Clinical Investigation Plan (CIP)

Post-Market Clinical Follow-Up Trial of a CE-marked Medical Device

Evaluation of Expiratory Muscle Strength Training in Parkinson´s Disease – a Randomized Controlled Trial

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Academic Trial Sponsor: Karolinska Institutet (KI)

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Protocol Amendment

Protocol Version *No:*	**Version Date** *YYYY-MM-DD*	**Summary of Amendments** *Provide a description of all amendments made since the initial final protocol.*

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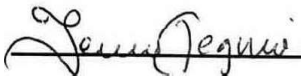
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Signature Page

Responsible Researcher

I am responsible for ensuring that this clinical investigation plan contains all the necessary elements required to conduct the study. By my signature, I confirm that the investigation will be carried out in accordance with this protocol, the EU Medical Device Regulation 2017/745 (MDR), the Declaration of Helsinki, SS-EN ISO 14155 (Good Clinical Practice), and applicable national legislation relevant to this clinical investigation.

I will provide the investigation plan and all other necessary information to the staff members and investigators participating in the study, enabling them to conduct the investigation appropriately. I acknowledge my responsibility to ensure that all personnel involved in the study are continuously informed and adequately trained.



2024-02-12

Signature of the Responsible Researcher — Date

Jenny Tegnevi

Printed Name

List of Abbreviations and Acronyms

Abbreviation	Definition
AE	Adverse Event = Any untoward medical occurrence in a study participant who has participated in the investigation, which does not necessarily have a causal relationship with the study.
CIF	Consent Information Form = Form for informed consent.
CIP	Clinical Investigation Plan= Clinical study protocol.
CRF	Case Report Form = Data collection tool.
GCP	Good Clinical Practice = International ethical and scientific quality standard for designing, conducting, recording, and reporting clinical trials involving human participants.
EMST	Expiratory Muscle Strength Trainer= Device for expiratory muscle strength training.
ICF	International Classification of Functioning, Disability, and Health (WHO, 2001). Standardized international framework for describing functioning and disability in relation to health.
ISF	Investigator Study File = Investigator site file containing all essential study documents in accordance with ICH-GCP.
ITT	Intention-to-Treat = Statistical analysis including data from all participants enrolled in the study.
LV	Medical Products Agency (Sweden) = National regulatory authority for medicinal products.
MEP	Maximal Expiratory Pressure
MPT	Maximum Phonation Time
PP	Per-Protocol Analysis= Statistical analysis including only participants who completed the study according to the protocol without major deviations.
RCT	Randomized Controlled Trial
SS-EN ISO	Swedish Standard – European Standard/International Organization for Standardization
SPL	Sound Pressure Level
SRP	Speech Range Profile = Graphical representation of a participant's speech range in terms of sound pressure level [dB] and frequency [Hz].

1. SYNOPSIS

Title:	Evaluation of Expiratory Muscle Strength Training in Parkinson´s Disease – a Randomized Controlled Trial
Background:	Parkinson's disease (PD) is currently one of the most common neurodegenerative disorders. Impairment of voice and speech can be observed already in the early stages of the disease and is associated with weakened respiratory musculature. In later stages, swallowing function is also affected. In Sweden, the Lee Silverman Voice Treatment (LSVT-LOUD®) method is recommended as a voice treatment intervention for PD (National Board of Health and Welfare, 2016). This is an intensive method that is not tolerated by all patients, which creates a need for complementary therapeutic approaches. One method that has shown positive effects in PD is Expiratory Muscle Strength Training (EMST). The training is performed using a device in which the patient exhales forcefully into a tube against a valve that opens only when a sufficiently high expiratory pressure is achieved. EMST has been part of clinical speech-language pathology practice for several years, both in Sweden and internationally. Improvements in respiratory function have been observed in patients with neurodegenerative diseases, but there is still a need for studies with larger sample sizes (Antonsson et al., 2023). International research has demonstrated that EMST may have beneficial effects on voice, speech, and swallowing function in PD (Brooks et al., 2019; Reyes et al., 2020; van de Wetering-van Dongen et al., 2020; Watson et al., 2022). However, few studies have included individuals in the later stages of the disease. Furthermore, there is a lack of studies that have systematically examined effects on respiratory, laryngeal, and oropharyngeal functions in a coordinated manner. The overall aim of this trial is to contribute to improved national and international treatment guidelines for individuals with PD.
Training Tool:	EMST 150/75
Study Design:	Single-blind randomized controlled trial (RCT). Participants are randomized to one of two study arms: (A) intervention with EMST or (B) passive control group (waitlist for treatment). The intervention is conducted over a period of 5 weeks, with a follow-up after 3 months.
Study Population:	All patients diagnosed with Parkinson's disease who are in contact with the Speech and Language Pathology Department or the Neurology Department at Danderyd Hospital will be invited to participate in the study. Discussions are ongoing regarding the inclusion of additional clinical sites in the Stockholm region.
Primary Research Question:	Does EMST result in a statistically significant improvement in sound pressure level (SPL) measures?
Secondary Research Questions:	Does EMST result in statistically significant improvements in secondary instrumental outcomes related to respiration, voice, speech, and swallowing?

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	Does EMST result in clinically relevant improvements in patient-reported outcomes related to respiration, voice, speech, and swallowing? Does the treatment effect differ with respect to disease severity? Are any observed treatment effects maintained three months after completion of the intervention?
Primary Outcome Measure:	Sound Pressure Level/SPL (dB)
Secondary Outcome Measures:	MPT, speech range, phrase length, MEP, swallowing capacity, patient-reported outcomes.
Sample Size:	Based on the performed power calculation, a total of 80 participants will be included in the study (40 participants in each study arm).
Inclusion Criteria:	A confirmed diagnosis of Parkinson's disease (G20.9), stable medication, and cognitive function corresponding to a score of ≥23 on the Mini-Mental State Examination (MMSE).
Exclusion Criteria:	Untreated hypertension, untreated gastroesophageal reflux disease, asthma, chronic obstructive pulmonary disease (COPD) or other pulmonary disease, and current smoking or smoking within the past 12 months prior to enrollment.
Aim:	The aim of this study is to systematically evaluate the effects of EMST in individuals with PD, from early to advanced stages, with respect to respiratory, voice, speech, and swallowing function.
Ethical Considerations:	The study will be conducted in accordance with Good Clinical Practice (GCP) and will comply with applicable laws and regulations. The content of the informed consent form is consistent with relevant privacy and data protection legislation. The processing of personal data in the study will adhere to the EU General Data Protection Regulation (GDPR) No. 2016/679, as well as supplementary provisions (2018:218). Ethical approval has been obtained (reference number: 2023-04536-01). Date of approval: 5 September, 2023.
Study Period:	First quarter of 2024 to fourth quarter of 2028.

2. DESCRIPTION OF THE MEDICAL DEVICE TRAINING TOOL

2.1 Intended Purpose

EMST is designed to increase the force-generating capacity of the expiratory and orofacial musculature. The device is CE-marked and has been used for several years in clinical practice for neurologically induced voice and speech disorders (dysarthria) to improve vocal loudness and speech intelligibility, as well as for swallowing disorders (dysphagia) to enhance swallowing function and protect against potential aspiration.

2.2 Manufacturer

Company name: Aspire Products, LLC
Address: 101 VFW Rd, Suite 2C
Cedar Point, NC 28584, USA
Fax: 800-861-2090

Swedish distributor: OPIVA Nordic AB www.opivanordic.se

2.3 Model

EMST 150 and EMST 75. The EMST 150 provides expiratory resistance ranging from 30 to 150 cmH_2O, and the EMST 75 from 0 to 75 cmH_2O. Each study participant will be assigned an individual EMST device prior to the start of the intervention, based on their measured maximal expiratory pressure (cmH_2O).





EMST 150; 30–150 cmH_2O.





EMST 75; 0–75 cmH_2O.

2.4. Administration

The intervention group will undergo a five-week home-based training program. The participant performs five forceful exhalations consecutively using the EMST device, constituting one set. According to the Power 5 Training System, five sets are performed per day, five days per week, over a period of five weeks. The training requires approximately 20 minutes per day. A training diary is provided to support adherence. Individual follow-up by a speech and language pathologist is conducted once weekly on a predetermined weekday throughout the training period. At these visits, the expiratory resistance is adjusted to correspond to 75% of the participant's maximal expiratory pressure. A nose

clip is used during all training sessions to prevent nasal air leakage. The participant is not permitted to adjust the preset resistance during the intervention period.

2.5 Target Population
Patients diagnosed with Parkinson's disease (G20.9).

2.6 Required Experience
The investigators involved have extensive clinical knowledge and experience of the target population. All investigators have received thorough training and calibration in the use of the EMST training device, taking into account risk management for medical devices in accordance with SS-EN ISO 14971:2020.

3. BACKGROUND
Parkinson's disease (PD) is currently one of the most common neurodegenerative disorders. More than 20,000 individuals are living with the diagnosis in Sweden (Swedish Neuro Registry, 2021). The disease course is progressive and can broadly be classified into five stages based on motor severity according to the Hoehn & Yahr scale (Hoehn & Yahr, 1967). Impaired respiratory function can be observed already in the early stages. Muscular weakness and rigidity of the respiratory muscles and thoracic cage result in reduced expiratory pressure and airflow (Vincken et al., 1984). Consequently, voice and speech function are affected, and dysarthria occurs in up to 90% of individuals. Common symptoms include reduced vocal loudness, imprecise articulation, and abnormalities in prosody and speech rate (Darley et al., 1969). Dysarthria impairs the ability to be heard and understood, leading to reduced communicative participation and decreased quality of life (Schalling et al., 2017). Swallowing function is also affected, and dysphagia occurs in up to 80% of individuals in the later stages of the disease (Kalf et al., 2012). Reduced expiratory pressure leads to an ineffective cough, impairing secretion clearance and compromising airway protection. This increases the risk of aspiration pneumonia, which is the most common cause of death in PD (Pinter et al., 2015).

Currently, no pharmacological treatments can cure or halt disease progression in PD. Pharmacological therapy typically alleviates motor symptoms, but its effects on axial symptoms are more variable (Rusz et al., 2016). In Sweden, Lee Silverman Voice Treatment (LSVT LOUD®) is recommended for the management of voice and speech disorders in PD (National Board of Health and Welfare, 2016). This is an intensive voice therapy approach that is not tolerated by all patients, highlighting the need for complementary evidence-based treatment methods. Expiratory muscle strength training (EMST) is a treatment method routinely used in clinical practice, both nationally and internationally. The method involves the use of a handheld device through which the individual performs forceful exhalations against an adjustable resistance. The device contains a valve that opens once a sufficient expiratory pressure has been achieved. The intervention is based on principles of motor learning, defined as the ability to acquire and retain motor skills through goal-directed practice (Kleim & Jones, 2008). The resistance of the device is typically set at 75% of the individual's maximal expiratory pressure and is progressively increased as muscle strength improves. Because the resistance is individualized, the training can also be performed in more advanced stages of the disease.

Several studies of EMST have demonstrated positive effects on respiratory function in individuals with neurodegenerative diseases, including increased maximal expiratory pressure, MEP (Antonsson et al., 2023; Watson et al., 2022). MEP represents the pressure generated during exhalation from total lung capacity and is measured at the mouth, reflecting the strength of the intercostal and abdominal muscles as well as the passive elastic recoil of the thorax. Positive effects have also been observed in phonation, including increased vocal intensity and maximum phonation time (Reyes et al., 2020). Furthermore, increased activity has been reported in the suprahyoid and laryngeal musculature, leading to more efficient swallowing and reduced aspiration (Brooks et al., 2019).

In the United Kingdom, EMST is recommended by the National Institute for Health and Care Excellence (NICE) for the management of PD. The method has been used clinically in Sweden for several years in neurodegenerative disorders; however, the scientific evidence has previously been considered insufficient (Swedish Agency for Health Technology Assessment and Assessment of Social Services [SBU], 2022). Positive treatment effects have been reported in PD, but there is a need for studies with larger sample sizes (Antonsson et al., 2023). Previous international research has demonstrated that EMST improves voice, speech, and swallowing function (Brooks et al., 2019; Reyes et al., 2020; van de Wetering-van Dongen et al., 2020; Watson et al., 2022), however few studies have included individuals in later stages of the disease. Moreover, studies simultaneously examining effects on respiratory, laryngeal, and oropharyngeal functions are lacking. As these functions share common anatomical and physiological structures, changes in one area may influence another. Finally, knowledge regarding the durability of treatment effects after completion of training remains limited, which is critical for determining the clinical relevance of the intervention. This clinical investigation will be among the first to evaluate the effects of EMST in early to advanced stages of PD with respect to respiratory, voice, speech, and swallowing functions. The long-term aim of this study is to contribute to the development of improved treatment guidelines at both the national and international levels.

4. BENEFIT-RISK ASSESSMENT

EMST imposes a cardiovascular load comparable to that of a Valsalva manoeuvre (Laciuga et al., 2012). The study has been designed with clearly defined inclusion and exclusion criteria to minimize potential risks to the participants' health. Based on SS-EN ISO 14971:2020, the investigation is not associated with any apparent medical risks or expected adverse effects for included participants. Measures such as randomization and blinding have been implemented to minimize sources of bias (see Sections 6.5 and 6.7). Participation in the study includes a comprehensive speech and language pathology assessment for all participants. Participants in the intervention group will receive EMST treatment and an individual training device (EMST 150/75), which they may retain after completion of the study. Participants in the control group will be offered EMST training after completion of the intervention period. The delay is not considered to have any clinical significance. The potential risks associated with the study in terms of participants' health, safety, and personal integrity are considered minimal and are outweighed by the scientific value and potential therapeutic benefits of the investigation.

5. OBJECTIVES

The overall objective of the study is to systematically evaluate the effects of EMST in early to advanced stages of Parkinson's disease with respect to respiratory, voice, speech, and swallowing functions. A further objective is to investigate the persistence of treatment effects following completion of the training. The overarching goal of the study is to contribute to improved treatment guidelines for Parkinson's disease.

5.1 Primary Research Question

- Does EMST result in a statistically significant improvement in sound pressure level (SPL) measures?

5.2 Secondary Research Questions

- Does EMST result in statistically significant improvements in secondary instrumental outcomes related to respiration, voice, speech, and swallowing?
- Does EMST result in clinically relevant improvements in patient-reported outcomes related to respiration, voice, speech, and swallowing?
- Does the treatment effect differ with respect to disease severity?
- Are any observed treatment effects maintained three months after completion of the intervention?

6. STUDY DESIGN AND PROCEDURE

6.1 General Information

The study is a single-blind randomized controlled trial (RCT) involving the Speech and Language Pathology Clinic and the Department of Neurology at Danderyd Hospital. Discussions are ongoing regarding the inclusion of additional sites in the Stockholm region.

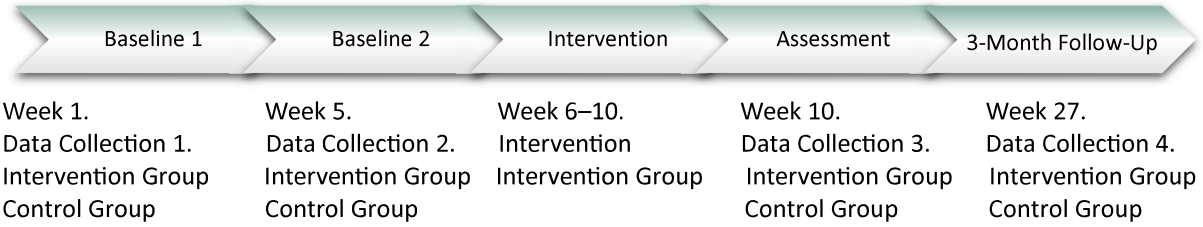


Figure 1. Schematic description of the study procedure.

At the time of enrollment at the clinic, an initial data collection is performed (Baseline assessment 1). For reliability testing, data collection is repeated after five weeks, corresponding to the duration of the intervention period (Baseline assessment 2). Data collection associated with completion of the intervention takes place at week 10. To assess retained effects after the intervention, a follow-up data collection is conducted at week 27, corresponding to three months (87–95 days) after the end of the intervention (Figure 1). All measurements are performed when the participant is optimally medicated with levodopa, based on the timing of the most recent dose intake—no more than 120 minutes and no less than 45 minutes prior to the assessment—as well as the current medication regimen (Silverman et al., 2006)

Table 1. Methods Table.

Outcome Measure	***Measurement Method***	***Unit of Measurement***
Respiration		
Maximal Expiratory Pressure/MEP	MicroRPM	Ratio Scale; cmH_20 [max]
Self-reported Respiratory Symptoms	Dyspnea Index/DI	Ordinal Scale [0–40]
Voice Function		
Speech Range and Vocal Intensity	Speech Range Profile/SRP	Interval Scale; dB [min/max/Leq SPL] Vocal Range in Semitones [Area ST dB]
Maximum Phonation Time/MPT		Ratio Scale; sustained vowel duration (seconds) [max]
Self-reported Voice Symptoms	Voice Handicap Index/VHI	Ordinal Scale [0–120]
Self-administred Symptoms	Self-report Questionnaire /SkaV	Ordinal Scale
Speech Function		
Speech Range and Fundamental Frequency (F0)	Speech Range Profile/SRP	Ratio Scale; Hz [min/max/mean/mode] Speech Range in Semitones [F0 range ST]
Phrase Length		Ratio Scale; syllables per breath group (mean)
Self-reported Speech Symptoms	Self-report Questionnaire on Acquired Speech Difficulties/SOFT	Ordinal Scale [0–30]
Speech-Language Pathologist Assessment of Dysarthria Severity (ICF)	Therapy Outcome Measures/TOMs	Ordinal Scale [0–5]
Swallowing Function		
Swallowing Capacity	The Timed Water Swallow Test/ TWST	Ratio Scale; mL per second
Self-reported Swallowing Symptoms	Sydney Swallow Questionnaire/SSQ	Ordinal Scale/VAS [100 mm]
Food and Fluid Consistency Classification System	International Dysphagia Diet Scale Initiative/IDDSI-FDS	Ordinal Scale [0–7]
Speech-Language Pathologist Assessment of Dysphagia Severity (ICF)	Therapy Outcome Measures/TOMs	Ordinal Scale [0–5]

6.2.1 Primary Outcome Measure

For the collection of measurements related to SPL and secondary phonatory outcomes, audio recordings will be conducted in a sound proof studio using calibrated sound settings. A head-mounted omnidirectional microphone will be used, with a fixed mouth-to-microphone distance of 15 cm. Recordings will be performed using a Speech Range Profile (SRP), which is a two-dimensional graphical representation with the x-axis showing fundamental frequency (Hz) and the y-axis showing vocal intensity (dB). During the recording, participants will read a standardized text at a habitual loudness level and produce spontaneous speech based on a given picture sequence.

6.2.2 Secondary Outcome Measures

Measurement of maximum phonation time (MPT) will be conducted by asking the participant to sustain the vowel /a/. To ensure reliable values, three measurements will be performed with approximately 15 seconds between each attempt. The highest value will be recorded for analysis. Phrase length will be assessed based on a recorded reading task, measured as the number of syllables per breath group (mean value). Maximum expiratory pressure (MEP, cmH_2O) will be measured using the MicroRPM (Respiratory Pressure Meter). Following a maximal inhalation, the participant will exhale as forcefully as possible into the device's mouthpiece for one to two seconds. To ensure reliability, three measurements will be conducted with approximately one-minute intervals. Pressures sustained for at least one second will be accepted, and the highest value will be recorded for analysis (ATS/ERS, 2002). Measurements will be performed in a seated position using a nose clip to prevent nasal air leakage. Swallowing capacity will be assessed using the Timed Water Swallow Test (TWST), in which the participant is instructed to drink a glass of water (150 mL) as quickly and safely as possible without pauses (Hägglund et al., 2022). The time in seconds from when the water touches the lips until the final swallow is completed will be recorded in the test protocol, along with any residual volume. Swallowing capacity (mL/s) will be calculated by subtracting any residual volume from the initial volume and dividing the result by the time. Patient-reported outcomes (PROs) for the respective functions will be measured using rating scales in accordance with the methods table (Table 1). To assess the participant's functional level regarding voice, speech, and swallowing, the Therapy Outcome Measures (TOMs) and the International Dysphagia Diet Standardisation Initiative Functional Diet Scale (IDDSI-FDS) will be used.

6.3 Study Population

All patients diagnosed with Parkinson's disease who are in contact with the Speech and Language Pathology Department or the Neurology Department at Danderyd Hospital will be invited to participate. They will receive both oral and written information about the study. Those who wish to participate will subsequently provide their consent by signing a written informed consent form.

6.3.1 Inclusion Criteria

- confirmed diagnosis of Parkinson's disease (G20.9)
- stable medication
- cognitive function corresponding to ≥23 on the Mini-Mental State Examination/MMSE

6.3.2 Exclusion Criteria

- untreated hypertension
- untreated gastroesophageal reflux disease
- asthma/COPD or other pulmonary disease
- smoking within ≤12 months prior to enrolment

6.3.3 Withdrawal of Consent

Participants may withdraw from the study at any time without any consequences for their ongoing care. In the event of withdrawal, the participant's study-specific ID will not be reassigned, and the participant will not be eligible for re-enrolment in the study.

6.4 Flow Chart

Table 2. Flow Chart.

	Enrolment	Data Collection 1	Data Collection 2	Data Collection 3	Data Collection 4
Patient Information	X				
Patient Consent	X				
Inclusion/Exclusion Criteria	X				
Randomization Protocol	X				
Medication Dose/Timing	X	X	X	X	X
Instruction/Distribution of EMST			X		
Distribution of Training Diary			X		
Collection of Training Diary				X	
Incidents (AE)			X	X	X
MEP		X	X	X	X
Audio Recording (SRP + MPT)		X	X	X	X
TWST (mL/sec)		X	X	X	X
TOM Dysarthria		X	X	X	X
TOM Dysphagia		X	X	X	X
Dyspnea Index		X	X	X	X
Self-report Qustionnaire/SkaV		X	X	X	X
VHI		X	X	X	X
SOFT		X	X	X	X
SSQ		X	X	X	X
IDDSI-FDS		X	X	X	X

6.5 Methods to Minimize Bias

All assessors have received thorough training and calibration regarding data collection procedures in order to avoid distortion of the results. To reduce the risk of performance bias, the assessor measuring outcome variables is not involved in delivering the intervention and is blinded to whether the participant has received the intervention or not. To minimize the risk of unequal distribution of characteristics that may influence outcomes (selection bias), stratified randomization is applied. Participants are initially divided into four subgroups (strata) based on likely influencing factors: motor severity (HY ≤ 2; HY ≥ 3) and sex (male/female). Thereafter, block randomization is performed to assign participants to the respective study arms: A. Intervention and B. Control group (see section 6.7). In order to minimize attrition bias, careful monitoring and analysis of dropouts will be conducted, and all attrition will be recorded in the Case Report Form (CRF). Dropouts occurring after randomization will be handled by including participants in the group to which they were originally randomized (intention-to-treat analysis, ITT), with an additional per-protocol (PP) analysis performed.

6.6 Code Breaking

The principal investigator has access to the code key for collected and electronically stored data in a database secured with two-factor authentication (SharePoint on-Prem). Information regarding data storage will be provided to the authorized representative of the research sponsor. Access to medical records, including demographic data, information on pharmacological treatment, and speech-language pathology–specific outcome measures necessary to achieve the aims of the study, will be requested. A written application for authorization and access to electronic medical records for research purposes will be submitted to the relevant head of department

6.7 Randomization

Participants are randomized consecutively as they are deemed eligible for inclusion in the trial. Randomization is based on a computer-generated randomization list assigning participants to one of two study arms: A. Intervention and B. Control group (www.randomization.com). To reduce the risk of unequal distribution of characteristics that may influence outcomes, participants are consecutively stratified based on potential influencing factors: motor severity according to the Hoehn & Yahr scale (HY ≤ 2; HY ≥ 3) and sex (male/female). This results in four distinct strata (Figure 2). Subsequently, block randomization is performed using sequentially numbered, sealed, opaque envelopes, which are stored in a locked, fireproof research cabinet. When a participant is enrolled in the study, a new envelope is opened, indicating the study arm to which the participant has been allocated. This procedure ensures a continuous flow of participants into both study arms. Participants in the passive control group are placed on a waiting list and are offered EMST treatment after completion of the intervention period.

6.8 End of Trial

The clinical trial will be concluded when the last randomized participant has completed the follow-up data collection three months (87–95 days) after the end of the intervention, in accordance with the instructions outlined in the Case Report Form (CRF) and the Investigator Site File (ISF).

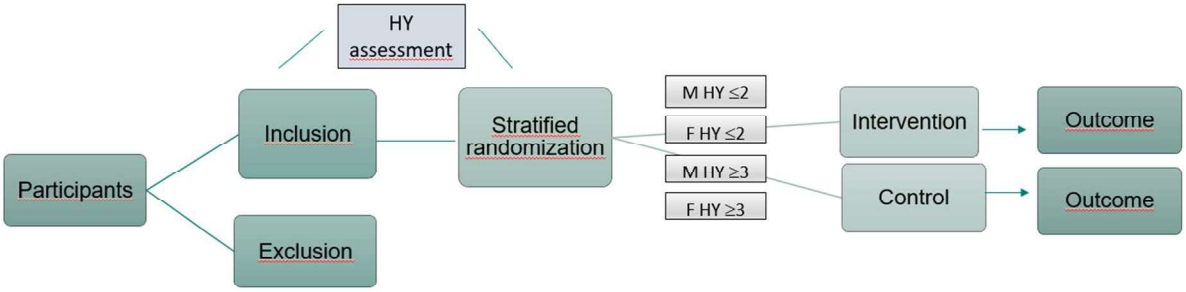


Figure 2. Study Flow Chart.

7. STATISTICS

7.1 Analysis Population

The primary analysis will follow the intention-to-treat (ITT) principle, whereby all participants will be analyzed in the groups to which they were originally randomized, regardless of whether they received the allocated intervention for the full duration of the study or adhered to the planned intervention.
A per-protocol (PP) analysis will be conducted as a sensitivity analysis, including only those participants who received and completed the intervention as planned.

7.2 *S*tatistical Analysis and Methods

To statistically quantify the mean difference before and after the intervention at the group level, effect size (Cohen's *d*) will be calculated, complemented by 95% confidence intervals. A significant intervention effect will be defined as an effect size of ≥0.8. To estimate clinically relevant improvement at the individual level following the intervention, the Reliable Change Index (RCI) will be used.

7.3 Withdrawals and Dropouts

Withdrawals and dropouts after randomization will be handled by including participants in the groups to which they were originally randomized (intention-to-treat, ITT), supplemented by a per-protocol (PP) analysis.

7.4 Sample Size Calculation

The study is powered based on the primary outcome measure, sound pressure level (dB). The sample size calculation is based on previous studies, with an estimated effect size of 1.5 and an expected standard deviation of approximately 2. The significance level is set at 0.05 with a statistical power of 0.8. As the study includes participants with moderate to severe disease, it has been adjusted for an estimated dropout rate of 20%, resulting in a total sample size of 40 participants per group (n = 80).

8. DATA COLLECTION, MANAGEMENT AND ARCHIVING

8.1 Case Report Form

During source data collection, a paper-based case report form (CRF) will be used, which will subsequently be transferred to an electronic CRF (eCRF) stored in a secure database with two-factor authentication (SharePoint on-Prem). All participants will be assigned a study-specific ID and registered on a subject enrolment and identification list, which links the participant's name and personal identity number to the study-specific ID. The code key will be stored in a locked, fireproof cabinet separate from the study data. All data will be recorded, handled, and stored in a manner that allows for accurate reporting, interpretation, and verification. The investigator is responsible for ensuring that data are recorded and that any corrections are made in accordance with established procedures. The investigator must also ensure that the recorded data are accurate and complete, and that reporting is conducted according to predefined timelines. If incorrect source data are entered into the CRF, a single line will be drawn through the incorrect value so that it remains legible. The correct value will be entered next to it, after which the correction will be dated and signed. If the reason for the correction is not self-evident, a brief explanation for the change will be provided.

8.2 Archiving

All source data will be pseudonymized and stored electronically in a secure database. Individual participants will not be identifiable in any presentation of the results. Audio recordings from participants will be stored directly in the digital system Picsara, which is currently used for multimedia management in Region Stockholm. Picsara is directly integrated with the electronic medical record system Take Care; therefore, audio recordings will be stored directly in each participant's medical record. All study data will be handled confidentially. Participants' medical records will be treated in accordance with confidentiality requirements under the Patient Data Act. The complete investigator site file, including essential documents, will be archived for 25 years in accordance with the EU Clinical Trials Regulation (536/2014). Source data in the medical record system will be stored and archived in accordance with national legislation. A copy of the completed case report form (CRF) will be archived at the study site.

8.3 Data Protection

The study will be conducted in accordance with ICH-GCP and applicable laws and regulations. The content of the informed consent form is consistent with relevant privacy and data protection legislation. The participant information explains how study data will be collected, used, published, and stored in order to ensure confidentiality in accordance with national data protection laws. The processing of personal data in the study complies with the EU General Data Protection Regulation (EU) 2016/679 and supplementary national legislation (2018:218).

9. DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN (CIP)

The investigator shall not deviate from the Clinical Investigation Plan unless such deviation is necessary to protect the rights, safety, or well-being of an individual participant in an emergency situation. Any deviations shall be documented and reported to the Medical Products Agency and/or the Swedish Ethical Review Authority (as applicable) as soon as possible.

10. COMPLIANCE AND QUALITY ASSURANCE

10.1 Protocol Compliance, GCP, and Regulatory Requirements

The clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the European Medical Device Regulation (EU) 2017/745 (MDR), the Declaration of Helsinki, SS-EN ISO 14155 (GCP), and applicable national regulations governing clinical investigations. This is to ensure the safety and integrity of the study participants, as well as the quality of the data collected. The clinical investigation will not commence earlier than 30 days after submission of the notification of the clinical investigation of a medical device to the Medical Products Agency. The investigator is responsible for ensuring that data are recorded and that any corrections in the Case Report Form (CRF) are made in accordance with the protocol and relevant instructions. The investigator shall ensure that the recorded data are accurate and complete, and that reporting is performed according to the predefined timelines. The Principal Investigator will sign the completed CRF. A copy of the completed CRF will be archived at the study site.

10.2 Ethics Approval

Ethical approval has been granted by the Swedish Ethical Review Authority (reference no. 2023-04536-01). Approval was issued on 5 September 2023 (Appendix 4). The Swedish Ethical Review Authority and the Medical Products Agency must be informed of any amendments to the ongoing study in accordance with applicable regulations. If the study needs to be terminated prematurely or if an individual study site must be closed early, this must also be reported to the Medical Products Agency.

10.3 Insurance

Patient insurance in accordance with the Swedish Patient Injury Act (SFS 1996:799).

11. INFORMED CONSENT

Potential participants will be approached regarding study participation during visits to the Speech and Language Pathology Clinic or the Department of Neurology at Danderyd Hospital. The investigator is responsible for ensuring that the participant receives complete and adequate oral and written information about the study, including its purpose, potential risks and benefits, and the inclusion and exclusion criteria. Participants will also be informed that they may withdraw from the study at any time without providing a reason. Participants will be given the opportunity to ask questions and sufficient time to consider the information provided. If the participant agrees to take part, they will sign the informed consent form (CIF). A copy of the participant information sheet and the signed consent form will be provided to the participant. Written informed consent must be obtained, signed, and dated before any study-specific procedures are performed. If new information becomes available during the course of the study, participants will have the right to reconsider their participation. If a participant chooses to withdraw from the study, the time of withdrawal and any stated reason will be recorded in the Case Report Form (CRF) and subsequently reported in the study results.

12. MANAGEMENT AND ASSESSMENT OF ADVERSE EVENTS (AE)

The risk of adverse events (AEs) in this study is considered minimal. In the event of unexpected findings or incidents, medical support is readily available, as the study is conducted at an acute care hospital. The guidelines outlined in the Adverse Event Tracking Log in the Case Report Form (CRF) will be followed. All adverse events will be recorded regardless of whether they are assessed as related to the study or not. At a minimum, each AE will be documented with a description of the event (symptoms), start and end date, potential causality, severity, action taken, and outcome.

13. REPORTING AND PUBLICATION

The study results form part of a doctoral project and are expected to be published in peer-reviewed scientific journals following completion of the study. The results are planned to be registered in the clinical trial registry ClinicalTrials.gov.

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