Statistical Analysis Plan

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Table of Contents

1 STUDY DETAILS

1.1 Study Objectives

The primary objective of this study is to investigate if an internet-delivered 8-week cognitive behavioural therapy (CBT)-based intervention is effective in terms of reducing gambling related behaviours in individuals with a gambling disorder, compared to a control treatment.

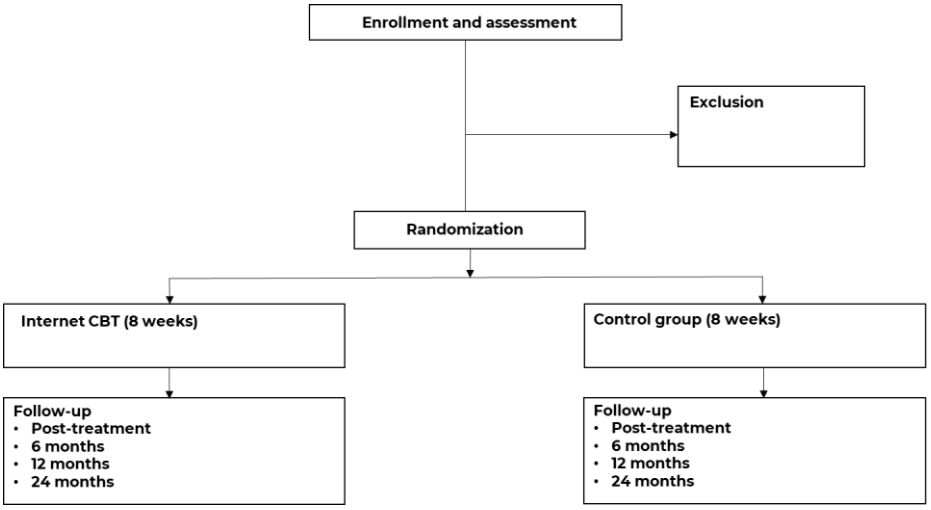
Secondary objectives are to investigate if an internet-delivered 8-week cognitive behavioural therapy (CBT)-based intervention is effective in terms of reducing gambling related irrational beliefs, symptoms of depression and anxiety, and increasing quality of life, in individuals with a gambling disorder, compared to a control treatment.

1.2 Study Design

Single-centre, participant-blinded, randomized controlled trial, with an active control group consisting of a non-CBT intervention.

The following information will be collected during the study:

- NORC Diagnostic Screen for Gambling Problems (NODS) (Wickwire et al., 2008), at start of treatment (pre-treatment, week 0) and every second week until end of treatment (week 8).
- Amount gambled/week (G-TLFB) (Hodgins & Makarchuk, 2003), at start of treatment and every week until end of treatment.
- Depressive symptoms via PHQ-9 (Kroenke, Spitzer, & Williams, 2001), at start of treatment and every week until end of treatment.
- Gambling related cognitive distortions measured by the GBQ-SE (Mide et al, 2022), at start of treatment, after four weeks, and end of treatment.
- Anxiety symptoms measured by the GAD-7 (Spitzer, Kroenke, Williams, & Löwe, 2006), at start of treatment, after four weeks, and end of treatment.
- Quality of life measured by the BBQ (Lindner et al., 2016), at start of treatment and end of treatment.



1.3 Treatment Groups

The ICBT treatment consists of an 8-week internet-delivered treatment based on cognitive behavioural therapy. Patients will work through modules containing psychoeducation and CBT-exercises, one module/week. They will have active therapist support, by short e-mail messages and short telephone contacts once a week.

The IMI is a Motivational Interviewing (MI) based active control treatment designed specifically for this study. The control treatment is similar to the evaluated treatment in its structure but does not contain CBT elements. It is designed to provide psychoeducation, motivational enhancement, and support. It also consists of 8 modules over 8 weeks. It will contain feedback via e-mail, and telephone support. However, the content of the modules is more limited. It mainly contains psychoeducation about gambling and gambling disorder and open-ended questions congruent with MI. MI will be used for the telephone support.

1.4 Sample Size

A total of 64 patients (32 per group) will be included in the study to demonstrate an improvement of 2 units in NORC Diagnostic Screen for Gambling Problems (NODS) (Wickwire et al., 2008) with ICBT compared to IMI treatment groups. Assumptions are a standard deviation of 2.5 units, significance level alpha=0.05, 80% power, two-sided T-test. Under these assumptions, a total of 52 subjects (n=26 per group) are needed. A sample size inflation of 20% was employed to account for missing data, resulting in a total sample size of 64 patients. Recruitment will continue until 64 patients have been randomised and started the treatment. With 10% pre-treatment drop-out, we expect that a total of 72 randomised patients (36 per group) are needed.

2 STUDY POPULATIONS

2.1 Definition of Study Populations

The Full Analysis Set (FAS) consists of all randomized subjects with at least one post-baseline measurement. The Intention-To-Treat (ITT) population consists of all randomised patients who started the treatment, i.e., with at least one measurement including baseline.

3 STUDY VARIABLES

3.1 Baseline Variables

3.1.1 Demographics and Baseline Characteristics

- Age,
- Sex,
- Place of birth,
- Education,
- Civil status,
- Occupation,
- Economic situation,
- Smoking,
- Duration of gambling problems,
- Previous treatment,
- NORC Diagnostic Screen for Gambling Problems (NODS) at treatment start,
- Amount gambled per week (G-TLFB) at treatment start,
- Depressive symptoms (PHQ-9) at treatment start,
- Gambling related cognitive distortions (GBQ-SE) at treatment start,

- Anxiety symptoms (GAD-7) at treatment start,
- Quality of life (BBQ) at treatment start.

3.2 Efficacy Variables

3.2.1 Primary Efficacy Variable

The primary efficacy variable is the NORC Diagnostic Screen for Gambling Problems (NODS) at end of treatment (8 weeks follow-up).

3.2.2 Secondary Efficacy Variables

Secondary efficacy variables are

- Amount gambled per week (G-TLFB) at end of treatment.
- Depressive symptoms (PHQ-9) at end of treatment.
- Gambling related cognitive distortions (GBQ-SE) at end of treatment.
- Anxiety symptoms (GAD-7) at end of treatment.
- Quality of life (BBQ) at end of treatment.

4 STATISTICAL METHODOLOGY

4.1 General Statistical Methodology

For descriptive purposes, data will be presented with mean and standard deviation or median and interquartile range for numeric variables, and as number and percent for categorical variables.

Statistical analyses will be performed using repeated measures analysis of covariance (ANCOVA) on all post-baseline measurements, and analysis of variance (ANOVA) on all baseline and post-baseline measurements. The response variable will be the efficacy variable at each visit. Explanatory variables will be treatment and visit as factors, baseline value as covariate, and visit times treatment and visit times baseline value interactions. For the ANOVA, all terms involving the baseline covariate will be omitted since baseline measurements are included in the response vectors. A general unstructured covariance matrix will be used to account for correlations between repeated measures on the same patient. In case of convergence issues, simplification to Toeplitz heterogeneous, AR(1) heterogeneous, compound symmetry heterogeneous, Toeplitz (homogeneous), AR(1) (homogeneous) and compound symmetry (homogeneous) covariance matrix will be considered in the order listed. Full information maximum likelihood estimation with REML method will be used to account for missing data under an assumption of missing at random. The treatment effect at end of treatment will be calculated using estimated marginal means and presented with 95% confidence interval. Denominator degrees of freedom will be calculated using Kenward-Roger approximation. Effect size will be calculated by dividing the estimated treatment effect by the pooled standard deviation at baseline. For descriptive purposes, the mean difference between treatments per visit will also be presented.

The primary and secondary efficacy analyses will be performed using repeated measures ANCOVA on the full analysis set. Sensitivity analyses will be performed using repeated measures ANOVA on the intention-to-treat population. All tests will be two-tailed and conducted at 0.05 significance level. All analyses will be performed using IBM SPSS Statistics version 28.0.1.1 (IBM Corp., Armonk, NY).

4.2 Patient Disposition

The number of subjects included in the FAS and ITT populations and subjects that withdrew from study prematurely will be summarized by treatment group.

4.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarised by treatment group for the FAS and ITT population.

4.4 Efficacy Analyses

4.4.1 Primary Efficacy Analysis

The mean difference in NODS between the ICBT and IMI treatments at end of treatment (week 8) will be estimated by estimated marginal means from repeated measures ANCOVA on the full analysis set, adjusted for visit, baseline values, visit treatment and visit with baseline value interactions, as detailed in section “General Statistical Methodology” above.

4.4.2 Secondary Efficacy Analyses

The mean difference in the secondary efficacy variables G-TLFG and PHQ-9 between the ICBT and IMI treatments at the end of treatment will be estimated by estimated marginal means from repeated measures ANCOVA on the full analysis set, adjusted for visit, baseline values, visit treatment and visit with baseline value interactions, as detailed in section “General Statistical Methodology” above.

The mean difference in the secondary efficacy variables GBQ-SE and GAD-7 between the ICBT and IMI treatments at the end of treatment will be estimated by estimated marginal means from repeated measures ANCOVA on the full analysis set as described above.

The mean difference in the secondary efficacy variables BBQ between the ICBT and IMI treatments at end of treatment (week 8) will be estimated using ANCOVA, adjusted for baseline values.

4.4.3 Sensitivity Analyses

Sensitivity analyses of primary and secondary efficacy variables will be performed using repeated measures ANOVA on the intention-to-treat population, with baseline included as visit and baseline measurement included as outcome.