Statistical Analysis plan (SAP)

Is an integrated treatment of vestibular rehabilitation and cognitive behavior therapy efficacious for persistent dizziness? A randomized controlled trial in a community-based population (the LODIP study)

Lene Kristiansen[1,4], Birgit Juul-Kristensen[2], Kjersti Wilhelmsen[1], Silje Meland[3], Stein-Helge Glad Nordahl[4,5], Richard Clendaniel[6], Anders Hovland[7,8], and Liv Heide Magnussen[1]

Affiliations:

[1] Department of health and functioning, Faculty of Health and Social sciences, Western Norway University of Applied Sciences, Bergen, Norway
[2] Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark.
[3]Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen, Bergen, Norway
[4] Norwegian National Advisory Unit on Vestibular Disorders, Dept of Otorhinolaryngol & Head Neck Surgery, Haukeland University Hospital, Bergen, Norway
[5] Department of Clinical Medicine, University of Bergen, Bergen, Norway
[6] Doctor of physical Therapy Division, Department of Orthopedics, Duke University of Medicine, Durham, NC, USA
[7] Department of Clinical Psychology, University of Bergen, Bergen, Norway
[8] Solli District Psychiatric Centre (DPS), Nesttun, Norway

SECTION 1. ADMINISTRATIVE INFORMATION

1. Title and trial registration

1.a. Title:
Efficacy of integrating vestibular rehabilitation and cognitive behaviour therapy for persons with persistent dizziness in primary care. A randomized controlled trial.

1.b. Trial registration:
The trail was registered on www.clinicaltrails.gov: NCT02655575.

Version

2. Version 1: Date: 22.03.22

3. Protocol version:
This statistical analysis plan (SAP) has been written based on the protocol approved by the Regional Committee for Medical and Health Research Ethics (2014-00921 and the published study protocol for the RCT (1). This SAP adheres to the Guidelines for the content of statistical analysis plans in clinical trials . The SAP was made publicly available before any outcome analyses commenced and before unblinding the data.

4a. Revision history: N/A
4b. Justification of revision: N/A
4c. Timing of revision: N/A

5. Roles and responsibility

Names, affiliations, and roles of SAP contributors:

Principal investigator/ study chair: Liv Heide Magnussen, Department of health and functioning, Faculty of Health and Social sciences, Western Norway University of Applied Sciences, Bergen, Norway

***Phd student/ SAP author*:** Lene Kristiansen, Department of health and functioning, Faculty of Health and Social sciences, Western Norway University of Applied Sciences, Bergen, Norway

Co-authors

Birgit Juul-Kristensen, Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark

Kjersti Wilhelmsen, Department of health and functioning, Faculty of Health and Social sciences, Western Norway University of Applied Sciences, Bergen, Norway

Silje Mæland, Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen, Bergen, Norway

Stein-Helge Glad Nordahl, Norwegian National Advisory Unit on Vestibular Disorders, Dept of Otorhinolaryngol & Head Neck Surgery, Haukeland University Hospital, Bergen, Norway, and Department of Clinical Medicine, University of Bergen, Bergen, Norway

Richard Clendaniel, Doctor of physical Therapy Division, Department of Orthopedics, Duke University of Medicine, Durham, NC, USA

Anders Hovland, Department of Clinical Psychology, University of Bergen, Bergen, Norway, and Solli District Psychiatric Centre (DPS), Nesttun, Norway

Biostatistician/ Statistical advisor:
Birgitte Espehaug, Western Norway University of Applied Sciences, Bergen, Norway

6. Signatures

SAP Author (date): L Knoh ansen 29/3-22

Primary investigator (date): Liv Heide Magnussen 25/3-22

Statistician (date): Birgitte Espehaug 30/3-22

SECTION 2: INTRODUCTION

7. Study synopsis / Background and rationale

Background

This is the statistical analysis plan for the randomised controlled study evaluating the efficacy of integrating vestibular rehabilitation and cognitive behaviour therapy as treatment for persons with persistent dizziness. The study is conducted in Bergen, Norway. This plan will be used as a work description of the analyses of the data collected.

The combination of Vestibular Rehabilitation (VR) and Cognitive Behaviour Therapy (CBT) is suggested to have positive effects on persons with dizziness (2-6). However, the studies included small sample sizes, no random allocation, or no standardised treatment manual. A feasibility study of a treatment integrating VR and CBT showed that such a treatment approach was feasible and safe (7), and the treatment approach is ready for evaluation in a randomised controlled trial.

8. Study objectives and hypothesis

The overall goal for this study is to evaluate the efficacy of a group-treatment integrating VR and CBT (TREATMENT group), compared with a tailored home-exercise program with telephone follow-up (CONTROL group) in persons with persistent dizziness.

Hypothesis:

Participants receiving the Vestibular Rehabilitation and Cognitive Behaviour Therapy (VR-CBT) programme will show significantly superior reduction in perceived dizziness related handicap in addition to increased preferred gait velocity, compared with persons completing a home-exercise program with telephone follow-up.

SECTION 3: TRIAL METHODS

9. Brief description of trial design

The study is designed as an assessor-blinded randomised controlled superiority trial with a two-group parallel design. All participants received a brief Intervention Vestibular rehabilitation session (BI-VR) (see study-protocol (1)) before being randomised, using block randomisation (with 16 participants in each block), into either CONTROL (home-exercises) or TREATMENT (VR-CBT) group.

All included participants went through baseline assessment comprising physical examination outcome measures and self-reported questionnaires. Prior to randomisation all participants received an individual one-hour BI-VR session with a physiotherapist. The session included physical examination, information regarding the vestibular system and possible causes of dizziness, advice related to findings, all with the intention of reducing fear of movement. In

addition, the participants were supervised in selected VR exercises related to their complaints. All participants were advised to be active. After the BI-VR session, the participants were randomised into a CONTROL or TREATMENT group.

The participants allocated to CONTROL were encouraged to work with the exercises prescribed by the BI-VR physiotherapist, and to stay active. The physiotherapist offered two telephone consultations during a 4-month period to encourage compliance with home-exercises and answer questions that may have arised.

The participants allocated to TREATMENT group attended a structed group-treatment program (VR-CBT). Each group included five to eight participants attending weekly group sessions for 8 weeks. Each session lasted 2 hours and was led by two physiotherapists, integrating VR and CBT following an established treatment manual.

The primary endpoints will be the between group difference in change of dizziness related handicap and preferred gait velocity from baseline to 6 and 12 months follow up.

The study has two primary outcomes;
Dizziness-related handicap is measured using the Dizziness Handicap Inventory (DHI). The DHI is designed to quantify the perceived impact of dizziness and unsteadiness. It contains 25 questions, each item has 3 alternative scores "0" (no), "2" (sometimes) and "4" (yes), giving a score range of 0 to 100 DHI points (8).

Preferred gait velocity is used as a measure of functional level. The participants are asked to walk down an 8-meter pathway, timed in the middle 6 meters. The trial is timed using a stopwatch, from when the first foot passes the start point, to where the last foot passes the stop point. The mean velocity over two trials is calculated and presented in m/s.

A more detailed description of the study is presented in the protocol (1).

10. Randomisation and blinding.
After BI-VR the participants were block-randomised (in blocks of 16) into two groups, the CONTROL or TREATMENT group (Group A or B). Group allocations were performed using a random number generator and presented in a concealed envelope after completing the BI-VR. After breaking the code, the BI-VR therapist and the participants were aware of group allocation, while the assessor, also analysing the data, remained blinded. Prior to testing at 6- and 12-months participants were reminded not to divulge group allocation.

Prior to breaking the blinding, the authors of this SAP will agree on how to interpret the results on the bases of a blinded review of the data from the primary endpoints. Two possible interpretations will be made. One assuming that group A was in the treatment group, and the other assuming that group B was in the treatment group. When all authors have agreed to the interpretations, the randomisation code may be open. This procedure is conducted to reduce bias in the interpretation of the results.

11. Sample size calculation

The sample size calculation was based on the between group difference in the mean change scores of the total DHI score and the preferred gait velocity. As two primary outcomes were chosen for the study power and sample size calculation was calculated for both outcomes (1). In order to obtain a clinically important group difference in the DHI of 11 points (9), with a significance level of 0.05 and a power of 80% (SD 18.95), 47 participants are required per group. In order to obtain a clinical important group difference in preferred gait velocity of 0.1 m/s (10, 11) with a significance level of 0.05 and a power of 80% (SD 0.15), 36 participants are required per group.

Therefore, the larger sample size of 47 in each group was used, resulting in at least 94 participants. To reduce the risk of dropouts affecting the analyses the preferred sample size was set to 124 participants, allowing for a conservatively estimated drop-out rate of 24%.

12. Description of hypothesis testing framework

All outcomes will be analyzed using a superiority framework, expecting that participants attending TREATMENT group will improve more than participants in the CONTROL group.

13. Planned interim analyses and stopping guidance

The published study protocol suggested possible interim analyses to adjust sample size. Apart from that no formal stopping guidelines or interim analyses were planned.

14. Details of timing of analyses

Participants were assessed at baseline, with follow-up testing after approximately 6 and 12 months. All analysis will be analysed after final data-collection. The primary outcomes will be analysed by a blinded biostatistician. The secondary outcomes will be analysed by LK. Data from baseline, 6- and 12-months follow-up will be included in these analyses. All primary and selected secondary outcomes presented at www.clinicaltrials.gov (NCT02655575) will be presented in the primary or subsequently secondary reports.

15. Timing of outcome assessments

Table 1. An overview of the different stages of the study, with a presentation of outcomes and their timepoint for testing.

	STUDY PERIOD			
	Enrolment		Post-allocation	
Timepoint	Month 0-2	Month 1-6	6 months	12 months
ENROLMENT				
Eligibility screen	X			
Informed consent	X			
Allocation	X			
INTERVENTIONS				
BI-VR	X			
VR-CBT/ Home exercises		X		
ASSESSMENTS				
Initial questionnaire and demographics	X			
Clinical dynamic visual acuity	X			
Grip strength	X			
PRIMARY OUTCOMES				
Dizziness Handicap Inventory	X		X	X
Preferred gait velocity	X		X	X
SECONDARY OUTCOMES				
Physical tests				
Fast gait velocity	X		X	X
Elements from GPE	X		X	X
Dual task walking	X		X	X
Body sway	X		X	X
Head movement induced dizziness	X		X	X
Questionnaires				
Mobility Index, Alone	X		X	X
Body Sensation Questionnaire	X		X	X
Agoraphobic Cognition Questionnaire	X		X	X
Panic Attack Scale	X		X	X
Hospital Anxiety and Depression Scale	X		X	X
Vertigo Symptom Scale- Short form	X		X	X
Chalders fatigue questionnaire	X		X	X
EQ5D-5L	X		X	X
Subjective Health Complaints	X		X	X
Patient Global impression of Change			X	X

SECTION 4: STATICAL 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 95% confidence level ($p < 0.05$).

17: Adjustment for multiplicity
Since this study has two primary outcomes post-hoc analysis the Holm-Bonferronni method will be used to control for a possible Type 1 error.

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

Adherence and protocol deviations

19.a. Definition of adherence to the intervention
Satisfactory adherence for the VR-CBT group was predefined as attending 6 of the 8 group treatment sessions (75%), and completion of at least 80% of the exercise diaries, where 100% was predefined as reporting exercising and following the walking program 5 times per week. Satisfactory compliance in the control group was predefined as completion of at least one phone call with the BI-VR therapist (1).

19.b. Description of how adherence will be presented
The adherence will be presented as the number and percentage of participants achieving satisfactory adherence (described above). For the intervention group the adherence to group attendance and home-exercises will be presented separately.

19c & 19d. Definition of protocol deviations and how they will be reported
Major deviations from adherence to protocol is defined as:

- Less than 50% attending more than 75% of the VR-CBT treatment.
- Less than 50% completing at least one follow-up telephone call.

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

Analysis populations

20. Definition of analysis populations

Intention-To-Treat: Primary analyses will be conducted according to intention to treat protocol, where all participants were included according to the treatment group they were randomized into. The distribution of the primary outcomes (change score of DHI and preferred gait velocity) will be visualized using scatterplots and described by mean and 95% CI for each group.

Per protocol: In addition, analyses will be conducted on the two groups with respect to treatment adherence (See definition of good adherence section 19a). Thus, analyses will be conducted using per protocol analysis, according to this comparison:

- Participants in the CONTROL group with good adherence, and no other interventions.
- Participants in the TREATMENT groups with good adherence, and no other interventions.

SECTION 5: TRIAL POPULATION

Screening data

- 21. Reporting of screening data

The total number of possible participants screened for eligibility throughout the recruitment period (start and end date) will be reported.

Eligibility

- 22. Summary of eligibility criteria

Inclusion criteria:

- 18-70 years
- Acute onset of dizziness, with symptoms lasting at least 3 months
- Dizziness triggered/ worsened by head movements

Exclusion criteria:

- Self-reported non-vestibular reason for dizziness (e.g. neurological condition)
- Fluctuating vestibular disease (e.g. Menières disease)
- Recently treated or organised future treatment for benign paroxysmal positional vertigo (1 month previously or in the future).
- Conditions where fast head movements are contraindicated (e.g. osteoporosis of the neck)
- Severe/ terminal pathology
- Participation of group therapy for dizziness in within the past year

- Inadequate Norwegian language proficiency (written and oral)
- Unable to attend test and treatment location.

Recruitment and withdrawals

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

The CONSORT flow diagram 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 randomized for both treatment arms
- All patients receiving and not receiving the allocated treatment for both treatment arms
- All patients with answered DHI questionnaire at 6- and 12-months follow-up
- All patients with registered preferred gait velocity at 6- and 12-months follow-up
- Withdrawals/lost to follow-up with reasons and timing for both treatment arms
- Patients included in the ITT and per protocol for both treatment arms

Baseline patient characteristics

- 25a: List of baseline characteristics to be summarized

Baseline data that will be presented include: Age, gender, duration of dizziness, education level, reported employment status, number of dizziness complaints, reported weekly activity level. In addition will primary and secondary outcome scores at baseline be presented.
For further details, please see the published study protocol (1).

- 25b: Details on descriptive summary of baseline characteristics

Categorical and binary data will be summarized by absolute and relative frequencies. Continuous and count data will be summarized by mean and median with standard deviation and percentiles as appropriate. In case of only few different values observed or unusual shape of the distribution (e.g. bimodality, extreme skewness), also absolute and relative frequencies will be reported, potentially after a suitable categorization. No formal tests for significant differences between groups at baseline will be performed, as this is not recommended by CONSORT.

SECTION 6. ANALYSIS

Outcome definitions

- 26. Specification of outcomes and timing.

Table 1 presents an overview of the outcomes and timing. A detailed presentation of the primary outcomes is presented in section 3, while the secondary outcomes are presented in the study protocol (1).

Analysis methods

- 27. What analysis methods will be used

All outcomes will be presented using descriptive statistics; normally distributed data by the mean and standard deviation (SD), and skewed distributions by median and interquartile range (IQR). Binary and categorical data will be presented using *counts* and percentages.

Primary outcomes:
The efficacy analysis will be based on the assessment of the between group differences in changes in DHI scores and preferred gait velocity at 6- and 12-month follow-up. A linear-mixed model with repeated measures will be applied, where group allocation (TREATMENT and CONTROL) and time (6 and 12 months) will be treated as categorical values. The estimated difference in change will be presented in group means and 95% confidence intervals with associated p-values.

Secondary outcomes
Continuous secondary outcomes will be analyzed using the same method as described above.

Missing data

- 28. Handling of missing data

The analysis will use the Intention to Treat (ITT) principle, analysing all randomised participants independent of compliance and withdrawals. In the event of missing data two methods will be used.

For missing single questions, the mean baseline value for the respected group will be assigned. If a complete questionnaire or physical outcome is missing a non-responder imputation will be used.

Loss to follow-up analyses: Dropouts are defined as those who did not complete both physical assessment and patient reported outcomes at 6- or 12-month follow-up. Multiple imputation will be utilised where data is missing.

Additional analysis

- 29. Details of any additional analysis

Additional reports may be presented on the outcomes presented at ClinicalTrials.gov (ID: NCT02655575).

Harms

- 30. Handling of adverse events

Participants may experience increased symptoms in the short term. However, serious adverse events (e.g death, life-threatening events, disability, and permanent damage) is not anticipated. We will report the number of adverse events if present.

Statistical software

- 31. Details of statistical package used for the analysis

STATA (StataCorp, College Station, Tx, USA) will be used for the analyses.

Operation procedures

- 32. Data management

Three assessors are involved in data collection. The principal investigator will register all data into files stored on a secure server. Paper copies, where applicable, will be stored securely, only accessible by the principal investigator. Personal information will be stored separate from the main data and will not be shared by anyone outside the central study team.

This SAP will form the basis for all analysis of the primary and secondary outcomes. An researcher not involved in the current project will code the two treatment arms into "Group A" and "Group B" as part of the randomization procedure. The division will help to ensure that the statistical analyses of the primary outcome will be performed blinded from treatment allocation. In a first step, the data will be passed to the epidemiologist/biostatistician without any information on the compliance and on adverse events to ensure blinding. The epidemiologist/ biostatistician will finalize the ITT analysis of the primary outcome. The phd candidate (LK) will complete the per-protocol analysis as well as the secondary analyses. To reduce risk of interpretation bias, blinded results from the ITT analysis (Group A vs. Group B) will be presented to all authors, who will agree on alternative written interpretations, one where group A is BI-VR and one where Group A is VR-CBT. After finalizing the blinded interpretation, and the blinded analyses of the primary outcomes, the project manager will unblind who is Group A and Group B.

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