

This document is the Statistical Analysis Plan for the study:

REG-80-2015

NCT03653312 Neuromuscular Electrical Stimulation in
Acute Ischemic Stroke (NESA)

Date: 11.06.2020

Statistical analysis plan

NESA - A randomized controlled trial of NeuroMuscular Electric Stimulation in patients with lower extremity paresis due to acute ischemic stroke

Section 1: Administrative information**Title & trial registration**

- 1a: Neuromuscular Electrical Stimulation in Acute Ischemic Stroke (The NESA study)

NESA is a parallel group, superiority, randomised controlled trial (RCT) investigating if early NMES during exercise is superior to exercise alone in improving walking distance and speed, function and quality of life in patients (40–85 years of age) with acute ischemic stroke.

- 1b: Trial registration: ClinicalTrials.gov Identifier: NCT03653312 (originally registered 31.08.2018)

Version

- 2: Version 1.0. Date: 03.04.2020

Protocol version

- 3: This statistical analysis plan (SAP) has been written based on the revised protocol approved by the Regional Committees on Health Research Ethics for Region Zealand (SJ-444; 25.09.2015). This SAP adheres to the Guidelines for the content of statistical analysis plans in clinical trials (1). The SAP was made publicly available before finalizing the data collection at the primary endpoint and before any analysis is commenced.

Revisions

- 4a: Revision history
- 4b: Justification for revision
- 4c: Timing of revision

Protocol version	Updated SAP version no.	Section number changed	Reason	Date changed

Roles and responsibility

- 5: Names, affiliations, and roles of SAP contributors

Principal investigator:

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Signatures

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- 6b: Senior statistician signature:



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Date: 11.06.2020,



Section 2: Introduction**Background**

- 7: Synopsis of trial background

Background

Annually there are about 15,000 new cases of stroke in Denmark and the number is expected to rise with about 40% by 2035 due to the increasing population of elderly (2). Stroke is associated with the highest odds of reporting severe disability and more individual domains of disability compared with other conditions and therefore might be considered to be the most common cause of complex disability (3); stroke survivors represent the largest group of Danes receiving early retirement incapacity benefits (4). Optimising exercise rehabilitation to improve functionality for stroke survivors would thus be of great importance for the individual patient, their relatives, and society (4, 5). Therapists perform functional motor ability rehabilitation with stroke patients, and early and intensive exercise has shown faster remission and improved functionality in patients with stroke (6-10). Muscle strength for stroke patients can be increased by the assistance of NMES (11-16). To our knowledge the effect of NMES in addition to exercise in the acute phase after an ischemic stroke (<2 days) has never been studied.

This would be of great importance for future rehabilitation worldwide.

Objectives

- 8: Description of specific objectives and hypotheses

The objective is to examine the added effect of NMES in addition to exercise in the acute phase after ischemic stroke in patients with paresis of the lower extremities. The primary endpoint is change in objectively-measured function at 90 days after ictus; secondary endpoints include self-reported quality of life, cognitive assessment, performance-based impairment and memory, and others at 90 days after ictus.

Hypotheses

We hypothesize that patients randomized to early NMES during exercise will improve significantly more in objectively-measured function than patients randomised to only exercising until 90 days after ictus.

Section 3: Study methods

Trial design

- 9: Brief description of design

This is a RCT (1:1 ratio) conducted at the Department of Acute Neurology at Zealand University Hospital, Region Zealand, Denmark, with blinded evaluation of the effect parameters. Interventions will be delivered by trained physiotherapists. The intervention group receive exercise combined with NMES. The control group receive only exercise. Patient and physiotherapist blinding cannot be maintained due to muscle contractions from electric stimulation. Exercise begins no later than day 2 after ictus. The exercise starts at the acute ward during hospitalisation. After 2 days at the acute ward, some patients will be

transferred to either another neurological ward at another hospital in the region, or they will be sent home. Exercise is conducted on all weekdays for two weeks with a physiotherapist at either the ward, the ward at the other hospital or in the patients' home. Every training session lasts for 12 minutes, with one session per day. The stimulation will be given through external pads on the paretic limb during all exercise sessions. Effect parameters will be evaluated at baseline as well as on days 14 and 90 respectively in order to observe changes over time. Evaluation on day 90 is the primary follow-up, to assess any lasting effects of the intervention.

The primary endpoint is the between-group difference in change in 6 minutes walk test (6MWT) between the group randomised to exercise with NMES and the group randomised to exercise therapy alone from baseline to the 90 days post ictus follow-up.

Randomisation

- 10: Randomisation details

A priori, a nurse independent from the study made a random distribution of the 50 participants. The allocation was stored in opaque sealed envelopes prepared by the nurse and after the distribution the envelopes were only accessible to the central study coordinator. The central study coordinator only opened the sealed envelopes after informed consent and baseline measures had been obtained.

Sample size

- 11: Full sample size calculation

The study is powered to detect a difference in change of 34.4 points between the two groups in the primary outcome 6MWT from baseline to 90 days follow-up. A 34.4-meter difference in change between groups in 6MWT is considered clinically relevant (17). To detect the difference 21 patients in each of the intervention groups is needed (assuming a common SD of 38.7 (17), power=80%, alpha level=0.05). We planned to recruit a total of 50 patients to account for loss to follow-up (20%).

Framework

- 12. Description of hypothesis testing framework

Both primary and secondary outcomes will be assessed using a superiority framework, expecting that patients undergoing intensive exercise with use of NMES in the acute phase of ischemic stroke will experience greater improvements in objectively-measured function than patients undergoing exercise alone.

Statistical interim analysis and stopping rules

- 13: Specification of planned interim analysis and/or stopping rules

Not applicable.

Timing of outcome assessments

- 14: Details of timing of all analyses

The primary follow-up (90 days) will be conducted 90 days post ictus. Primary and secondary outcomes will be analysed collectively by the Principal Investigator under supervision and control from an independent statistician. Data from all follow-ups (baseline, 14 days and 90 days) will be included in this analysis. Outcomes presented under Primary or Secondary Outcome Measures at ClinicalTrials.gov (ID: NCT03653312) will be reported in the RCT report.

15: Timing of outcome assessments

Table 1 presents an overview of baseline characteristics and outcomes assessed and their timing.

Table 1: Baseline Characteristics and outcomes of the NESA-trial

	<u>Baseline</u>	<u>14 days</u>	<u>90 days</u>
Baseline characteristics			
Age	X		
Gender	X		
SSS-Score	X		
Height	X		
Weight	X	X	X
Favourite hand	X		
Smoking and years	X		
Weekly alcohol consumption	X		
Walking aids before hospitalisation -indoors	X		
Walking aids before hospitalisation -outdoors	X		
Residential circumstance	X		
Stairs in the house	X		
Force reduction	X		
Social status	X		
Employment status	X		
Side of infarction	X		

Smoking status	X		
Co-morbidities known before Hospitalisation	X		
Co-morbidities identified during hospitalisation	X		
Earlier identified function-limited diseases	X		
<u>Cognitive assessments</u>			
Montreal Cognitive Assessment		X	X
Becks Depression Inventory		X	x
<u>Patient reported outcomes</u>			
EQ-5D-5L		X	X
<u>Physical performance tests</u>			
6MWT	X	X	X
10 MWT	X	X	X
Sit to stand	X	X	X
Timed up and go	X	X	X
Guralnik	X	X	X
Fugl-Meyer UE motor part	X	X	X
Fugl-Meyer total UE score	X	X	X
<u>Adverse events</u>			
Patient-reported at Follow-up		X	X
Medical record review			X
Data in the surgery column are only collected for patients undergoing surgery. EQ-5D-5L = EuroQol Group 5-Dimension Self-Report Questionnaire, MoCA = Montreal Cognitive Assessment, 6MWT = 6 Minutes Walk Test, 10 MWT = 10 Meter Walk Test			

Statistical principles

Confidence intervals and p values

- 16: Level of statistical significance and confidence intervals

All statistical tests carried out to assess the between-group effects, will consist of two-sided tests with a 5% significance level (p=.05).

- 17: Adjustment for multiplicity

Since this study has one clearly defined primary outcome and all other outcomes serve as supportive outcomes, no adjustments for multiplicity are needed.

- 18: Confidence intervals

All confidence intervals presented will be 95% and two-sided.

Adherence and protocol deviations

- 19a: Definition of adherence to the intervention

Poor compliance is defined as participating in less than 8 of the 10 exercise sessions (80%) in both the intervention and the control group. Compliance with the supervised exercise sessions will be registered by the physiotherapist delivering the interventions.

- 19b: Description of how adherence will be presented

Adherence will be presented as the number and percentage of patients who participate in 8 or more supervised exercise therapy sessions.

- 19c & 19d: Definition of protocol deviations and how they will be reported

The following is defined as a major protocol deviation which may compromise the scientific value of the trial:

- More than 20% loss to follow-up
- Less than 50% participated in at least 8 of the supervised exercise therapy sessions.

All major protocol deviations will be reported in the primary report.

Analysis population

- 20: Definition of analysis populations

In the primary analysis of the trial outcomes and the safety analysis (adverse events), all patients will be included according to the treatment they were randomised to receive, following the Intention-To-Treat (ITT) principle. This is the full analysis set, defined as an analysis set being as complete and as close to the ITT principle of including all randomised patients as possible (18).

In addition, a secondary per protocol analysis will be performed. The per protocol population excludes patients with poor compliance (see 19a and 19b), and patients that withdrew their consent to participate.

Trial population

Screening data

- 21: Reporting of screening data

The duration of the recruitment period (start and end date) and the total number of subjects screened for eligibility throughout the recruitment period will be reported. See also item 23 & 24.

Eligibility

- 22: Summary of eligibility criteria

Inclusion criteria

- Adults aged 40 to 85 years diagnosed (CT/MRI or clinically diagnosed) with ischemic stroke within 2 days after debut.
- Leg paresis (muscle strength 2-4)
- Modified Ranking Scale (mRS) 0-1
- Cognitive capacity to participate in the study

Exclusion criteria

- Pacemaker or other implanted electrical appliances
- Current or previous leg blood clot
- Absolutely absent sensitivity in affected extremity
- Pregnancy
- Depression (insufficient medical treatment)
- Anamnestic alcohol or drug abuse
- Untreated hypertension (BT> 150/90) at inclusion
- Functional limiting heart disease
- Epilepsy
- Dementia and/or malign diseases

Recruitment and withdrawals

- 23 & 24: Information to be included in the CONSORT flow diagram

The CONSORT flow diagram (19) will consist of the following:

- All patients assessed for eligibility throughout the recruitment period
- All patients meeting one or more of the exclusion criteria, with reasons
- All patients eligible for inclusion in the trial
- All eligible patients not consenting, with reasons
- All patients randomised for both treatment arms
- All patients receiving and not receiving the allocated treatment for both treatment arms

- All patients with follow-up assessments at the 14 and 90 days post ictus follow-up¹
- Withdrawals/lost to follow-up, with reasons, and timing for both treatment arms
- Patients included in the ITT and per protocol analyses for both treatment arms

¹Patients with complete primary outcomes (6MWT) will be summarised at each follow-up for both treatment arms.

Baseline patient characteristics

- 25a: List of baseline characteristics to be summarised

MOCK table 1 (below) presents an overview of baseline characteristics that will be presented in the primary report.

- 25b: Details on descriptive summary of baseline characteristics

Categorical data will be summarised by numbers (%). Continuous data will be summarised by mean (SD) if data is normal and median (IQR) if data is skewed. No formal tests for significant differences between groups at baseline will be performed, as this is not recommended by CONSORT (19).

Section 6: Analysis

Outcome definitions

- 26: Specification of outcomes and timing

Table 1 presents an overview of outcomes assessed and their timing. MOCK table 2 and 3 illustrate how the results of the primary and secondary outcomes and the safety analysis will be presented in the primary report.

Analysis method

- 27: What analysis methods will be used

Outcomes presented under Primary or Secondary Outcome Measures at ClinicalTrials.gov (ID: NCT03653312) will be reported in the primary RCT report.

The primary endpoint i.e. between-group differences in change in the 6MWT from baseline to 90 days follow up will be analysed in repeated measures mixed effect model with subject being a random factor and visit (i.e. baseline, 14 days- and 90 days follow up) and interaction between visit and treatment arm (exercise with NMES or exercise alone) being fixed factors (20). A confidence interval not including 34.4 meters or more in the 6MWT will be interpreted as a lack of a clinically meaningful difference. Secondary outcomes will be analysed using the same model if appropriate. Model assumptions will be analysed for

normal distribution of residuals and if the assumption of normality is violated, confidence intervals will be estimated using Bootstrapping estimation methods. We will report estimated marginal means with p-values and 95% CI for superiority assessment.

The occurrence of adverse events (AE) will be compared between groups at the 90-days follow up using the appropriate method, if sufficient number of AE occurs the Poisson regression model with a robust error variance or similar.

Missing data

- 28: Handling of missing data

No imputation methods will be applied, as a repeated measures mixed model do not require complete cases (21).

Additional analysis

- 29: Details of any additional analysis

No additional analyses are planned. However, if found relevant, secondary, exploratory analyses might be conducted.

Harms

- 30: Handling of adverse events

Non-serious adverse events (AE) and serious adverse events (SAE) are recorded by asking patients face to face at the follow-up assessments. Additionally, the medical records from the recruiting hospitals will be examined for all AEs occurring from inclusion until the 90 days post ictus follow-up. An AE is defined as any undesirable experience during follow-up leading to contact with the health care system (general practitioner or hospital). AEs will be analysed for AEs and SAEs separately. If an AE results in hospitalisation, prolonged inpatient hospital care, result in surgery, or if an AE is life-threatening, result in death, permanent disability or damage, they will be categorised as SAEs, according to the FDA definition (22). SAEs will include cardiovascular disease and stroke, gastrointestinal and pulmonary events, systemic and local infection (and treatment with antibiotics) and deep vein thrombosis, but also other AEs will be categorized as an SAE in accordance with the FDA definition above.

For all AEs, date of health care system contact is noted. Furthermore, duration of SAEs and potential consequences of SAEs will be registered if possible.

AEs and SAEs will be presented as illustrated in MOCK table 3.

Statistical software

- 31: Details of statistical package used for the analysis

The statistical analysis will be performed in R-studio version 1.1.264

Operating procedures

- 32: Data management

The procedures for data collection and management was approved by the Danish Data Protection Agency (Region Zealand, REG-80-2015). Data entry and coding of the de-identified data will be conducted by trained staff. Personal information about patients is kept separate from the main data set and will not be shared with anyone outside the central study team. To protect confidentiality before, during and after the trial, all personal data is stored securely.

This SAP will form the basis for all analyses of the primary and secondary endpoints, which will be carried out by the Principal Investigator without any involvement from the study chairs. An assistant not involved in the study will code the two treatment arms into 'Group A' and 'Group B' before analysing the data. This will help ensure that the statistical analyses will be performed blinded from treatment allocation.

To reduce risk of interpretation bias, blinded results from the statistical analyses (Group A vs. Group B) will be presented to all authors, who will agree on two alternative written interpretations, one where group A is exercise WITH NMES and one where Group A is Exercise WITHOUT NMES. After finalising the blinded interpretation, the assistant will unblind who is Group A and Group B (23).

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Mock tables**Mock Table 1. Baseline characteristics**

Baseline characteristics	Exercise and NMES	Exercise
Sex		
Age (years)		
Weight (kg)		
Body Mass Index		
Comorbidities		
Earlier function-limited diseases		
Weekly alcohol consumption		
Smoking status		
Smoking (package-years)		
Walking aids prior hospitalisation		
Current Walking aids		
Side of infarction		
Level of force reduction		
Received thrombolysis		
SSS-score		
Fugl-Meyer UE Motor Part		
Fugl-Meyer Total score UE		
6 MWT		
10 MWT		
Timed up and go		
Sit to stand		
Guralnik		

MOCA

Becks Inventory Depression Scale

EQ-5D-5L

Mock Table 2. Outcome at 90 days

	Total no. of assessments (exercise and NMES group/Exercise Only group) ¹	Mean score at 90 days in Exercise and NMES group (95% CI)	Mean score at 90 days in Exercise only group (95% CI)	Mean improvement in exercise and MNES group (95% CI)	Mean improvement in Exercise Only-group (95% CI)	Mean difference in improvement in Exercise (crude) (95% CI)	Mean difference in improvement (adjusted) ² (95% CI)	Between-Group difference in mean improvement (adjusted) (95% CI)
<u>Primary outcome</u>								
6 MWT								
<u>Secondary Outcomes</u>								
10 MWT								
Sit to stand								
Timed up and go								

Fugl-Meyer UE						
Motor part						
Fugl-Meyer UE						
Total						
Guralnik						
MOCA						
Becks						
Depression						
QOL Score						

There were 1200 ($(25 \times 8) + (25 \times 10 \times 2)$) possible assessments for each group (200 at baseline, and 500 at 14 days and at 90 days)

² The results will be adjusted for baseline imbalance