TALKING WITH VOICES

NHS Greater Manchester Mental Health NHS Foundation Trust

A Feasibility and Acceptability Study of the Talking With Voices Intervention Amongst Adults With Psychosis

Statistical Analysis Plan

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CONTENTS

1. INTRODUCTION

1.1. Aim

To investigate whether a novel intervention for auditory hallucinations, Talking With Voices (TwV), is an acceptable, feasible and potentially effective treatment option to offer within NHS settings in order to inform a definitive phase III trial.

1.2. Trial design

The study is a single site, single-blinded randomised controlled trial to compare TwV plus treatment as usual (TAU) to TAU alone in adults with psychosis.

1.3. Randomisation procedure, allocation concealment and blinding

Blinded randomisation and allocation concealment will be undertaken using the online service SealedEnvelope.com, which is fully encrypted and secure with no personal data being transferred. Randomisation (at the individual level) will be in the ratio of 1:1 and will be independent and concealed using randomised-permuted blocks of 4, 6 and 8. Allocation is communicated to the Chief Investigator (to monitor adherence to the randomisation algorithm), the trial therapists, and made known to the participant and their care team by letter from the trial administrator. Blinding of allocation will be maintained for the research assistant until all outcome measures for all participants have been collected. Blindness will be maintained using a range of measures (e.g. separate offices for therapist and researchers, protocols for answering phones, message taking and secretarial support, separate diaries and pigeon holes; and datafile security, such as using passwords and encryption of randomisation information). A combined Trial Steering Committee and Data Monitoring and Ethics Committee (TSDMEC) will monitor any unblindings that may occur and implement corrective action if necessary.

2. ANALYSIS OBJECTIVES

The objectives, under randomised conditions, are to:

1. assess recruitment/retention rates (including willingness to be randomised), quality of data collection, proportion of participants receiving the allocated intervention, and follow-up;
2. provide data from which a sample size can be calculated for a definitive trial;
3. provide a final check of the protocol in order to test its integrity to ensure all procedures are set-up prior to a definitive trial and to clarify inclusion and exclusion criteria;
4. test the randomisation procedure;
5. examine the appropriateness, feasibility and acceptability of the treatment intervention and measures under randomised conditions;
6. clarify training and supervision needs for implementing interventions and assessments prior to the commencement of a definitive trial.

A nested qualitative approach will also be employed amongst service-users and staff to identify key aspects of acceptability that could not be detected by quantitative measures alone, including: experiences of trial involvement, wanted and unwanted intervention effects, and disincentives to participate.

3. ANALYSIS SETS/POPULATIONS/SUBGROUPS

Statistical analysis will be based on an intention-to-treat approach, using all randomised participants with outcome data.

3.1. Inclusion and exclusion criteria

Participants must meet the following criteria to be eligible for enrolment:

1. adults aged ≥18 years;
2. who have heard voices for at least one year and score ≥4 on the auditory hallucination subscale of the Positive and Negative Syndrome Scale (PANSS [45]);
3. who have had no changes to medication within the past month;
4. who meet criteria for ICD schizophrenia spectrum disorder;
5. who are able to provide written, informed consent;
6. who are not currently receiving structured psychological therapy for psychosis;
7. who are willing and able to communicate with their voices and relay what the voices say to a therapist, and;
8. whose voices are sufficiently personified to engage in dialogical work (i.e., voices which can engage in conversation and dynamically interact with the hearer).

Exclusion criteria will be factors that could adversely affect service-user safety, or could affect the ability to engage with therapy:

1. individuals at immediate risk of harm to self or others;
2. non-English speaking;
3. primary diagnosis of alcohol/substance dependence or autism spectrum disorder;
4. moderate/severe learning disability;
5. organic brain injury or illness implicated in the aetiology of psychotic symptoms;
6. a score of >5 on the conceptual disorganisation subscale of the PANSS; and
7. homeless and/or of no fixed abode.

4. OUTCOMES

4.1. Primary feasibility outcomes

The aims and objectives of the feasibility study will be measured using:

1. referral rates and recording the proportion of individuals eligible for the trial;
2. rates of recruitment and retention (including willingness to be randomised and compliance with allocation);
3. estimating selection bias by gauging how representative participants are of general psychosis populations using demographic and clinical data;
4. number and duration of attended sessions;
5. satisfactory delivery of competent and adherent therapy;
6. adherence to treatment (including between session work);
7. follow-up and questionnaire response rate;

8. any necessity for substantive changes to protocol;
9. assessing signals of safety and efficacy and no clear signals of harm using secondary outcomes measures and incidence of adverse events; and
10. qualitative data on acceptability from both service-users and staff.

4.2. Secondary clinical outcomes

The secondary clinical outcome measures have been chosen to inform the design of a future trial by highlighting potential methods of action for TwV and identifying relevant clinical variables to ensure future protocols target key mechanisms:

Targeted measures of voice hearing will be:

1. The Positive and Negative Syndrome Scale (PANSS); hallucinations subscale [1];
2. The Revised Beliefs about Voices Questionnaire (BAVQ-R) [2]; and
3. The Voice and You scale (VAY) [3]; and
4. The Subtypes of Voice Hearing Questionnaire (SOV-Q) [4].

General clinical presentation will be assessed with:

1. The Revised Dissociative Experiences Scale (DES-II) [5];
2. The PANSS [1]; and
3. The Questionnaire about the Process of Recovery (QPR) [6].

Adversity exposure will be assessed with The Life Stressor Checklist – Revised (LSC-R) [7].

Data on health status will be collected using the EQ-5D [8] and the use of health and social care services will also be recorded. Additional demographic data will be collected using a standardised form. As a measure of acceptability, the short form Working Alliance Inventory [9] will also be completed by therapists and participants in the treatment arm of the trial.

5. ENDPOINTS AND COVARIATES (FREQUENCY OF MEASUREMENTS)

	Baseline	12 weeks	26 weeks
Measures of voice hearing			
PANSS-H	X		X
BAVQ-R	X		X
VAY	X		X
SOV-Q	X		X
General clinical presentation			
DES-II	X		X
PANSS	X		X
QPR	X		X
Adversity exposure			
LSC-R	X		

Health status			
EQ-5D	X		X
Treatment group only			
Therapeutic alliance			
WAI		X	X
Talking With Voices therapy satisfaction questionnaire			X

6. MISSING DATA

Missing data on individual measures will be pro-rated if more than 90% of the items are completed; otherwise the measure will be considered as missing. Missingness predictors on key baseline variables will be checked by comparing those with outcome data to those without. Any significant predictors will be included in a sensitivity analysis. This accounts for missing outcome data under different missing at random assumptions, conditional on the covariates included in the model.

7. DATA ANALYSIS

The main aims of the pilot study will be delivered both via the continued monitoring of descriptive data and the analysis of data at the end of the last scheduled follow-up assessment. We will report data in line with the Consolidated Standards of Reporting Trials (CONSORT) Statement for randomised pilot and feasibility trials [10] showing attrition rates and loss to follow-up.

Given that hypothesis testing is considered inappropriate for feasibility trials the quantitative analysis will focus on descriptive statistics, point estimates and associated 95% confidence intervals rather than tests of statistical significance (although some *p* values may be reported).

7.1. Primary feasibility outcomes

The main focus will be on tabulated and associated graphical summaries of the key indicators of success of the feasibility trial, including participant recruitment, checks for absence of selective recruitment of participants, baseline balance and participant flow.

Important summary statistics will be the number of participants referred through case managers and mental health staff, number of referrals found to be eligible, and number of consenting individuals and recruited individuals to each arm. Numbers for drop-out from the allocated interventions, withdrawal of consent, and failure to provide follow-up outcome data will also be generated. The proportion of participants who received their allocated intervention *vs* those who did not will also be reported.

7.2. Secondary outcomes

Summary statistics of the measures proposed as the primary (PANSS) and secondary clinical outcomes (BAVQ-R, VAY, SOV-Q, DES-II and QPR) for a potential Phase III trial will be presented

separately by each randomised group. We will fit a linear regression model for each with baseline values of the outcome and randomised group as fixed effects. The presentation of the intention to treat (ITT) analysis will focus on point estimates and associated 95% confidence intervals rather than statistical significance (p-values), although it is likely we will include p-values in any journal publications. The sensitivities of all treatment effect estimates to missing outcome data arising from drop-out will also be examined.

Further analysis will assess the correlations of each measure across both time points and the variation within the proposed outcome measure (mean and standard deviation) to inform a definitive sample size calculation for a Phase III trial. To account for departures from the randomised intervention, we will also examine the effect of actual treatment received on outcomes in an as treated analysis, which will report point estimates and associated 95% confidence intervals for these groups. Since safety and unwanted effects should be analysed on the basis of the most accurate information, these analyses will be as treated rather than ITT.

An analysis strategy for a definitive trial will also be developed as an output of the feasibility study.

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