FOCUS

Focusing on Clozapine Unresponsive Symptoms (FOCUS): a randomised controlled trial

Centre for Healthcare Randomised Trials

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1 Study Design

Parallel-group randomised controlled trial in five centres across the UK.

1.1 Primary research question

The main research question is what is the clinical-effectiveness, cost-effectiveness and acceptability of Cognitive Behavioural Therapy (CBT) compared to treatment as usual for people with schizophrenia who are unable to tolerate or have an inadequate response to clozapine?

1.2 Randomisation and blinding

Following informed and written consent, eligible participants will be randomised within 2 working days. Randomisation is via a web-based system called openCDMS developed with the MHRN. Randomisation will be in the ratio 1:1 to the two groups and will be stratified by centre. Randomisation is independent and concealed, using randomised-permuted blocks of random size (block sizes of 4 or 6) administered via a study-specific web-based portal. Therapists and participants cannot be blinded to treatment allocation. However, outcomes assessors will be blinded to treatment allocation.

2 Outcome measures

2.1 Primary outcome

The primary outcome measure will be the total score on the Positive and Negative Syndrome Scale (PANSS) at 21 months. [12] [13]

2.2 Secondary outcomes

Secondary outcome measures are:

- Total score on the PANSS at 9 months
- Positive and negative symptom subscale scores the PANSS
- Depression using the Calgary Depression Rating Scale for Schizophrenia (CDSS) [1]
- Anxiety using the self-reported measure AnTI [17]
- Dimensions of psychotic experiences using PSYRATS [11]
- Health status and health related utility using the EQ-5D [9]
- Social functioning using PSP [14]
- User-defined recovery using QPR [16]
- Alcohol and illicit drug use using the AUDIT and DAST [4]
- Global illness severity and improvement using CGI
- Participant version of CGI
- Hospital admissions and HONOS PBR (payment-by-results) cluster will also be measured.

2.3 Treatment mediators

Psychological factors that may act as potential mediators of treatment outcome are:

- Appraisals of psychotic experiences using the Interpretations of Voices Inventory for voices (IVI) [15]
- Beliefs about paranoia scale for paranoia (BAPS) [10]
- Beliefs about self and others using the brief core schema scale (BCSS) [8]
- Attachment style using the psychosis attachment measure (PAM) [3]
- Experience of childhood trauma using the childhood trauma questionnaire (CTQ) [2]
- Working memory using the Memory-Letter Number Span (LN)

2.4 Timing of outcome measurements

All outcomes are measured at baseline, 9 months and 21 months (12 months after treatment finishes).

2.5 Adverse events

Adverse events will be reported in line with National Research Ethics Committee (NREC) guidance. Any of the following events will be reported as an adverse event if the Chief Investigator and Independent DMC consider the event to be related and unexpected:

- results in death
- is life threatening
- results in self-harm
- results in harm to others
- requires voluntary hospitalisation or prolongation of existing voluntary hospitalisation
- required involuntary hospitalisation or prolongation of existing involuntary hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect or
- is otherwise considered medically significant by the investigator.

In addition to the above, scores of 6 or more on the GCI Improvement Scales will be reported as indication a potential serious adverse effect of trial participation. Please see the Protocol for more detail on AE.

2.6 Potential unwanted side effects of trial participation

Additional outcomes are potential unwanted effects of trial participation. These are defined as:

- A deterioration of 25% or more from baseline on the PANSS
- Suicidal crisis (explicit plan for serious suicidal activity without suicide attempt) will be reported as defined in Calgary Depression Rating Scale for Schizophrenia [CDSS], item 8, rating 2) at 9 and 21 months.

3 Sample size and power calculation

Analysis of effect sizes on positive symptoms from six existing trials that have focused on a treatment-resistant and/or clozapine-resistant population showed a difference in means between CBT and control groups of an average of 0.53 standard deviations (the effect size). A recent review of CBT for psychosis found an overall effect size of 0.4. FOCUS will estimate treatment effects across a range of outcomes, including quality of life and recovery, in addition to psychiatric symptoms, we powered the study to detect a generic effect size of 0.33. With 194 participants per group, using a t-test with a significance level of 0.05 we will have 90% power to detect an effect size of 0.33. A target recruitment of 485 (97 per site) would allow for a dropout rate of 20%.

4 Statistical methods

All the main analyses will be based on the Intention-to-Treat principle. Analysis will take place after full recruitment and follow-up. There are no planned interim analyses for efficacy. An independent Data Monitoring Committee will monitor trial progress and specifically any safety issues, although none are expected as this is a cognitive behavioural therapy intervention, on a regular basis. The results of the trial will be presented following the standard CONSORT recommendations. Baseline and follow-up data will be summarised using the appropriate descriptive statistics and graphical summaries. Treatment effects will be presented with 95% confidence intervals. There will be no adjustment to secondary outcomes CIs for multiple testing.

4.1 Primary outcome

The primary outcome (PANSS at 21 months) will be analysed using a linear model that adjusts for pre-specified baseline covariates (baseline PANSS, sex, age) and includes a random effect for site. The development of treatment effects over time will be explored using repeated measures mixed effect models that makes use of all available data using `xtmixed` in Stata. The primary analysis will be intention-to-treat on available data (i.e. analyse as randomised), see missing data section for treatment of missing outcome data.

4.2 Secondary outcomes and adverse events

Secondary outcomes will be analysed in a similar way with generalised linear models appropriate for the distribution of the outcome.

4.3 Potential unwanted side effects of trial participation

Potential unwanted side effects of trial participation, as measured by the adverse effects measure, will be reported for trial completers at 21 months and for participants who withdraw and agree to complete the adverse effects measure.

4.4 Subgroup analyses/risk modelling

Subgroup analysis will included analysis on four outcomes:

- The primary outcome PANSS
- Recovery using QPR
- functioning
- PSYRATS Voices subscale for those who hear voices

4.4.1 Draft Pre-specified subgroups

The potential moderating effect of covariates will be explored by including a treatment-by-subgroup interaction in models. The interaction effect will be summarised with a 95% confidence interval for each outcome and model. The subgroups to be explored are:

- Age
- Gender
- Positive & negative core beliefs from the BCSS
- Working memory using LNS
- Trauma in childhood using the CTQ
- Substance use from DAST
- Alcohol use AUDIT
- Difficulty with abstract thinking using item N5 on the PANSS
- Conceptual disorganisation using item P2 on the PANSS
- Duration of illness
- Duration of untreated psychosis
- Age of onset of psychotic symptoms
- Dose of clozapine at baseline
- Number of anti-psychotics at baseline
- Attachment using attachment avoidance sub-scale taken from PAM-SR
- Psychosis sub groups

4.4.2 Risk modelling

We will model response to treatment (defined as change change in PANSS from baseline to 21 months) in a general linear model. Covariates will include age; age of onset; duration of illness; duration of untreated psychosis; number of antipsychotics at baseline; dose of clozapine at baseline; PANSS items conceptual disorganisation and difficulty in abstract thinking (at baseline); gender; memory; and treatment allocated. Continuous variables will be included initially in the natural metric measured on. We will explore the impact of any missing data at 21 months using a range of strategies, e.g. using 9 months data if available, multiple imputation based on observed covariates.

4.5 Mediation analyses

Mediation analysis aims to decompose a total effect (ITT effect) into an indirect effect, which measures how much of the effect acts through an intermediate variable, and a residual direct effect which measures how much of the effect does not act through the mediator under consideration. All the mediation analyses will be based on the Intention-to-Treat principle.

We will use parametric regression models to:

- test for mediation of the intervention on the primary outcome;
- test for mediation of the intervention on the secondary outcomes;

We will test each of the mediators in listed section 3.3 for a between-group difference using a linear model that adjusts for pre-specified baseline covariates (baseline PANSS, baseline mediator value, gender, age and site). Separate models will be fit for each mediator. The coefficient of randomisation is an estimate of the target effect. The rationale is that for a variable to be a mediator, a significant target effect must be detected. Only those putative mediators which have a significant target effect will be used in the mediation analysis.

We fit the same form of outcome model as for the primary analysis, including the mediator as a covariate. All models will adjust for baseline measures of the set of mediators, outcomes and putative measured confounders. Since all the measures are continuous, the indirect effects are calculated by multiplying the target effect and the coefficient of the mediator in the outcome model. These gives an estimate of the natural indirect effect. Bootstrapping is used to produce valid standard errors for the indirect effects.

Mediation analyses are potentially biased by measurement error in mediators and hidden confounding between mediators and outcomes; we will build on our previous methodological and applied work in this context to include repeated measurement of mediators and outcomes to account for classical measurement error and baseline confounding [5]. We will investigate the sensitivity of the estimates to these problems and that of unmeasured confounding using instrumental variable (IV) methods with baseline covariate by randomization interactions as potential instruments [7] [6]. These baseline covariates will be identified from the set of pre-defined subgroups.

Treatment compliance will be considered separately. We will estimate a complier average causal effect (CACE) using instrumental variable methods, considering six or more sessions as a measure of compliance and randomisation as the instrumental variable [5].

4.6 Missing data

4.6.1 Missing outcome data

The sensitivities of all treatment effect estimates to missing outcome data will be explored; these models will explore the robustness of the treatment estimates to whatever small amount of missing data there is. We will follow the strategy outlined in White et al. [18] The main analysis will use all available data that we believe are valid under the assumption of missing at random (see Primary outcome analysis above). We will then use a suite of sensitivity analysis to explore the robustness of the primary analysis to departures from assumptions, including all randomised participants. If required, sensitivity analyses will include multiple imputation, and imputing a range of values for missing data under missing not at random assumptions e.g. using `rctmiss` in Stata.

4.6.2 Missing outcome baseline data

Data missing at baseline will reported as such. If required for models for primary or secondary outcomes continuous data will be imputed with the centre specific mean of that variable, missing binary/categorical data will include a missing indicator.

5 CONSORT diagram

Currently see Protocol

6 Dummy tables

Table 1. Baseline

Variable	CT plus TAU (N=)	TAU only (N=)
Age		
Male		
PANSS Total		
PANSS Positive		
PANSS Negative		
PANSS Disorganised		
PANSS Excitement		
PANSS Emotional Distress		
PSYRATS Delusion - Cognitive		
PSYRATS Delusion - Emotional		
PSYRATS Voices - Cognitive		
PSYRATS Voices - Emotional		
PSYRATS Voices - Physical		
PSP		
QPR		
Calgary total		
ATI total		
CGI		

Table 2. PANSS Outcomes

Variable	Time	CT plus TAU (N=)	TAU only (N=)	Estimate (95%CI); p-value
PANSS total	Baseline			
	9 months			
	21 months			
PANSS Positive	Baseline			
	9 months			
	21 months			
PANSS Negative	Baseline			
	9 months			
	21 months			
PANSS Disorganised	Baseline			
	9 months			
	21 months			
PANSS Excitement	Baseline			
	9 months			
	21 months			
PANSS Emotional Distress	Baseline			
	9 months			
	21 months			

Table 3. Secondary Outcomes

Variable	Time	CT plus TAU (N=)	TAU only (N=)	Estimate (95%CI); p-value
QPR	Baseline			
	9 months			
	21 months			
PSP	Baseline			
	9 months			
	21 months			
Calgary	Baseline			
	9 months			
	21 months			
ATI	Baseline			
	9 months			
	21 months			
PSYRATS Delusions - cognitive	Baseline			
	9 months			
	21 months			
PSYRATS Delusions - Emotional	Baseline			
	9 months			
	21 months			
PSYRATS Voices - Cognitive	Baseline			
	9 months			
	21 months			
PSYRATS Voices - Emotional	Baseline			
	9 months			
	21 months			
PSYRATS Voices - Physical	Baseline			
	9 months			
	21 months			
CGI Scale	Baseline			
	9 months			
	21 months			
CGI Scale (Patient)	Baseline			
	9 months			
	21 months			

Table 4. Adverse events

Adverse event	CT plus TAU (N=)	TAU only (N=)
Death		
Self-harm		
⋮		
Total		

Table 5. Hospital admissions during the treatment phase

	CT plus TAU (N=)	TAU only (N=)
Voluntary admission		
Number (%) participants admitted		
Mean (SD) days in hospital		
Compulsory admission		
Number (%) participants admitted		
Mean (SD) days in hospital		

Table 6. Participants achieving improvement/deterioration on PANSS total score at 9 and 21 months

Variable	CT plus TAU (N=)	TAU only (N=)
9months		
Increase (deterioration)		
Decrease (improvement)		
21 months		
Increase (deterioration)		
Decrease (improvement)		

Table 7. Risk modelling

Variable	Coefficient	95% CI	p-value
Age			
Male			
Baseline			
⋮			
⋮			

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