) and alternative (H1) hypothesis:

H0: Proportion of participants achieving at least a 2-point improvement in COPM-P in those randomized to receive NMES using Revitive Medic© Program 1 is equal to the proportion of participants achieving at least a 2-point improvement in COPM-P in those randomized to receive Revitive sham.

vs.

H1: Proportion of participants achieving at least a 2-point improvement in COPM-P in those randomized to receive NMES using Revitive Medic© Program 1 is not equal to the proportion of participants achieving at least a 2-point improvement in COPM-P in those randomized to receive Revitive sham.

For the above analyses (ANCOVA and logistic regression), a hierarchical testing procedure will be used to maintain the Type I error rate at 5%. Firstly, the statistical significance of Program 1 versus Sham will be calculated, and if the p-value≤0.05, testing will proceed to Program 2 versus Sham (also at the 5% level of significance). If Program 1 versus Sham has a p-value >0.05, then Program 2 versus Sham will be considered non-significant. However, a p-value will still be presented for descriptive purposes.

7.3.2 COPM-S

The COPM-S score is a measure of each participants self-evaluation towards their current satisfaction and will be recorded by the assessor at each visit (baseline, Week 8 and Week 12). COPM-S will be summarised and analysed in the same way as COPM-P. The best possible score for COMP-S is 10 points. Any participant who has a score of 10 at baseline will be excluded from the MITT analysis since the condition of interest is absent in these participants. The MCID for COPM-S is 2 points, and participants will be classified as responders or non-responders based on this threshold. The same hierarchical testing procedure described in Section 7.3.1 will be used for evaluating the effectiveness of the Program 1 and Program 2 regimens. The COPM-S analyses will be performed for the same study populations as defined for COPM-P.

7.3.3 Leg Pain

Participants rate the pain in their legs using an 11-point Numerical Rating Scale (NRS) at baseline, Week 8 and Week 12.

At each visit, summary statistics (n, mean, SD, median, minimum, and maximum) for leg pain will be presented. Summary statistics will also be presented for the change from baseline and percentage change from baseline to each visit. Analysis of covariance (ANCOVA) with change from baseline as the dependent variable, and treatment group and baseline pain as the independent variables will be used to

compare Program 1 with Sham and Program 2 with Sham, at both Week 8 (end of treatment) and Week 12 (end of follow-up). Least square means for each group, treatment differences, 95% confidence intervals (CI) and p-values between each test group versus sham will be calculated. Model assumptions will be checked and if departures from Normality are evident, a Wilcoxon rank sum test and associated 95% CI using the Hodges Lehmann estimator will be used to compare groups.

Any participant who has no pain (pain score of 0) at baseline will be excluded from the MITT analysis since the condition of interest is absent in these participants. A change in pain score of 2 (when measured on an 11-point NRS) is often recognised as a clinically meaningful change to a patient (Salaffi 2004, Suzuki 2020, Bahreini 2020). Therefore, the participants will be classified as a responder if their pain score improves by at least 2 points from baseline, or non-responder otherwise. The percentage of responders at each time point (Week 8 and Week 12) will be summarised by treatment group. Logistic regression with baseline leg pain as a covariate and treatment group as a classification variable will be used to compare the percentage of responders in each test group versus the sham group. The treatment effect will be estimated as an odds ratio (test/sham), with a 95% CI and associated p-value. An odds ratio greater than 1 will indicate greater pain reduction in the test group. The responder analysis will be performed for the ITT, MITT, PP and also the subset of participants who have a baseline pain score of 2 or more (since participants with a baseline score <2 do not have the ability to meet the clinically meaningful change).

The same hierarchical testing procedure described in Section 7.3.1 will be used for evaluating the effectiveness of the Program 1 and Program 2 regimens.

7.3.4 Symptom Score

The symptom diary asks participants to indicate which, if any, of 4 symptoms (heaviness, tiredness, aching and cramps) they have experienced over the last 7 days, and if so, on how many days. Participants are asked to rate the average intensity from 0 to 10 on a rating scale. The symptom diary is completed at baseline, Week 8 and Week 12. A total symptom score is calculated as:

(the number of days multiplied by the average intensity, summed across all 4 symptoms) / 7

The total score can range from 0 (best outcome) to 40 (worst outcome).

A score of 0 indicates the symptom was not present. Scores of 0 will be included in the calculation of total symptom score since they provide valuable data on the totality of symptoms.

Any participant whose total symptom score at baseline is zero will be excluded from the MITT analysis since the condition of interest is absent in these participants.

A domain score for each item is calculated as:

(the number of days multiplied by the average intensity) / 7

Each domain score can range from 0 (best outcome) to 10 (worst outcome). For calculation of individual domain scores, only symptoms that are present at baseline will contribute to the baseline and post-baseline symptom scores for the MITT analysis. Changes to Week 8 and Week 12 will then indicate the evolution of symptoms that were present at baseline.

At each visit, summary statistics (n, mean, SD, median, minimum, and maximum) for each domain score and total score will be presented. Summary statistics will also be presented for the change from baseline and percentage change from baseline to each visit. Analysis of covariance (ANCOVA) with change from baseline as the dependent variable, and treatment group and baseline score as the independent variables will be used to compare Program 1 with Sham and Program 2 with Sham, at both Week 8 (end of treatment) and Week 12 (end of follow-up). Least square means for each group, treatment differences, 95% confidence intervals (CI) and p-values between each test group versus sham will be calculated. Model assumptions will be checked and if departures from Normality are evident, a Wilcoxon rank sum test and associated 95% CI using the Hodges Lehmann estimator will be used to compare groups.

The same hierarchical testing procedure described in Section 7.3.1 will be used for evaluating the effectiveness of the Program 1 and Program 2 regimens.

7.3.5 Deep leg blood flow

Blood volume and blood intensity will be measured using a Doppler ultrasound at Week 0, before and during use with the NMES. If the Week 0 data were deemed erroneous, the assessment was repeated at Week 8, and the data point that was considered the best quality with minimal noise was recorded. Since blood flow is only measured under a single waveform, the Program 1 and Program 2 regimens are not distinguishable for this assessment. Therefore, for this endpoint, the Program 1 and Program 2 participants will be combined and summarised as a single group (Program 1/Program 2). Summary statistics (n, mean, SD, median, minimum, and maximum) for each parameter before use (baseline) and during use will be presented. Summary statistics will also be presented for the change from baseline and percentage change from baseline. Analysis of covariance (ANCOVA) with change from baseline as the dependent variable, and treatment group and baseline value as the independent variables will be used to compare Sham with Program 1 and Program 2 combined. Least square means for each group, treatment differences, 95% confidence intervals (CI) and p-values between the combined test groups versus sham will be calculated. Model assumptions will be checked and if departures from Normality are evident, a Wilcoxon rank sum test and associated 95% CI using the Hodges Lehmann estimator will be used to compare groups.

7.3.6 Exploratory Analyses

Further exploratory analyses, investigating the effects of other covariates (such as BMI), may be undertaken for the study outcomes.

8 REFERENCES

Study Protocol for " The effect of an eight-week treatment program using a novel foot neuromuscular electrical stimulator (NMES) on physical function and leg pain, symptoms and blood flow in community dwelling older adults: a randomised sham-controlled trial".

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9 TABLE OF CONTENTS FOR TABLES AND DATA LISTINGS

The planned tables, figures and data listings are shown below. These are indicative of the final outputs and may be subject to minor alteration.

In the presentation of data in summary tables, figures and data listings, the treatment groups will be labelled as:

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Program 2

Sham

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8	**BLOOD VOLUME AND INTENSITY**

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