Caloric Vestibular Stimulation in Parkinson's Disease

NCT02703844

July 25, 2018

Statistical Analysis Plan (SAP)

Caloric Vestibular Stimulation to Treat Symptoms Associated with Parkinson's Disease

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Final Version: 10 August 2017

Amended: 15 August 2018

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Signatures for approval of SAP

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Reviewed and approved by:

Principal Investigator: Professor David Wilkinson

Signature: Date:

1. Research question

Do repeated sessions of caloric vestibular stimulation (CVS) induce durable, potentially clinically meaningful improvements in the persistent and disabling motor and non-motor symptoms of Parkinson's disease?

2. Study design

This is a prospective single-blind randomised parallel group pilot study. The study was designed to recruit a diverse sample of 32 individuals diagnosed with idiopathic Parkinson's disease from community and outpatient settings. Participants will be individually randomised to active and placebo arms.

Diagnosis	**Treatment (2 x 20 mins sessions per day for 8 weeks)**	**Number of patients (N)**
Idiopathic	Active stimulation (cohort 1)	16
	Placebo (cohort 2)	16

Randomisation will be conducted using online randomisation software (www.randomiser.org). All participants will be blinded to the treatment being administered.

Prior to the treatment phase of the study, there will be a 4 week baseline phase to measure the rate of natural and spontaneous recovery. Outcome measures will be recorded at week 1 and week 4, and after the beginning of the treatment phase, every 4 weeks until the end of the study.

3. Outcome measures

The primary assessment time will be 12 weeks follow-up and the following outcome measures will be analysed:

- Non-motor symptom scale total score (NMSS)
- MDS-UPDRS 1 (Non-motor aspects of experiences of daily living)
- MDS-UPDRS 2 (Motor aspects of experiences of daily living)
- MDS-UPDRS 3 (Motor Examination)
- MDS-UPDRS 4 (Motor complications)
- MDS-UPDRS total score
- PD-39 total score
- Hospital Anxiety and Depression scale (HADS)
    - Depression total
    - Anxiety total
- Epworth sleepiness scale
- Fatigue severity scale
- Montreal Cognitive exam
- Timed up and go

4. Sample size

The sample size of 32 participants is based on recommendations by Brown[1] and Lancaster et al[2] as a minimum sample size required to estimate the variance of outcome measures to inform the design of a subsequent multi-site randomized control effectiveness trial. Based on previous studies, the expected dropout at 12 weeks was estimated as 20% and a total sample of 40 participants is planned to allow for dropout during the treatment and follow-up phase of the study.

5. Description of the dataset used for the analysis

An Excel database of study data will be created by Dr Kristen Ade. This will contain a separate sheet for each outcome measure and will include baseline data, participant information (demographic and randomisation details, medical history including time since diagnosis, time on levodopa and use of other medications), outcome measures, treatment and visit dates and compliance data.

Data will be reformatted and imported from the excel database to SAS datasets prior to Statistical Analysis, using the SAS IMPORT procedure.

6. Statistical methods

Composite scores of the individual items of each measure will be calculated. Changes from baseline (average of two baseline measures at week 1 and week 4) will be calculated from the composite scores for statistical analysis.

Outcomes will be analysed using analysis of covariance (ANCOVA) to compare the change in the mean response across treatment groups. The outcomes will be adjusted for baseline by including the baseline measure (average of week 1 and 4) as a covariate.

Diagnostic tests and plots to assess the assumptions of normality will be performed prior to analysis. In the case of non-normality, equivalent non-parametric approaches will be utilised, or where appropriate, the data will be transformed prior to analysis.

The primary analysis will be intention to treat, including all available data for participants enrolled in the study. Non-compliance will be reported as an outcome for each group, and the level of missing data will be reported. Sensitivity analysis may be performed to assess the impact of missing data.

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[1] Brown, R. (1995). On the use of a pilot sample for sample size determination. Stat Med 14, pp1933-1940.
[2] Lancaster, G.A. et al. (2004). Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Practice 19, pp307-312.

An exploratory covariate analysis of the outcomes NMSS total score, MDS-UPDRS 2 and MDS-UPDRS 3 will be performed to explore the relationship with response and the interaction between treatment group and the covariates age, gender, time since diagnosis, disease severity, compliance, time on levodopa, and other medication use. A sensitivity analysis of these outcomes will be performed excluding participants who have dementia, to reflect the study population of the follow-on study.

Summary statistics of the outcome measures will be calculated and presented in tables. Summary level data will be presented graphically to illustrate the main findings from the statistical analysis. The brief statistical analysis report will include an overview of methods, including details of data transformations and information about missing data, a summary of the main findings from the statistical analysis and summary tables and plots to support these findings.

The data will be analysed using the SAS software package (version 9.2).

7. Planned start and end of analysis

- Start of analysis: 08/2017
- End of analysis: 09/2017