Cognitive behavioural therapy or medication for psychosis - a randomised evaluation (COMPARE)

Statistical Analysis Plan (SAP)

Version: 1.0
Authors: Richard Emsley, Anthony Morrison

Trial Registration Number: ISRCTN06022197

Principal investigator:	Professor Anthony Morrison anthony.p.morrison@manchester.ac.uk
Trial co-ordinator:	Dr Heather Law
Trial statistician:	Dr Richard Emsley Richard.Emsley@manchester.ac.uk

CONTENTS

1. INTRODUCTION

1.1. Aim

To conduct a pilot randomised controlled trial (RCT) of antipsychotic medication in comparison to cognitive behavioural therapy (CBT) and a combined treatment in adults with Psychosis, to inform a definitive phase III trial.

1.2. Trial design

Our study is a single site, pilot randomised controlled trial to compare a standardised CBT intervention to treatment with APs and a combined treatment (CBT plus APs) in adults with psychosis.

Analysis of treatment effects will be on an intention-to-treat basis.

1.3. Randomisation procedure, allocation concealment and blinding

Randomisation will be undertaken using Sealed Envelope a web-based application which we have successfully used in several trials.

Randomisation will be in the ratio of 1:1:1 to the three groups and will be stratified by gender and first-episode status. Randomisation (at the individual level) will be independent and concealed, using randomised permuted blocks of 4 to 6, which will be administered via a study-specific web-based portal. The allocation is made known to the trial manager (in order to monitor adherence to the randomisation algorithm), the trial administrator and trial therapists by email. The allocation is also made known to the participant by letter from the trial administrator. Blinding of the allocation code will be maintained for research assistants until all outcome measures for all subjects have been collected.

Single blind-assessors will be blind to treatment condition. Blindness will be maintained using a wide range of measures, such as separate offices for the therapists and research assistants, protocols for answering telephones, message-taking and secretarial support, separate diaries and pigeon holes and data file security, using passwords and encryption of randomisation information. Maintaining rater blindness to treatment allocation is crucial, and the DMEC will regularly monitor unblindings, and implement corrective action if necessary.

2. ANALYSIS OBJECTIVES

The objectives are to assess, under randomised conditions:

a) The recruitment rate (including willingness to be randomised), quality of data collection and follow up
b) The integrity of the treatment protocols and ensure all procedures are in place prior to a definitive trial
c) The randomisation procedure
d) The appropriateness, feasibility, safety and acceptability of the interventions
e) The relevance and validity of the measures to assess effectiveness, safety, acceptability and cost effectiveness

And to

f) Provide data for sample size estimates (specifically between-group effect sizes) for the definitive trial
g) Clarify training and supervision needs for delivering these interventions and conducting assessments prior to a definitive trial
h) Conduct a qualitative evaluation to inform the next trial, using service user-led interviews

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 criteria

Patients must meet the following criteria to be eligible for enrolment

1. In contact with mental health care services (under the care of a consultant)
2. Either meet ICD-10 criteria for schizophrenia, schizoaffective disorder or delusional disorder or meet entry criteria for an Early Intervention for Psychosis service (operationally defined using PANSS) in order to allow for diagnostic uncertainty in early phases of psychosis
3. Aged 16+
4. Competent and willing to provide written, informed consent
5. Score at least 4 on PANSS delusions or hallucinations or at least 5 on Suspiciousness/Grandiosity
6. Help seeking

3.2. Exclusion criteria

1. Primary diagnosis of alcohol/substance misuse
2. Moderate or severe learning disability
3. Score 5+ on PANSS conceptual disorganisation
4. Non-English speaking
5. Current receipt of structured CBT from a qualified psychologist in accordance with NICE guideline recommendations (as opposed to more generic psychosocial interventions) OR receipt of antipsychotics, OR receipt of either within the past 3 months.
6. Immediate risk to self or others
7. Organic Impairment

4. OUTCOMES

4.1. Primary feasibility outcomes

A measure to inform feasibility will record referral rates, recruitment, attendance at sessions, adherence to homework, compliance with medication and follow-up and questionnaire response rates. Acceptability of treatment will be measured using rates of drop-out from treatment.

4.2. Secondary clinical outcomes

In order to examine effectiveness, preliminary analyses will focus on the following measures:

a) Primary effectiveness outcome will be total score on the Positive and Negative Syndrome Scale (PANSS)
b) specific symptoms on the PANSS,
c) depression and anxiety subscales on Hospital Anxiety and Depression Scale (HADS).
d) quality of life (WHOQOL),
e) social functioning (PSP),
f) a user-defined measure of recovery (QPR)
g) clinician's impression of the client's illness severity, improvement and response to treatment, using the clinical global impression scales (CGI).
h) antipsychotic non-neurological side effects scale (ANNSERS).
i) Metabolic side effects including body mass index, blood pressure and plasma glucose HbA, lipids (total cholesterol, LDL, HDL, triglycerides) and serum prolactin levels.
j) Hospital admissions
k) HONOS PBR (payment by results) cluster

5. ENDPOINTS AND COVARIATES (FREQUENCY OF MEASUREMENTS)

Assessors blind and independent to treatment group will conduct all assessments at baseline, at 6 weeks, 12 weeks and 24 weeks (immediately post the end of treatment) and at 12 months (6 months follow-up after the end of treatment).

	Baseline	6 weeks	12 weeks	24 weeks	52 weeks
Physical examination					
Blood test (plasma glucose, lipid profile, serum prolactin levels,)	√		√		√
Weight	√	√	√	√	√
BMI	√	√	√	√	√
BP	√		√		√
Pregnancy test offered	√				
Symptomatology and Functioning					
PANSS	√	√	√	√	√
PSP	√			√	√
WHOQOL	√	√	√	√	√
HADS	√			√	√
CGI	√	√	√	√	√
QPR	√			√	√
Adverse effects/side effects					
ANNSERS	√	√	√	√	√
Other					
Medication adherence form	√	√	√	√	√

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.

We will check for differential predictors of missing outcomes by comparing responders to non-responders on key baseline variables. Any significant predictors will be included in the analysis. This accounts for missing outcome data under a missing at random assumption, conditional on the covariates included in the model.

We have designed a variable length follow-up period. Participants recruited in the first 22 months will receive the full 52 week follow up, whereas participants recruited thereafter would be offered assessments up to the end of treatment (24 weeks).

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) 2010 Statement showing attrition rates and loss to follow-up.

7.1. Primary outcome

The main focus of will be on tabulated and associated graphical summaries of the key indicators of success of the pilot, 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 finally, failure to provide follow-up outcome data, will also be generated. Proportion of participants who received allocated intervention vs not and proportion of participants who moved to combined arm due to deterioration will also be reported.

7.2. Secondary outcomes

The measures proposed as the primary (PANSS) and secondary outcomes (QPR) for the phase III study will be analysed using analysis of repeated measures using a mixed effects model to take into account the discrete timing of the follow-up assessments and the random censoring introduced by the shorter follow-up period for participants' recruited towards the end of the trial.

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 be examined.

Further analysis will assess the correlations of each measure across all 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.

7.3 Secondary analysis

Exploratory analyses will involve investigation of treatment effects and possible mediation mechanisms using appropriate statistical methods.

An analysis strategy for a definitive trial will also be developed as an output of the feasibility study. This will vary according to the research question (e.g. Non-inferiority hypothesis for monotherapy, superiority hypothesis for combined vs monotherapy, both using ITT to be conservative; safety/adverse effects analysis likely to use as treated; we may propose to examine the effect of actual treatment received on primary outcome using instrumental variable procedures to estimate complier average causal effects).