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**STATISTICAL ANALYSIS PLAN**

**Trial Name**: A pilot randomised controlled trial of Problem-Solving Treatment for Visual Impairment (POSITIVE)

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**Protocol Paper**: Riazi A. et al. A pilot randomised controlled trial of Problem-Solving Treatment for Visual Impairment (POSITIVE): protocol paper. Ophthalmic Physiol Opt 2014; 34: 489–497.

**Version:** 0.2

**Date**: 17 October 2014

**Version History**

0 (06 June 2014) Draft analysis plan.

0.1 (08 September 2014) Draft analysis plan

0.2 (17 October 2014) Draft analysis plan

**BACKGROUND**

**From Protocol**

This trial is a pilot, multicentre, individually randomised controlled trial. The aims of this study are to evaluate whether Problem-Solving Treatment (PST), a brief, structured psychological intervention, leads to better psychological well-being, in people who have been recently diagnosed as blind or partially sighted.

**OUTCOME MEASURES**

**From Protocol**

**Primary Outcome Measures**

Our primary outcome measure is psychological well-being, measured by the Warwick-Edinburgh Mental Well-being Scale (WEMWBS).

**Secondary Outcome Measures**

Secondary outcomes are as follows:

1. Psychological distress: Hospital Anxiety and Depression Scale
2. Functional mobility:
3. Self-assessed Instrument for Perceived Visual Ability for Independent Mobility
4. Life Spaces Questionnaire
5. Quality of life:
6. Impact of Vision Impairment Questionnaire
7. VISQOL
8. Problem-solving ability: Social Problem Solving Inventory – Revised: Short
9. Self-efficacy: Generalized Self-efficacy Scale
10. Self-reported information on health resource use over the previous 4 weeks will also be gathered by a health resource use questionnaire developed for a previous study.

**SAMPLE SIZE CALCULATIONS**

**From Protocol**

Approximately 120 patients will be entered into the study, 60 in the Problem-solving Treatment arm and 60 in the control arm. With this sample size the study will have 80% power to detect a statistically significant treatment difference between the groups on the Warwick-Edinburgh Mental Well-being Scale at the 5% significance level, assuming a true difference of 5 points, a standard deviation of 8.8 (a conservative estimate derived from a Scottish population survey23, and a 15% rate of attrition.

**ANALYSIS SUMMARY**

**From Protocol**

The primary analysis will be a comparison of the primary outcome measure, WEMWBS, across treatment groups using an analysis of covariance (ANCOVA) approach via a mixed model to adjust for baseline scores and stratification factor and measurements at multiple time-points. Analysis will be conducted once the outcome measures have been transformed to interval-level measurement using Rasch analysis.37

Baseline comparability of the two groups, acceptance of and adherence to treatment, and descriptive statistics for all outcome measures will be presented. Analyses will be carried out using all randomised patients using the principle of Intention-To-Treat (ITT). Effect sizes will be reported with confidence intervals. If sufficient numbers are not collected then only descriptive statistics will be presented, rather than *p*-values. Secondary analyses will adjust for covariates including age, gender, cause and degree of visual impairment. Additional secondary analyses will explore whether there are any subgroup effects such as between those who have severe or moderate/slight vision loss.

Supplementary, exploratory analyses will be carried out to determine predictors of response to treatment. These will include: 1) dichotomous variables e.g. whether the individual has severe or moderate/slight vision loss; and 2) continuous variables e.g. scores on baseline questionnaires. Preliminary mediation analyses will be conducted to examine self-efficacy as a possible mediator of the treatment effect. Further exploratory analyses to examine the extent of vision loss, as a potential moderator of response to treatment, will also be conducted. The impact of missing data will be investigated via imputation and sensitivity analyses.

**ANALYSIS DETAILS**

General Principles

The assumptions underpinning each method will be checked. For example, residuals will be checked for normality and constant of variances for linear mixed models. The use of transformations or non-parametric methods will be considered if assumptions do not hold. Adjusted analyses will be performed if baseline imbalances are observed. The impact of missing data will be explored in all analyses; sensitivity analyses/multiple imputation will be performed as appropriate. Secondary ‘per protocol’ / ‘as treated’ analyses will be performed if non-compliance is thought to be a problem. Regression models with interaction terms will be used to perform pre-specified subgroup analyses; the results from these will considered as exploratory because the study is not powered for these.

Patient Characteristics

A consort diagram will be presented. Baseline patient characteristics will be described using means (SDs) or medians (interquartile range) for continuous measures, and proportions for categorical measures. These values will be presented by randomisation group. A visual assessment will be made regarding the balance achieved by randomisation.

Missing items for Outcomes

Total scores will be computed using the recommended algorithm for each scale. Where there are missing items on a scale, mean imputation will be performed if:

* There is a maximum of three items missing on the WEMWBS scale.
* There is a maximum of one item missing per subscale on the HADS, or two items missing from the total HADS.
* There is a maximum of two items missing on the VISQOL.
* There is a maximum of one item missing on each subscale, and a maximum of two missing on the total scale for SPSI-RS.
* There is a maximum of three items missing on the Generalised Self-Efficacy scale.

Missing items on the Impact of Vision Impairment Questionnaire, Independent mobility Questionnaire, and Life Spaces Questionnaire will be imputed using mean imputation if no more than 50% of items on the scale are missing.

**Primary Outcome Analysis**

Primary Analysis

Our primary outcome measure is the Rasch WEMWBS score at 3, 6, and 9 months. A linear mixed model will be used to analyse the repeated measures, with a fixed effect for treatment and time, and an adjustment for baseline Rasch WEMWBS score and severity of vision loss (stratification factor). A random effect for patients will be included. The effect size will be presented with a 95% confidence interval and corresponding p-value. The assumptions of the test will be checked. If these are not satisfied, a suitable transformation or non-parametric test will be performed as appropriate.

Sensitivity Analysis

1. The primary analysis will be repeated using raw WEMWBS scores. The effect size will be presented with a 95% confidence interval and corresponding p-value.
2. The primary analysis will be repeated, including additional covariates of age, gender, and cause of visual impairment as fixed effects in the model. The effect size will be presented with a 95% confidence interval and corresponding p-value.
3. A sensitivity analysis will be performed to exclude patients who did not complete the treatment. We will characterise the patients who did not complete the treatment and match patients from the control group with the excluded patients in the treatment group. An appropriate analysis will then be performed to preserve balance between the treatment groups.

Secondary Analysis

1. The primary analysis will be repeated to explore an interaction between treatment and time, although no formal conclusions will be made as the study is not powered for this. This will be done by including an interaction between treatment and time in the primary analysis model as a fixed effect.
2. The primary analysis will be repeated to explore an interaction between severity of vision loss and treatment effect. A linear mixed model will be used with a fixed effect for treatment and time, and adjusting for the covariates baseline Rasch WEMWBS score and severity of vision loss, including an interaction term between treatment and severity of vision loss.
3. We will explore problem solving ability (**SPSI-RS**) and self-efficacy (**Generalised Self-Efficacy Scale**) as possible mediators of the treatment effect. The primary analysis will be repeated including each score at baseline to determine if this changes the effect of treatment on psychological well-being.

**Secondary Outcome Analysis**

These secondary analyses should be viewed as exploratory as the study is not powered for these. The effect sizes will be presented with 95% confidence intervals.

The secondary outcomes measured are:

1. symptoms of distress:

**HADS** total and subscale scores

1. functional mobility

**Independent Mobility Questionnaire:** Total score and Rasch converted score

**Life Spaces Questionnaire** total score

1. quality of life

**Impact of Vision Impairment Questionnaire**: Total score, subscale score, and Rasch converted score

**VISQOL** total and subscale scores

1. problem-solving ability

**SPSI-RS** total and subscale scores

1. self-efficacy

**Generalised Self-Efficacy Scale** total score

Secondary outcomes 1-3 have been measured at 3, 6, and 9 months. Secondary outcomes 4 and 5 have been measure at baseline, 6 and 9 months.

A linear mixed model will be run for each secondary outcome separately with fixed effects for treatment group, time, baseline score and severity of vision loss. A random effect for patient will be included in the model. The effect size will be presented with a 95% confidence interval.