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

## PLANNED INVESTIGATION

The main question to be addressed is whether, for people with confirmed treatment-resistant schizophrenia that is poorly responsive to an adequate trial of clozapine (or unable to tolerate such a trial), Cognitive Behavioural Therapy (CBT) is clinically and cost effective and an acceptable treatment?

### Research objectives

We will test the hypotheses that:

1. In people with a diagnosis of a schizophrenia spectrum disorder who have an inadequate response to or are unable to tolerate clozapine, CBT plus Treatment As Usual (TAU) will lead to improvement in psychotic symptoms, measured using a psychiatric interview (PANSS), over a 21-month follow-up period compared with TAU alone
2. CBT plus TAU will lead to improved quality of life and user-defined recovery compared to TAU alone
3. CBT plus TAU will lead to a reduction in affective symptoms and negative symptoms compared to TAU alone
4. CBT plus TAU will be cost effective compared to TAU alone
5. It will be possible to develop a risk model that identifies baseline factors that predict good outcome to CBT

### Existing research

Background

In around a third of people with schizophrenia, the illness shows a poor response to standard treatment with antipsychotic medication. While a relatively small proportion will fail to achieve remission even after the first exposure to antipsychotic medication, with either first or second generation drugs [1], more commonly the illness becomes progressively more unresponsive to medication with subsequent relapses [2]. This 'treatment-resistant' subgroup of patients represents a major clinical challenge in everyday psychiatry, and consumes a disproportionate amount of NHS funding [3 4]. It is estimated that the total societal cost of schizophrenia in the UK in 2004/5 was £6.7 billion [5]. The direct cost of treatment and care, falling on the UK public purse, was around £2 billion, while the burden of indirect costs to society was approaching £4.7 billion. The cost of informal care and private expenditures by families and carers was around £615 million, while the loss of productivity due to unemployment, absence from work and premature mortality of people with schizophrenia was estimated to be £3.4 billion and the lost productivity of their carers at around £32 million. Further, it has been calculated that in addition to costs to the criminal justice system, around £570 million was being paid out in benefit payments, associated with about £14 million administration costs [5]. Treatment resistant illnesses are the most costly, usually requiring longer term residential and intensive community treatments. Even in first episode patients, over 10% fail to remit in the 12 months following initiation of treatment. There is clinical and economic need to evaluate treatments to improve outcomes in this deprived group of patients.

Clozapine is the only antipsychotic with convincing evidence for efficacy in strictly-defined treatment-resistant schizophrenia. But even in people in this category, clozapine has limited efficacy, with 30-40% showing an inadequate response to the drug [6]. In some patients, a range of potentially serious side effects such as seizures, sedation and tachycardia may prevent the optimal dose being reached. In the short term, metabolic side effects that increase the risk of diabetes and cardiovascular disease become apparent in many. The long-term effects of antipsychotics are becoming increasingly recognised as problematic [7], so a demonstration of long-term benefits of CBT in a treatment-resistant population is highly likely to benefit physical health as well as mental health.

CBT for psychosis

In recent years, the generic cognitive model [8] has been applied to our understanding and treatment of psychosis. This model suggests that the way that we interpret events will have consequences for how we feel and behave, and that such interpretations are often maintained by unhelpful thinking biases and behavioural responses. There have been several cognitive models of psychosis and psychotic experiences outlined [9-11], which suggest that it is the way that people interpret psychotic phenomena that accounts for distress and disability, rather than the psychotic experiences themselves. There are several comprehensive treatment manuals that describe the application of such models in greater detail [12-15]. CBT has been shown to be highly effective when delivered in combination with antipsychotic medication, with several meta-analyses showing robust support for this approach [16-19].

A systematic literature search identified 6 eligible RCTs of CBT for treatment resistant schizophrenia, with a total of 361 participants; of these, 5 trials targeted a participant population that met criteria similar to those for the initiation of clozapine treatment [20]. Only one small study has examined the efficacy of CBT for clozapine-resistant psychosis [21]. Analysis of effect sizes on positive symptoms from 6 existing trials that have focused on a treatment-resistant and/or clozapine-resistant population ([22]: ES= 0.37, n=60; [23]: ES=0.79, n=87; [24]: ES=0.99, n=41; [25]: ES=0.14, n=90; [26]: ES=0.32, n=62; [21]: ES=0.59, n=21) shows a mean effect size of 0.53. Wykes et al's recent review of CBTp found an overall effect size of 0.4 [17].

In order to inform the likelihood of response to CBT for patients who are unable to tolerate clozapine, and may revert to previously ineffective medication or become unmedicated, there is little literature on which to estimate effect sizes. CBT for psychosis has yet to be formally evaluated in the absence of antipsychotic medication, although there have been a few case studies (e.g. [27]) that have demonstrated acceptability and provided some support. More recently, two case series have demonstrated some benefits, with 4 cases of patients experiencing auditory hallucinations showing some gains in terms of symptoms, distress and disability [28] and 3 cases with a diagnosis of schizophrenia showing improvements in positive and negative symptoms [29]. A very recent open trial with 20 participants that we have conducted suggests that CBT may be an effective intervention for people not taking antipsychotics (either naïve or having discontinued for at least 6 months).

Considering the above literature, it would appear that there are significant numbers of patients with a schizophrenia spectrum disorder who either fail to respond to an adequate trial of clozapine or are unable to tolerate such medication due to adverse reactions. CBT clearly has the potential to help alleviate symptoms and improve quality of life in people meeting criteria for treatment-resistant schizophrenia and there are suggestions that it can help those who are not taking antipsychotics; however, there is insufficient research regarding CBT for patients with an inadequate response to or unable to tolerate clozapine.

## RESEARCH METHODS

### Design

Our study is a parallel group randomised outcome blinded evaluation (PROBE) to compare the addition of a standardised CBT intervention to treatment for individuals who are unable to tolerate or have an inadequate response to clozapine, across 5 sites. Our trial will be a definitive, pragmatic clinical and cost effectiveness trial lasting 4 years. The comparator group will receive treatment as usual. We will not be asking referrers to withhold any treatment. Randomisation (at the individual level) will be independent and concealed, using randomised-permuted blocks of random size and will be stratified by site. Assessors will be masked to allocated treatment. Masking will be maintained using a wide range of measures (e.g. separate offices for therapists and researchers, protocols for answering phones, message taking and secretarial support, separate diaries and security for electronic randomisation information).

### Setting

The study will be conducted in secondary care, specifically mental health services (community mental health, residential rehabilitation and inpatient settings), at five UK centres (Manchester, Edinburgh, Glasgow, Newcastle and Southampton).

### Target population

People aged 16- 65 years with a schizophrenic illness that has been unresponsive, at a criterion level of persistent symptom severity, to an adequate trial of clozapine in terms of dosage, duration and adherence.

### Measurement of costs and outcomes

Therapeutic improvement will be assessed in terms of overall symptom severity, but also using broader, clinically-relevant outcome measures of social and occupational function and target symptoms and/or behaviours as well as overall health status and utility. Both psychiatric and psychological outcomes will be included. Assessors blind and independent to treatment group will conduct all assessments at baseline, at 9 months (immediately post the end of treatment) and at 21 months (12 months follow-up after the end of treatment).

The primary outcome measure will be the total score on the Positive and Negative Syndrome Scale (PANSS: [30] [31]). This is a commonly used outcome for response in schizophrenia trials, and will allow for comparison with similar published studies. Both positive and negative symptom subscale scores can be derived from the PANSS, and these will be used to assess specific symptoms, while depression will be assessed using the Calgary Depression Rating Scale for Schizophrenia (CDSS [32]), a scale designed to minimise the potentially confounding symptom overlap between depressive features and both negative symptoms and extrapyramidal symptoms. Anxiety will be assessed using a self-report measure (AnTI [33]). We will also measure dimensions of psychotic experiences such as severity and distress (PSYRATS [34]), health status and health related utility (EQ5D [35])

quality of life (QLS [36]), social functioning (PSP [37]), a user-defined measure of recovery (QPR [38]). We will also measure alcohol and illicit drug use using the AUDIT [39] and DAST [40]which will permit a secondary analysis regarding the possible role that this could play with regard to compliance with CBT. Hospital admissions and HONOS PBR (payment-by-results) cluster will also be measured. We will also measure psychological factors as potential mediators of treatment outcome, including appraisals of psychotic experiences using the Interpretations of Voices Inventory for voices (IVI [41]) and the beliefs about paranoia scale for paranoia (BAPS [42]). We will also assess beliefs about self and others using the brief core schema scale (BCSS [43]), attachment style using the psychosis attachment measure (PAM [44]) and experience of childhood trauma using the childhood trauma questionnaire (CTQ [45]).

The economic analysis will estimate the costs of health and social care and quality adjusted life years (QALYs) from a broadly societal perspective. This will include NHS secondary and primary care services, formal, independent and voluntary social care services and patient and family expenditure. The key determinants of total direct costs are expected to be those associated with the use of NHS hospital inpatient, outpatient and clinic services provided for the initial trial interventions and associated follow-up. These items comprised approximately 90% of the total costs for participants in the recent CUtLASS trial [46] who were randomised to SGAs. The time horizon for the economic analysis will be the 21 months from recruitment to end of scheduled follow up. Cost data will be collected using data collection forms held by the applicants and successfully used in previous completed trials of in schizophrenia (see proposed outcome measures for more details). Quality adjusted life years (QALYs) will be the measure of health benefit for the primary analysis. Changes on key clinical measures from baseline to follow up will be used in sensitivity analyses. QALYs will be measured using the EQ-5D health status measure and associated utility tariffs [47].

**Project timetables**

The study will be conducted over 48 months. The initial 2 months will be used for staff training, liaison with referrers and establishing site protocols. We estimate a target recruitment of 485 (97 per centre) over the 24-month recruitment period, which would allow for a dropout rate of 20% (see sample size calculations below). The final 22 months will allow for completion of treatment and follow-up, with the last month within this period being used to clean and analyse data, prepare reports and plan dissemination. Thus, we require a recruitment rate of 4 patients per month per trial centre, which is achievable based on current surveys of patient populations and previous performance in RCTs run by the applicants at our sites. Recruitment rates will be monitored by the Trial Manager and the Trial Executive Committee, with regular quarterly reports for the TSC and DMC.

## PLANNED INTERVENTIONS

**Health technologies being assessed**

CBT will be delivered by appropriately qualified psychological therapists on an individual basis over 9-months and will include up to 30 treatment sessions on an approximately weekly basis over the nine month treatment window (sessions are likely to be less frequent towards the end of this period). CBT will be based on a specific cognitive model [11], since there is good evidence that CBT based on empirically validated models is far superior to more eclectic cognitive behavioural approaches [48]. CBT allows an individualised approach within clear boundaries, and incorporates a process of assessment and formulation, which is manualised. The specific interventions are dependent on the individual formulation, but the range of permissible interventions is described in our published manuals [12 49]. The aims of CBT will be to reduce distress (particularly that associated with psychotic symptoms) and improve quality of life. It is a collaborative therapy that works with the problems and goals that are agreed between patient and therapist. Thus, treatment targets often include positive symptoms, but frequently also include social issues such as improving relationships or developing meaningful social roles and issues of comorbidity including anxiety and depression. If comorbidity includes problematic drug or alcohol use, this can also be prioritised. Fidelity to the treatment protocol will be ensured by regular supervision of the therapists and assessed by rating audio recordings of therapy sessions using the Cognitive Therapy Scale - Revised [50]. This is a widely-accepted approach to the standardisation of CT, which we have used successfully in previous large-scale trials. All therapists in participating centres will be trained initially, and therapy supervision will be provided by means of weekly meetings. All CBT sessions will be taped with the patient's consent (patients will be asked to listen to the tapes as part of their homework) and a random sample of tapes (stratified for stage of therapy) will be rated using the CTSR in order to monitor fidelity and assist supervision; this will be done throughout the lifetime of the trial in order to provide some quality assurance and ensure action can be taken if required. Following each session, therapists will complete a session record that monitors content of sessions in terms of agenda targets, homework tasks and change strategies used, which is another strategy we have used in previous trials; thus, fidelity can be used as a mediating variable in analyses the session records will be anonymised and stored electronically in a database called OpenCDMS which is only accessible to specific members of staff who have been granted the necessary privileges.. Attempts will also be made to ensure the equivalence of therapist skills at baseline by recruiting staff with post-qualification training in cognitive

therapy and suitable experience (all sites have a successful record of recruiting and retaining skilled cognitive therapists for research trials).

The control condition is treatment as usual. We will not be asking referrers to withhold any treatment. Our assessments (baseline, 9 months and 21 months) will identify any risks to self or others that require immediate action. In addition, the TAU group will also receive a crisis card providing emergency contact details. In addition, all participants will have an allocated keyworker/care coordinator, will be receiving regular outpatient follow-up from a multi-disciplinary team within secondary mental health services, and will be receiving outpatient psychiatric follow-up. As in previous trials we have undertaken, there will be a clear safety protocol to alert clinicians should suicidal or dangerous ideation emerge, and clinicians involved in participants care will receive a manual summarising current best practice and evidence-based treatment guidelines in an attempt to promote standardisation of good quality TAU. All routine or additional treatments in both conditions will be monitored using a Treatment Documentation Sheet.

**Randomisation**
Following informed and written consent, eligible participants will be randomised within 2 working days. Randomisation will be undertaken using openCDMS, a web-based system developed with the MHRN, which we have used successfully in several multisite trials. CHaRT, Health Services Research Unit, University of Aberdeen, a fully registered (registration number 007 ) UK CRC Clinical Trials Unit will advise regarding the development of the randomisation algorithms and will also be consulted regarding the web-based technology.

Randomisation will be in the ratio 1:1 to the two groups and will be stratified by centre. Randomisation (at the individual level) will be independent and concealed, using randomised-permuted blocks of random size (block sizes of 4 or 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 and SMS text message. 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.

**Protection against bias**
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 datafile security, using passwords and encryption of randomisation information. Maintaining rater blindness to treatment allocation is crucial, and the DMC and TSC will regularly monitor unblindings by each centre, and implement corrective action if necessary. Following entry assessment and completion of baseline assessments, participants will be allocated to treatment groups through our web-based randomisation service and the Trial administrator will inform the participants of this decision. Any accidental unblindings will be recorded and outcome analyses will be repeated excluding these participants to determine the robustness of the findings.

**Concomitant therapy**
It would be unethical to restrict the therapeutic options of the clinical teams participating. Our approach will, therefore, be primarily to record the use of all other medication and psychological therapies, document details of dosage, and ensure the follow-up of all randomised participants, irrespective of the interventions that they subsequently receive. However, we will carry out a secondary analysis using causal modelling (e.g. CACE methods) in which we investigate issues of compliance with therapy, and the therapeutic alliance between therapist and participant on the treatment effects.

## PLANNED INCLUSION/EXCLUSION CRITERIA

**Inclusion criteria**
Patients must meet the following criteria to be eligible for enrolment:

1. A criterion level of persistent symptom severity despite an adequate trial of clozapine in terms of dosage, duration and adherence (as used by Honer et al 2006):
    - Treatment of clozapine at a stable dose of 400mg or more (unless limited by tolerability) for at least 12 weeks, or if currently augmented with a second antipsychotic that this has been given for at least 12 weeks, without remission of psychotic symptoms, or have discontinued clozapine due to adverse reactions (including agranulocytosis) or lack of efficacy in the past 24 months
    - presence of at least one psychotic symptom with severity $\geq$4 (for hallucinations/delusions) or $\geq$5 (for suspiciousness/grandiosity) on the PANSS in addition to a PANSS total score of at least 58, which is equivalent to a clinical global impression (CGI) of being at least mildly ill [51]
2. be in contact with mental health services and have a care coordinator

3. 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
4. Aged at least 16 years old
5. Competent and willing to provide written, informed consent.

Exclusion criteria
1. Primary diagnosis of alcohol/substance dependence, where this is clearly the cause of their psychotic symptoms
2. Developmental disability
3. Non-English speaking
4. Current receipt (or within the last 12 months) of structured CBT from a qualified psychological therapist in accordance with NICE guideline recommendations (as opposed to more generic psychosocial interventions)

**ETHICAL ARRANGEMENTS**

Multi-centre and Local Research Ethics Committee approval will be obtained prior to the start of data collection. Only those who agree to provide written informed consent will be included in the study. Each potential participant will be provided with a copy of an information sheet that includes a contact number for the study team.

**RISKS AND ANTICIPATED BENEFITS FOR TRIAL PARTICIPANTS AND SOCIETY, INCLUDING HOW BENEFITS JUSTIFY RISKS**

This study will add to the evidence base for the range of medical, psychological and social interventions that should be provided to improve outcomes for people with treatment-resistant schizophrenia, who remain among the most socially excluded groups in society. If CBT were found to be significantly superior to TAU in improving symptoms and quality of life, without a side effect burden, this could have implications for the future evidence-based management of similar patients within primary and secondary care mental health services. Furthermore, if CBT were also found to be cost-effective, this could have implications for the primary care commissioning of local mental health services, and for the development of national guidelines for the provision of care for patients with schizophrenia.

**INFORMING POTENTIAL TRIAL PARTICIPANTS OF POSSIBLE BENEFITS & KNOWN RISKS**

CBT is a recommended intervention for treatment-resistant schizophrenia [52]. The investigators have considerable experience of administering the assessments and rating scales included in this study, and are not aware of any risks to patients. During assessment and testing, breaks will be provided to minimise possible fatigue or stress, and if indicated, can be spread over several days.

**OBTAINING INFORMED CONSENT FROM PARTICIPANTS WHENEVER POSSIBLE OR PROPOSED ACTION WHERE INFORMED CONSENT NOT POSSIBLE**

Written informed consent will be obtained from each subject prior to their inclusion in this study in line with the Information Sheets and Consent Forms, Guidance for Researchers and Reviewers, Version 3.2 May 2007 (National Research Ethics Service: NRES).

**PROPOSED TIME PERIOD FOR RETENTION OF RELEVANT TRIAL DOCUMENTATION**

All trial documentation and data will be retained for a minimum of 5 years, as stated in Clinical Trials Regulations.

**PROPOSED SAMPLE SIZE AND RECRUITMENT**

**Sample size**

Analysis of effect sizes on positive symptoms from 6 existing trials that have focused on a treatment-resistant and/or clozapine-resistant population shows 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. As we intend to estimate treatment effects across a range of outcomes, including quality of life and recovery, in addition to psychiatric symptoms, we will power 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%. CBT is usually a very acceptable intervention; in our own studies drop out rates have all been below 20%, and we will use evidence based strategies to maximise retention and minimise loss to follow up (such as inclusion of crisis card provision and signposting in the assessment sessions).

**Recruitment**

We estimate conservatively, on the basis of local pharmacy data, that there are 5000 patients treated with clozapine shared between the five sites: Edinburgh, Glasgow, Manchester, Newcastle and Southampton (see separate flow diagram). Given a rate of clozapine resistance of 30-40% [6], this would render 1500-2000 eligible patients. Of these patients, we conservatively estimate that 50% would be unable or unwilling to consent, and 10% would already be receiving CBT, leaving a potential patient pool of 600 at the start of the trial, with additional numbers becoming eligible throughout the lifetime of the trial. Participants will be identified using lists from clozapine clinics, Trust pharmacies and patient monitoring services, as well as screening electronic patient data systems. Site leads have strong clinical links with relevant services for people with psychotic disorders, and all sites have extensive experience of liaison with clinical teams, the use of launch events for awareness raising, and liaison with voluntary sector organisations. We have had considerable past success with recruitment using these procedures, as demonstrated by our strong track record of recruiting to CBT for schizophrenia / psychosis trials; for example, the EDIE-2 trial (which included Manchester and Glasgow), recruited 90% of the target within the original timeframe (288 of 320). Similarly, the INSIGHT trial recruited 422 participants, involving both our Newcastle and Southampton research teams who recruited 87% and 92% of target respectively [53].

The local research networks have Clinical Studies Officers, Research Assistants and / or Research Nurses that have robust links with consultant psychiatrists and multi-disciplinary teams, and all site leads have a strong history of successful collaboration with the MHRN hubs. All 5 sites are hubs of the Mental Health Research Network (MHRN) in England and Scotland (SMHRN), and the trial will be conducted within this infrastructure, as this is designed and resourced to support recruitment to clinical studies, and our combined catchment areas will have a population of more than 5 million people. We will apply to these networks for adoption and we will request support from the networks in developing recruitment. We would seek the support of local Mental Health Research Network (MHRN) hubs in the recruitment process, specifically the North West, North East and South West hubs. Adoption will support the trial team in engaging with services and referrers, and facilitate recruitment of potential participants.

The SMHRN Protocol Development Service supported the design of a web-based survey to help determine feasibility of recruitment which we have conducted across our sites. A total of 49 psychiatrists responded, stating that, of their caseload of individuals with schizophrenia and in receipt of clozapine (total n = 630), 53% (n = 331) continue to experience persisting distressing positive symptoms and 11% (n = 68) have discontinued in the last two years following failure to tolerate clozapine. These actual rates are higher than the estimated 30-40% that we have based our recruitment estimates on.

**STATISTICAL ANALYSIS**

All the main analyses will be based on the Intention-to-Treat principle. Analysis will take place after full recruitment and follow-up (i.e. there will be no interim analyses for efficacy, although 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 primary outcome (PANSS) will be analysed using a linear model that adjusts for pre-specified baseline covariates strongly associated with outcome. Secondary outcomes will be analysed in a similar way with generalised linear models appropriate for the distribution of the outcome. The development of treatment effects over time will be explored using repeated measures models. We will try to identify subgroups for whom the treatment effect is greatest using a risk model using baseline information. The sensitivities of all treatment effect estimates to missing outcome data will be explored (we will use best evidence based methods to keep the loss to follow up to a minimum; these models will explore the robustness of the treatment estimates to whatever small amount of missing data there is, using multiple imputation method under the assumption of missing at random, and if required, and the data permit, exploring informative missingness mechanisms using e.g. pattern mixture models). All statistical analyses will be pre-specified in a comprehensive Statistical Analysis Plan which will be agreed with TSC and DMEC. The results of the trial will be presented following the standard CONSORT recommendations.

As indicated, we will also address the influence of compliance via causal or 'mediation' models (statistical lead: Professor Graham Dunn, Manchester). Traditional approaches to mediation [54] assume that confounding between the putative mediator and clinical outcome is absent (i.e. there is no omitted variable bias). We will compare the results of three sets of assumptions: (a) no confounding, (b) that we have measured and are able to adjust for all important confounders [55], and (c) that we are able to effectively adjust for unmeasured confounders (hidden confounding) using instrumental variable-based methods, specifically analyses based on principal stratification [56].

**Health economics**

Multiple imputation and censored data analysis techniques will be used to separately impute missing data due to missing observations in participants who complete follow, and missing follow up data for participants who do

not complete follow up. The primary analysis will use an intent to treat approach. The primary and sensitivity economic analyses will be controlled for key baseline covariates or characteristics. The covariates will be pre-specified and identified from previous studies that they may affect the costs or outcomes of care (Davies et al, 2008). Regression models will be used to estimate incremental costs and outcomes.

The cost and outcome effects will be bootstrapped to generate incremental cost effectiveness ratios, cost effectiveness acceptability curves and net benefit statistics of CBT plus TAU compared to TAU. Cost-effectiveness acceptability curves (CEACs) will be plotted to summarise uncertainty associated with the ICER, rather than using parametric methods of analysis that do not allow variance in the ICER to be interpreted in any meaningful way [57]. To derive CEACs, the incremental cost and QALY (effect) estimates from the regression analyses will be bootstrapped to simulate the sample data of costs and QALY [58]. The bootstrapped estimates of net QALYs will be revalued, using a range of ceiling ratios or willingness to pay thresholds (WTPT) to gain 1 QALY. For each WTPT, a net benefit statistic (NB) will be estimated as:

$$NB = E * WTP - C$$

*Where E = incremental QALY gained by CBTs, WTP = willingness to pay to gain 1 QALY, C = incremental cost of CBT.*

The WTPT values will range from decision makers being willing to pay £0 to gain 1 QALY to decision makers being willing to pay £35000 to gain 1 QALY. This includes the range of implied values that are acceptable to policy makers in the UK [59]. This Bayesian approach estimates the likelihood that CBT is cost effective without hypothesis testing and risk of a Type II error. The primary analysis will use the within trial time horizon of 21 months. Sensitivity analyses will be used to assess the impact of structural uncertainty introduced by the design of the economic evaluation. These include re-estimating the results using (i) high and low sets of unit costs; (ii) key clinical measures as the measure of health benefit; (iii) different approaches to missing data (eg complete cases only, impute missing observations only); (iv) predictions of costs and QALYs over longer time horizons of 5 and 10 years.

## PROPOSED OUTCOME MEASURES

### Primary outcome

The primary outcome measure will be the total PANSS scale score, which will allow for comparison with other published trials (including those of CBT for treatment resistant schizophrenia mentioned above) and inclusion of our results in any future, appropriate Cochrane systematic review or similar. The PANSS is a 30-item rating scale designed to provide a comprehensive assessment of psychopathology in adult patients with schizophrenia. Five components have been reported: positive, negative, depression-anxiety, agitation-excitement, and disorganisation.

### Secondary outcomes

*Positive and Negative symptoms*

The PANSS positive and negative symptom subscale scores will be used to assess these symptoms. The validity of these subscales has been demonstrated [60].

*Hallucinations and Delusions*

Psychotic Symptom Rating Scales [34], which is a clinician administered semi-structured interview consisting of eleven items assessing dimensions of auditory hallucinations and six items assessing dimensions of delusional beliefs. All items are scored 0 to 4, with higher scores indicating more severe phenomena. The items assess frequency, preoccupation, location, loudness, conviction, amount of unpleasant content, severity of unpleasant content, amount of distress, intensity of distress, degree of impairment and control.

*Social and occupational function*

Personal and Social Performance Scale (PSP: [37]) derived from the Global Assessment Scale (GAS) but more focussed on a patient's social and occupational functioning; for an impairment to be rated, it must relate to psychological problems not lack of opportunity. It is a 100–point single-item rating scale based on the assessment of patient's functioning in four areas (socially useful activities, personal and social relationships, self-care and disturbing and aggressive behaviour).

*Depression*

Depression will be assessed using the Calgary Depression Rating Scale for Schizophrenia. (CDSS: [32]), a scale designed to minimise the potentially confounding symptom overlap between depressive features and both negative symptoms and extrapyramidal symptoms.

*Anxiety*

Anxiety will be assessed using the Anxious Thoughts Inventory ([33]), which is a self-report measure that assesses dimensions of worry including health-related concerns and social concerns. It assesses the cognitive components of anxiety, and does not incorporate the physiological components, which is advantageous given that our participants will be taking medication that has common physical side effects that may confound such measurement. For the purpose of this study we will be using the meta-worry subscale only.

*Recovery*
Recovery will be assessed using the questionnaire about the process of recovery, a user-defined measure (QPR [38]), which is a 15-item questionnaire developed collaboratively with service users, measuring subjective recovery in two domains: intrapersonal functioning and interpersonal functioning.

*Substance Use*
Alcohol Use Disorder Identification Test (AUDIT) was developed by the World Health Organisation (WHO). It can be administered via clinical interview or self-report questionnaire. It comprises 10 questions pertaining to harmful alcohol use, hazardous alcohol use, and alcohol-dependence symptoms, with cut-off scores to identify problem drinking related patterns. Scores range from 0-4 on each item, with total AUDIT scores ranging from 0 - 40, the higher the score, the more severe the alcohol use related problems. AUDIT scores are highly predictive of Structured Clinical Interview for DSM-IV (SCID) defined alcohol use disorder in first episode psychosis ([39]).

Drug Abuse Screening Test (DAST [40]) is available in 10, 20, and 28-item formats;
our research will employ the 10 item DAST. Response format is in the style of dichotomous 'yes'/'no' categories in response to such statements as, "Can you get through the week without using drugs?". Scores range from 0 – 20, with cut-off scores indicating presence of drug-misuse (different cut-off scores are recommended for different populations). A recent review of the DAST confirmed that its psychometric properties of reliability and validity suggest it is a satisfactory screening instrument to identify drug misuse and dependence problems [63]. DAST scores are statistically predictive of SCID defined drug misuse problems in psychosis [39].

*Clinical Global Impression*
The Clinical Global Impression Scale (CGI-S) is a widely used measure of global illness severity score on 1 7-item scale. The CGI-S has two components the CGI-S severity, which rates illness severity, and the CGI-S Improvement, which rates change from the initiation of treatment. Also, in addition to the clinician version described above, a participant version of the CGI (CGI-P) will be utilised. The participant will be asked on a scale on '1' to '7' where '1' is not at all ill and '7' is the worst that your illness has ever been to rate the severity of their experiences of psychosis.

*Working Memory*
Our research will employ a measure of working memory, the measure of working memory-letter-number (LN) span (Gold, Carpenter, Randolph, Goldberg & Weinberger, 1997). This will be administered at baseline (0 months) and end of treatment (9 months) only.

**Psychological measures**
Several psychological measures will be used in order to identify mechanisms of change and predictors of outcome. All are brief self-report scales, which have good psychometric properties and have been approved by our service user reference group. We have successfully used all of these measures in several large studies including CBT trials.

*Appraisals of voices*
A measure of interpretations of voices, the Interpretation of Voices Inventory (IVI [41]) will be used.

*Appraisals of paranoia*
A measure of beliefs about paranoia, the Beliefs About Paranoia Scale (BAPS [42]) will be used.

*Beliefs about self and others*
The Brief Core Schema Scale (BCSS [43]) will be used to measure positive and negative beliefs about self and others.

*Attachment style*
The Psychosis Attachment Measure (PAM-SR [44]) will be used to examine attachment styles.

*Childhood trauma*

The Childhood Trauma Questionnaire [45] will be used to retrospectively assess histories of abuse and neglect. This will be carried out at the end of treatment (9 month) assessment only.

*Stigma and beliefs about illness*
A measure of stigma, The Internalised Stigma of Mental Illness Scale (ISMIS 68).

*Therapeutic Relationship*
The 12 item therapist version of the California Psychotherapy Alliance Scale (CALPAS: [65]) will be used to assess the therapeutic relationship. This will be completed by the therapist at sessions 3 and 15.

*Common responses*
This will be evaluated using a common responses questionnaire.

*Semi-structured Clinical Interview for Psychosis Subgroups (SCIPS)* [69]
The SCIPS is a semi-structured interview looking at different areas and events prior to the onset of psychotic symptoms. The items cover psychosocial factors and co-morbid conditions which have been proven to be associated with psychosis to allow for the classification of a specified sub-group: either traumatic, drug related, anxiety or stress sensitivity. The SCIPS will be administered at 12 month follow-up (21 months) for all participants who reach this time-point by October 2015. Participants who do not reach this time-point by October 2015 will be offered the SCIPS at the end of treatment (9 months) assessment.

**Health economics measures**
Each participant will be asked to complete an economic patient questionnaire (EPQ) at baseline and each follow up assessment, in addition to this participants will be contacted by the researcher by telephone to complete the economic patient questionnaire at 3, 6 13 and 17 months. This will ask whether the participant has been admitted to inpatient care (psychiatric or non psychiatric) or used hospital outpatient services and the names of the hospitals attended. This information will be used by the researchers to identify case notes at the relevant hospitals and extract details of each admission and use of outpatient services. The EPQ will also ask for detailed information about what other, non hospital based health and social care services were used and how often they were used.

Each item of resource use will be multiplied by the unit cost specific to that item. Standard national unit costs will be used. Mental health hospital services will be costed using the relevant national reference costs for each type of admission or ward (published annually by the Department of Health). Medications will be costed using the British National Formulary. Other services will be costed using the most detailed national unit cost available (e.g. Unit costs of health and social care published annually by the PSSRU, University of Kent).

QALYs gained from baseline to end of scheduled follow up will be estimated as the number of weeks multiplied by the utility of observed survival. The utility values will be estimated from the Euroqol EQ-5D health status questionnaire completed at each follow up assessment and the associated published societal utility tariffs. The Euroqol is a generic and validated health status questionnaire shown to have acceptable validity in people with schizophrenia in European countries [66]. The EQ-5D has been used successfully in two recent UK trials of antipsychotics in schizophrenia [46 67] and a cognitive therapy trial for people at risk of psychosis (Morrison et al., 2011). Data from these trials demonstrated that the Euroqol correlates with clinical measures of quality of life and effectiveness and is sensitive to change. The EQ-5D will be collected for all participants at baseline and scheduled follow up.

Measuring adverse events
Understanding and quantifying the risk of potential adverse effects of cognitive behavioural therapy for psychosis (CBTp) is important, but difficult to do. Early CBTp trials have been criticised for not giving this issue adequate consideration (Jones et al., 2012). More recently, Klingberg and colleagues have provided a useful template for assessing adverse effects (Klingberg et al 2012; 2010). We propose to incorporate this into our assessment protocol, but also build on it by including strategies to assess perspectives of participants as well as reasons for early discontinuation. Klingberg et al assessed the following:

1. Death caused by suicide
2. Suicide attempt

3. Suicidal crisis (explicit plan for serious suicidal activity without suicide attempt) as defined in Calgary Depression Rating Scale for Schizophrenia [CDSS], item 8, rating 2)
4. Severe symptomatic exacerbation, defined by the Clinical Global Impression Scale (CGI) which includes ratings of illness severity, changes in overall clinical status, and therapeutic effects. A rating of CGI2 ≥ 6 and CGI 1≥ 6 would be regarded as severe adverse event.

We already measure 1, 2 and 3. We propose to add in Clinical Global Impressions (CGI) – Severity and CGI – Improvement scales, and classify scores of 6 or more on both measures as indicating a potential serious adverse effect of trial participation. The measure will take 30-60 seconds to complete and as it this measure uses the clinicans ratings it will not add any additional burden to the participants. One problem with all these measures is that they do not necessarily capture the participant's experience or perspective. The influential CATIE trial used a patient version of the CGI (Hermes et al., 2010). We propose to use this in FOCUS, employing the same cut-off for adverse effects as the clinician-rated version. The measure will take 30-60 second to complete.

We will administer a measure of potential adverse effects from trial involvement at point of exit. Many of the measures cannot be easily used to assess reasons for early discontinuation from the trial; However, our measure of adverse effects has been designed with this in mind and was designed to measure these broad categories: worsening difficulties; poor engagement (including low motivation); situational change; not getting benefit; stigma; increased conflict with others (care team, family etc.); felt better.

One ethical consideration is that participant may feel obliged to complete the measure. We make it explicit in the information at the start of the measure that they are under no obligation to complete the measure and if they decided not to do so that this will not affect any care they receive now or in the future. If people discontinue from the trial we will ask permission to administer this measure to assess their reasons for discontinuation. If we cannot contact the participant we will ask their care coordinator to attempt to administer the measure on our behalf.

Assessments: schedule, administration, staff training, reliability and validity

All outcome measures will be administered at baseline and subsequently at 9 and 21 months by research assistants who will have been trained in the use of all the instruments and scales, to achieve a satisfactory level of inter-rater reliability. Regular training sessions including the use of video and role play will be conducted with all research assistants in order to maintain reliability and prevent rater drift. Participants will be offered choices regarding length of assessments, including the option of breaks and multiple occasions. Assessment measures will be clearly prioritised so that the most important will be collected first to avoid missing data. We will have a standard protocol for managing any distress that is associated with the completion of measures, which we have successfully utilised in several trials and has been developed in collaboration with service users; this includes telephone contact within 48 hours of assessments in order to check on participant well-being

**RESEARCH GOVERNANCE**

Greater Manchester West Mental Health Foundation Trust would view itself as the primary sponsor. Given that the Department of Heath, with the HTA programme acting as their agent, is prepared, in principle, to be nominated as the sponsor, then co-sponsorship responsibilities could be agreed with Imperial if the application is successful. In accordance with high standards of research governance we would ensure researchers receive training in the International Conference on Harmonisation (ICH) Guidelines - Good Clinical Practice. We will set up a Trial Steering Group (TSC) and an Independent Data Monitoring and Ethics Committee (IDMEC) prior to the start of the study. The TSC will comprise study applicants, a representative of the HTA, and representatives of service users and providers, and have an independent chairman. An IDMEC will also be established to monitor (1) recruitment of study participants, (2) ethical issues of consent, (3) quality of data (including missing data), (4) the incidence of adverse events, and (5) any other factors that might compromise the progress and satisfactory completion of the trial. This will also have an independent chairman, and include an independent statistician.

Data management

Each study participant will be assigned a unique trial identification number at the start of the assessment process. This number will be written on all clinical assessment forms/datasheets and databases used to record data on study participants. A hard copy of a record sheet linking patient identity, contact details and trial identification number for all participants will be kept at each site. It will be placed securely in a locked filling cabinet separate from datasheets. The local study co-ordinator will enter the data on to an electronic database, and all such data will be checked for errors before being transferred to the appropriate statistical package. All data will be kept secure at all times and maintained in accordance with the requirements of the Data Protection Act, and archived according to clinical trial GCP regulations.

**PROJECT TIMETABLE AND MILESTONES**

This will be a four-year study: Prior to commencement of the study, we will ensure that all recruiting of staff, establishing premises, ethics approval and organisation recruitment will be in place. For the trial to start, the sponsor will need to review and approve all procedures and materials. The first 2 months of the trial will involve final preparations; specifically, finalising protocols, training of staff in assessments and therapy protocols, preparation of materials, research governance approvals and purchasing of equipment. There will then be 24 months for recruitment, plus 21 months for the follow-up assessments. Recruitment targets and milestones will be reviewed on a monthly basis by the TEC; these targets will be approved by the TSC and DMC. The trial manager will also produce lists of all assessments that are due each month. The final month will allow for obtaining any overdue final assessments and data cleaning and analyses and the writing of final reports and publications.

**EXPERTISE**

The study applicants provide expertise in clinical trial design, organisation and supervision (JN, AM, AG, DK, DT, TB), cognitive models of psychosis (AM, AG, MS), the development and evaluation of CBT for psychosis including RCTs (AM, AG, DK, DT, MS, PF), and implementation of CBT research into clinical practice and public policy (AM, DK, DT, AG), the psychopharmacology of schizophrenia, antipsychotic drugs and their side effects (TB), clinical experience in the clinical management of treatment-resistant schizophrenia (TB), involving service users in research and facilitating user-led research (RB, AM, AG, SJ, TB), clinical trial statistics (JN), and mental health economics (LD), specifically in relation to clinical trials in psychosis. The trial will be supported by the CHaRT, Health Services Research Unit, University of Aberdeen, a fully registered (registration number 007 ) UK CRC Clinical Trials Unit. The team members have wide ranging experience of successfully recruiting and retaining people with psychosis in clinical trials within the field of CBT, including in pioneering work on treatment-resistant schizophrenia. In the 90s, two applicants (Kingdon and Turkington) were PIs in one of the world's first trials of CBT for treatment-resistant psychosis. More recently, Morrison has been CI of the MRC-funded EDIE-2 trial, a 5 site RCT examining CBT for prevention of psychosis in those at high-risk (2006-2010), and CI of a 5 year NIHR funded programme grant examining psychological approaches to recovery from psychosis (2008-2012). Both Morrison (CI) and Turkington (PI) lead a NIHR-funded ACTION trial examining the effectiveness of CBT for people with psychosis who are refusing antipsychotic medication (2010-2013); Byrne is also an investigator on this grant. Gumley conducted the world's first study of CBT for relapse prevention in people with schizophrenia. He was also a PI on the EDIE-2 trial, and is CI for the recently completed Scottish Government funded Scottish Study of Engagement Attachment and Recovery following first episode psychosis (in which Schwannauer is also involved). Kingdon is currently investigator on two MRC EME, two NIHR and a number of international studies in CBT for psychosis. Barnes is CI of HTA-funded trials of pharmacological interventions for negative symptoms and for clozapine-resistant schizophrenia. We will also draw on a range of collaborators with appropriate expertise, including Professor Graham Dunn (lead for MHRN methodology research group), who has agreed to be a collaborator with regard to the analyses of mediator/moderator effects.

<u>The Trial Steering Committee</u>

An independently chaired steering committee will meet annually, and initially before the trial begins for approval of the protocol. The TSC will monitor and supervise progress, consider reports and recommendations. An observer from the HTA will be invited to all meetings. The proposed membership of the TSC is as follows: An independent chairperson, an independent academic, an independent clinician, the principal investigator, two additional investigators and a service user representative.

<u>Independent Data Monitoring Committee</u>

A DMC will also be established to monitor: recruitment of study participants; ethical issues of consent; quality of data (including missing data); safety and the incidence of adverse events; plans for data analysis; confidentiality; adherence to NRES protocol; and any other factors that might compromise the progress and satisfactory completion of the trial. This will have an independent chairman, and include an independent statistician, an independent CBT expert and an invited HTA representative. The DMC will meet on a 6-monthly basis. An evaluation committee (all applicants and at least one independent member of the DMC) will be responsible for the consistency of recruitment, assessments and intervention.

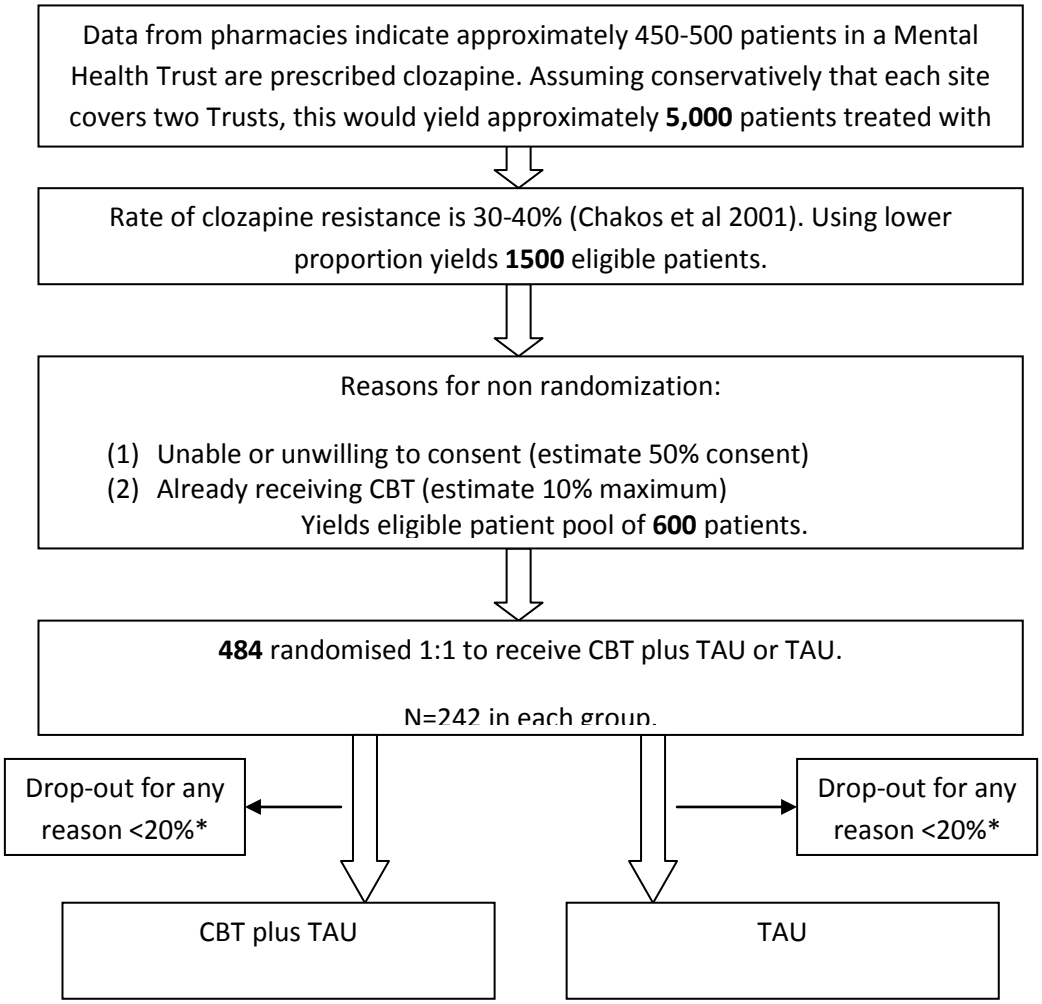
**SERVICE USERS**

It is clear from our contact with the service user reference group (SURG) in Manchester that consumers welcome the proposed study. The members of the group have already contributed to the design of the study, with feedback from discussions with service users confirming the relevance of the research question, the proposed outcome measures and the specific methodologies. The SURG has agreed to assist the Trial Management Group in the design of participant information sheets and consent forms, advise the TMG on the methods to use for providing feedback on the study to study participants, and contribute to the production of the final project report. Members of the SURG have also agreed to contribute to the process of communicating study findings, such as helping to generate a user-friendly sheet summarising findings for study participants, and preparing a summary of study findings suitable for publication in a service user journal. Two members of the Trial Management Committee will be service users, and a study-specific service user reference group will be established, derived from membership of the service user research groups associated with existing CBT trials in the North of Britain and Southampton. The members will be paid appropriately for their time and travel. We have a track record of successful user-led research into psychosis: Byrne has experience as an Investigator on NIHR funded research and of coordination of service user steering committees; one of the studies in Professor Morrison's existing NIHR programme grant won the national MHRN gold award for user involvement in 2009; Professor Morrison also won the MHRN North West hub award in 2010 for service user involvement in research.

**Flow Diagrams**

The following flow diagrams illustrate the participant flow through the study. Figure 1 illustrates the feasibility of recruitment, and figure 2 illustrates the CONSORT diagram that will be used to report the study, which is based on the CONSORT guidance specific to psychological intervention trials.

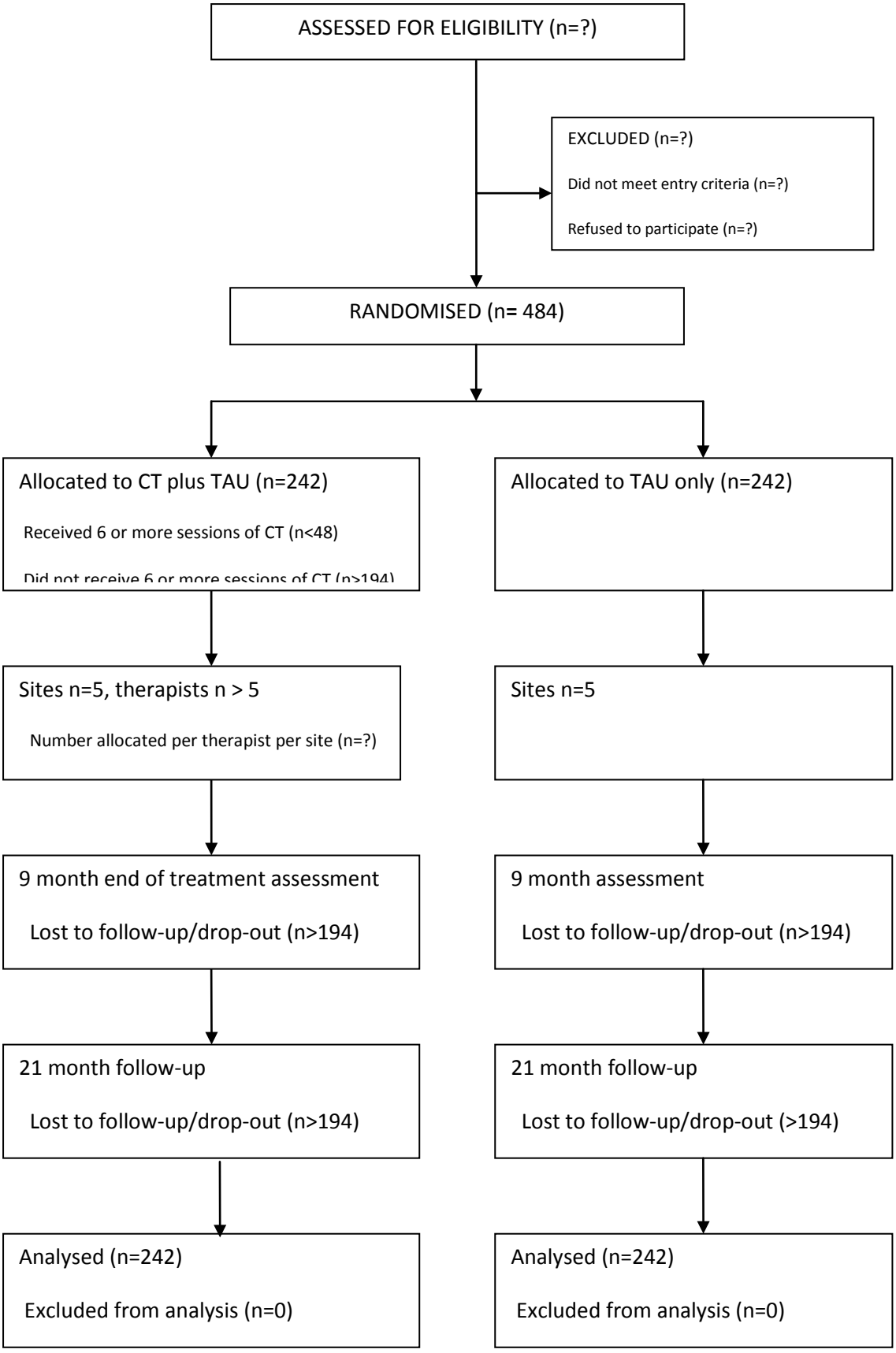
**FIGURE 1: FLOW DIAGRAM TO SHOW RECRUITMENT AND RETENTION OF PARTICIPANTS**




*Drop-out rate: All of our previous studies of CBT report completion rates of >80%

(e.g. Gumley et al., 2003 ; Morrison et al., 2004 ; Morrison et al., 2011 ; Sensky et al., 2000; Turkington et al., 2002).

**Figure 2: CONSORT Diagram for reporting participant flow**



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Annex 1

## The FOCUS Trial: Qualitative Component (Protocol)

### Introduction

The FOCUS randomised clinical trial will test whether, for people with confirmed treatment-resistant schizophrenia that is poorly responsive to an adequate trial of clozapine (or unable to tolerate such a trial), Cognitive Behavioural Therapy (CBT) is clinically and cost effective, and an acceptable treatment. This Qualitative component of the trial will evaluate in particular the acceptability of CBT for participants.

### Background

In around a third of people who experience psychosis or receive a diagnosis of schizophrenia, these difficulties show a poor response to standard treatment with antipsychotic medication. While a relatively small proportion will fail to achieve remission even after the first exposure to antipsychotic medication, with either first or second generation drugs,[1] more commonly the illness becomes progressively more unresponsive to medication with subsequent relapses.[2] This 'treatment-resistant' subgroup of individuals represent a major clinical challenge in everyday psychiatry, and their treatment consumes a disproportionate amount of NHS funding.[3,4] It is estimated that the total societal cost of schizophrenia in the UK in 2004/5 was £6.7 billion.[5] Treatment resistant psychological problems are the most costly, usually requiring longer term residential and intensive community treatments. Even among people experiencing a first episode of psychosis, over 10% fail to remit in the 12 months

following initiation of treatment. There is clinical and economic need to evaluate treatments to improve outcomes in this deprived group of individuals.

Clozapine is the only antipsychotic with convincing evidence for efficacy in strictly-defined treatment-resistant psychosis or schizophrenia. But even in people in this category, clozapine has limited efficacy, with 30-40% showing an inadequate response to the drug.[6] For some service users, a range of potentially serious side effects such as seizures, sedation and tachycardia may prevent the optimal dose being reached. In the short term, metabolic side effects that increase the risk of diabetes and cardiovascular disease become apparent in many. The long-term effects of antipsychotics are becoming increasingly recognised as problematic,[7] so a demonstration of long-term benefits of CBT in a treatment-resistant population is highly likely to benefit physical health as well as mental health.

**CBT for psychosis**

In recent years, the generic cognitive model[8] has been applied to our understanding and treatment of psychosis. This model suggests that the way that we interpret events will have consequences for how we feel and behave, and that such interpretations are often maintained by unhelpful thinking biases and behavioural responses. There have been several cognitive models of psychosis and psychotic experiences outlined,[9-11] which suggest that it is the way that people interpret psychotic phenomena that accounts for distress and disability, rather than the psychotic experiences themselves. There are several comprehensive treatment manuals that describe the application of such models in greater detail.[12-15] CBT has been shown to be highly effective when delivered in combination with antipsychotic medication, with several meta-analyses showing robust support for this approach.[16-19]

Considering the above literature, it would appear that there are significant numbers of service users with a schizophrenia spectrum disorder who either fail to respond to an adequate trial of clozapine or are unable to tolerate such medication due to adverse reactions. CBT clearly has the potential to help alleviate symptoms and improve quality of life in people meeting criteria for treatment-resistant psychosis or schizophrenia and there are suggestions that it can help those who are not taking antipsychotics; however, there is insufficient research regarding CBT for service users with an inadequate response to or unable to tolerate clozapine. Qualitative evidence in this area is also particularly limited, and so a Qualitative evaluation is considered valuable in the context of the Focus trial.

**CBT for Psychosis: Qualitative research**

Qualitative research into service user experiences has been acknowledged as an important addition to the evidence base for CBT for psychosis (CBTp),[20] because of peoples' expert knowledge about what works for them individually.[21] A recent review of the qualitative literature on this topic[22] reported that Qualitative studies of CBTp to date have focused on a variety of aspects of the treatment (eg., psychological formulation or 'homework'), and explored a number of therapy contexts (eg., individual or group therapies). Because of the variety of study methods, it is difficult to analyse them as a group. However a number of findings seem to reflect common themes across studies; for example Messari and Hallam[23] identified several central themes, echoed in similar studies, including: CBT as an educational process; CBT as a respectful relationship between equals; and CBT as a healing process. [23]

It has been suggested that future studies of CBTp will benefit from greater involvement of service users in the research process. User-involvement in mental health research has been recommended by the Department of Health and by NICE.[24,25] User-led research may offer advantages such as equalising the balance of power between researchers and service users, increased rapport between interviewers and interviewees, and may reduce interviewees' potential concerns regarding confidentiality and criticism of professionals, and may also offer "a different view of the world of mental health" to that produced within mainstream research.[26] Therefore the present study is designed and will be conducted as a user-led qualitative evaluation of service users' subjective experiences and perceptions of CBTp during the FOCUS trial, especially in relation to the acceptability of the treatment.

## Method

**This proposed methodology may be subject to change pending advice given from either the Data Monitoring or Trial Steering Committees associated with the FOCUS trial.**

**Grounded Theory methodology**

Grounded Theory (GT) is a widely used qualitative method. It may be defined as 'the discovery of theory from data systematically obtained from social research'.[27] It allows for the discovery of meaning and underlying processes of a phenomenon, by interpretatively considering each individual's perspective. Given the subject of study and consistent with previous qualitative work in recovery after psychosis,[28,29] the use of a social construction version of GT30 appears to be the most suitable methodology for exploring the topic of interest.[30] This version has its roots in 'social interactionism'31, which assumes that it is the meanings people give to situations which determine human behaviour. These meanings are

influenced by history, culture and language, and actively constructed within social interactions, mediated by an interpretive process used by each person. Hence, meaning is to be viewed as a constructed process. As a result, GT arises from the interaction between researcher and participants – it is actively constructed, rather than representing an objective reality. The existence of a unidimensional external reality is not assumed.[31] To increase methodological rigour, credibility and utility, criteria for improving the quality of qualitative research would be considered in the design and implementation of the qualitative study.[32]

**Participants**

In order to meaningfully explore the aim stated above, it is proposed for the project to purposively recruit a sample of trial participants who are allocated to the treatment (CBTp) arm of the FOCUS trial.

**Inclusion criteria for this trial are as follows:**

6. A criterion level of persistent symptom severity despite an adequate trial of clozapine in terms of dosage, duration and adherence:[33]
    - Treatment of clozapine at a stable dose of 400mg or more (unless limited by tolerability) for at least 12 weeks, or if currently augmented with a second antipsychotic that this has been given for at least 12 weeks, without remission of psychotic symptoms, or have discontinued clozapine due to adverse reactions (including agranulocytosis) or lack of efficacy in the past 24 months
    - presence of at least one psychotic symptom with severity ≥4 (for hallucinations/delusions) or ≥5 (for suspiciousness/grandiosity) on the PANSS in addition to a PANSS total score of at least 58, which is equivalent to a clinical global impression (CGI) of being at least mildly unwell
7. be in contact with mental health services and have a care coordinator
8. 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
9. Aged at least 16 years old
10. Competent and willing to provide written, informed consent.

**Exclusion criteria are:**

5. Primary diagnosis of alcohol/substance dependence, where this is clearly the cause of their psychotic symptoms
6. Developmental disability
7. Non-English speaking
8. Current receipt (or within the last 12 months) of structured CBT from a qualified psychological therapist in accordance with NICE guideline recommendations (as opposed to more generic psychosocial interventions)

Inclusion criteria for this Qualitative study are therefore those detailed above, along with inclusion in the treatment arm of the trial. Given the research approach, sample size need not be determined. Rather, data collection would continue until saturation of the topics emerging from the interviews, as required by a Grounded theory approach, is reached.

**Sensitivity to context**

Relevant literature on subjective experiences of CBTp will be reviewed in depth before commencing data collection, which will allow identifying gaps in knowledge. In line with the proposed methodology of GT, reviewed literature is not to form the basis of an emerging theory, but rather will serve as a guide for developing initial interview questions. Open discourse will be encouraged during the initial interviews to gain insight into participants perspective of CBTp experience. A stepped/phased approach of data collection would ensure that interview questions remain flexible and are adapted to evolving theory. Such an approach further will allow the exploration of different perspectives from different groups, facilitating triangulation (see below).

It is hoped that the project can be supported and actively guided by the existing Trial Management Group, along with the Service User Reference Group (SURG) associated with the trial, to advise and feedback both in terms of practical concerns as well as data analysis (e.g. the development of the semi-structured interview, information sheet and consent form).

**Health and Safety Issues** (researcher and participants)

Regular supervision by academic and field supervisors could ensure that required support is provided for the researcher. Informed consent (including notification that participants are free to terminate interviewing at any point) would be obtained of all participants. Appropriate debriefing and support arrangements accessible to all participants should be available at the place of data collection. Furthermore, strict adherence to local NHS data protection

guidelines would ensure that confidentiality is maintained at all times. Prior to approaching participants for their participation in the qualitative interview, the researcher will check with the participants therapist, their suitability to be approached.

**Ethical Issues**

Participation, as per Research Ethics and R&D approval, would be voluntary and informed. Recruitment will be sensitive to avoid coercion. All data, verbal and written, would be treated in accordance with local NHS guidelines on data protection. That is, all data would be rendered anonymous and confidentiality respected at all times, with all person-identifiable items being removed from any written material. Participants would be advised about the potential use of anonymous quotations within the written report. We will inform the Sponsor of the study of the interview development at each stage of the project and based on their advice we will apply an amendments to ethics as appropriate. Participants will be compensated £10 for their time as a token of appreciation.

## Procedure

**Data collection and analysis**

As outlined above, it is proposed for the data collection to proceed in phases, whereby data analysis will follow each phase and inform the interview questions for the next phase (or group of participants). As such, the emerging theory will unfold dynamically and flexibly out of triangulation between the different data sets, thereby staying true to the spirit of GT. The following way of proceeding is proposed:

***Phase 1:***

Development of semi-structured interview questions (with guidance from steering group and supervisors). The researchers will then go on to conduct in-depth qualitative interviews with an initial sample of participants, exploring experiences of CBTp, with a particular focus on the acceptability of the treatment, and participants' preferences. Following transcription and qualitative analysis of the collected data (see data analysis below), the results (i.e. emerging themes) are used to modify and inform the content and structure of the next phase of interviews, in collaboration with members of the two group mentioned (Management and Service Users).

***Phase 2:***

Further semi-structured interviews will be conducted with an additional, purposively-recruited sample of trial participants. The content of the interviews will have arisen from analyses following the first phase.

## Data Analysis

Following the principles of GT, the data analysis would start with line-by-line coding and the more significant and frequent codes emerging from the process are extracted. The use of constant comparative methods and memos written throughout the interpretative process would guide further theoretical sampling and help to raise the codes to conceptual categories. When categories are deemed to be coping adequately with new data, without requiring continual revision and when no new relationships or codes are emerging from the data analysis, the process of theory generation will have met 'theoretical sufficiency'.[34] The triangulation of the different views of service users, carers and professionals would be used to develop a more comprehensive understanding through methods of constant comparison rather than as a measure of internal validity.[35] Grounded theory would then be constructed as a synthesis of categories, memos and relationships between concepts noted in the process of data analysis.

## Settings and Equipment

It is proposed that where appropriate and acceptable to participants, interviews will be conducted with participants in their own homes, or in a suitable, mutually-agreed location (eg., at their GP's surgery or local counselling service). Electronic audio recording equipment will be used to record the interviews. An encrypted NHS laptop and memory stick would be used for transcription and storage of collected data.

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Annex 2

## Focus site specific study: Manchester site only

### An experimental investigation in to the effect of manipulating response styles to an ambiguous auditory task in participants with a diagnosis of schizophrenia.

### INTRODUCTION

An experimental study will be conducted looking at the impact of manipulating response styles on distress and frequency of words detected in an ambiguous auditory task. Much research in this area to date has been cross sectional and so further experimental work is needed to be able to answer questions about direction of causation as opposed to simply associations. This study could therefore advance understanding around the advantages and disadvantages of certain response styles which could in turn have implications for therapeutic work with people experiencing distressing voices.

### BACKGROUND

The idea that interpretations and beliefs influence our emotional and behavioural responses is central to the cognitive model of mood (Beck, 1963). For example, an individual will feel anxious if physical sensations, such as palpitations, are appraised as threatening (Clark, 1986). As a result of these threat appraisals the individual will then take action to protect themselves from this perceived threat (Salkovskis, 1991). This is known as safety seeking behaviour and is understandable in the context of a very strong conviction that harm is imminent (Salkovskis, 1991). Salkovskis et al (1996) proposed three categories of safety seeking behaviours. These are avoidance of the feared situation, escape from it and behaviours carried out to cope whilst in the situation (Salkovskis, et al., 1996). Such safety seeking behaviour can contribute to the maintenance of anxiety as it can be interpreted that harm did not arise only because the safety seeking response was employed (Salkovskis, 1991). For example, for someone who interprets their palpitations as a sign that they are about to have a heart attack, they may immediately lie down to try and prevent this from happening. This is interpreted as a "near miss", that a heart attack was only prevented because they lay down and anxiety in the situation is reduced (Salkovskis, 1991). However, anxiety in the longer term is maintained as the belief that palpitations is a sign of imminent threat has not been disconfirmed (Salkovskis, 1991).

Response styles have been looked at in more detail by Birchwood, Chadwick and colleagues in a series of studies using their measure, the BAVQ (Chadwick & Birchwood, 1995; Chadwick, Lees, & Birchwood, 2000). The BAVQ classifies beliefs about voices as either malevolent or benevolent and behavioural responses as either resistance or engagement. Responses classified as resistance includes trying to stop the voice whereas engagement includes listening to the voice and following its advice. It has been consistently found that resistance is positively related to voice malevolence and negatively to voice benevolence, while the opposite relationship is observed with the response style engagement. However, findings have been less consistent in terms of the association between response styles and distress. One study has reported that their participants classified as depressed used more of both resistance and engagement than the participants considered "not depressed" (Upthegrove, Ross, Brunet, McCollum, & Jones, 2014). Others have reported that resistance is positively associated with depression and anxiety while engagement is negatively associated with the same measures (Chadwick, et al., 2000; Soppitt & Birchwood, 1997). Finally, the most recent study found no significant relationships between these response

styles and various measures of distress (Morris, Garety, & Peters, 2014). This research Project is therefore needed to try and gain a clearer understanding of how these response styles might relate to voice related distress. This could have implications for therapeutic work as it might be possible to teach people more adaptive ways of responding to their distressing voices that could help to lower this distress and perhaps also challenge beliefs about the threat associated with the voice.

## PROJECT OBJECTIVES

### Primary Question/Objective:

Does manipulating the response styles of resistance and engagement have an effect on distress and the number of words detected in an ambiguous auditory task in people with a diagnosis of schizophrenia?

### Secondary Question/Objective:

Is there a difference in the above outcomes in participants who report hearing voices compared to those who do not?

## PROJECT DESIGN & PROTOCOL

### Participant Identification

Participants will be approached at the end their final assessment (21 months) as part of a the FOCUS Trial. The participants will have already been made aware of this extra study at the time of their consent to the main clinical trial. The research assistant will remind the participant about the study and ask if they would like to take part.

### Study Intervention

An independent measures design will be used with two groups of participants. The independent variable is response style; half the participants will be allocated to the resistance group and the other to the engagement group.

Throughout the task participants will be asked to wear a small electrode on their finger in order to measure galvanic skin response. The period of time whilst filling in questionnaires at the beginning will be taken as a baseline. The period of time while they are listening to the recording and responding will then be looked at. The device will record data every second and an average will be calculated from this.

All participants will first be asked to complete four measures at baseline. These will be the Beliefs about voices questionnaire (BAVQ), the thought control questionnaire (TCQ), the Measure of Common Responses (MCR) and the metacognitions questionnaire (MCQ-30).

Participants will then be randomised either in to the resistance group or the engagement group. This will be stratified by voice hearing to ensure equal numbers in each group.

The resistance group will be given the following instructions:
“You are going to be asked to listen to 5 minutes of a recording of people speaking. Sometimes people hear words during the recording that they may find unpleasant. While you

are listening to the recording please try and distract yourself and ignore these words as much as possible."

The engagement group will be given the following instructions:
"You are going to be asked to listen to 5 minutes of a recording of people speaking. Sometimes people hear words during the recording that they may find unpleasant. While you are listening to the recording please try and focus on the words and listen out for them as much as possible."

All participants will then listen to the same ambiguous auditory task. This is a recording of voices with randomly spliced one second sections played backwards as described by Feelgood and Rantzen (Feelgood & Rantzen, 1994). It has been found that use of this stimulus can cause participants scoring highly on a measure of susceptibility to hearing voices, to hear words and phrases in the tape when in fact none are present. Participants will listen to the recording for five minutes. At the end of the task they will be asked to rate their distress levels and how much they had felt able to resist or engage during the task. They will also be asked to estimate how many words they heard during the task.

All participants will then listen to the same recording again but this time they will be asked to keep a tally of any words they hear during the task and make a note of them if they are able to. Finally they will rate their distress levels again at the end of the task.

All participants will then be debriefed, thanked for their time and it will be made sure that they are not feeling distressed following completion of the task. They will be paid £10 for their time.

PROJECT SUBJECT SELECTION

Inclusion Criteria:

Schizophrenia spectrum diagnosis
Aged 16 and above
Regular contact with a health professional (Psychiatrist, Care Coordinator or GP)

Exclusion Criteria:
Developmental disability
Organic impairment
Primary diagnosis of substance misuse
Non-English speaking
Unable to provide informed consent

Recruitment:

A participant information sheet has been developed as part of the FOCUS trial and this has been amended to include information about this study which will be conducted after the participant completes their final (21 month) assessment. A brief information sheet has been developed for those participants who had already consented in to the trial before this amendment to the study. The researcher will meet with the client at a venue they feel comfortable with such as their own home and reads through the information sheet with them. The researcher will give the individual the opportunity to ask any questions they might have about the research. The client will also be asked to reflect back their understanding of the research and consider the pros and cons of taking part to ensure they have understood and

considered the information provided. The researcher is an Assistant Clinical Research Psychologist and so has experience of taking informed consent. The researcher will also be working under the supervision of a Professor in Clinical Psychology who will be consulted if any concerns regarding capacity to consent arise. If it is felt that a client does not have capacity to consent, the researcher will not take consent and the supervisor will be immediately consulted. If an individual appears to have an understanding of the information and would like to take part they will be asked to sign the consent form that has been developed as part of the main clinical trial.

Randomisation:

Randomisation will be conducted using opaque sealed envelopes. This will be stratified by voice hearing status so there will be one set of envelopes for those participants who report hearing voices over the past 6 weeks and one set of envelopes for those who do not. In order to balance group sizes and also to ensure allocation concealment permuted block randomisation will be used. Some envelopes will contain 6 randomisation slips and others 8; the researcher will not know how many are in each envelope and therefore will be less likely to be able to guess the allocation that is coming next. Each envelope will contain an equal number of each response style, resistance and engagement (i.e. 3 or 4 of each).

6.5 Patients who withdraw consent:

Participants can withdraw consent at any time without giving any reason, as participation in the research is voluntary, without their care or legal rights being affected. This will be detailed in the information sheet provided to all participants.

## OUTCOME MEASURES

This study will help to determine if different response styles to ambiguous auditory stimuli has an impact on the level of distress experienced. This could have implications for therapeutic work with people experiencing distressing voices as they could be taught about different response styles and helped to see if the way they are responding is helpful or unhelpful. It may also be possible to teach people more helpful ways of responding to their distressing experiences.

## DATA COLLECTION, SOURCE DATA AND CONFIDENTIALITY

Data will be collected using questionnaire measures. This will be stored in a locked filing cabinet in a locked office on NHS premises. Participant identifying information will be kept separately to the research data generated and this will be labelled with a participant number so as to further protect confidentiality.

## STATISTICAL CONSIDERATIONS

### Statistical Analysis

Analysis will be conducted using two separate one way ANOVA. The first will compare distress ratings between the resistance and engagement groups and the second the number of words detected. Separate analyses will be conducted rather than using a MANOVA because there is no theoretical reason why these two dependent variables would be related.

A secondary sensitivity analysis will be conducted using a 2x2 ANOVA to see if there is any interaction with voice hearing status.

Sample Size:

A power calculation was performed using sealedenvelope.com. 44 participants (22 in each group) are required to have a 90% chance of detecting, as significant at the 5% level, a difference of 10 points on the distress ratings made by the two groups (resistance and engagement).

DATA MONITORING AND QUALITY ASSURANCE

The study will be subject to the audit and monitoring regime of Greater Manchester West Mental Health NHS Foundation Trust.

ETHICAL CONSIDERATIONS

Application for NHS and University Ethics will be made.

The study will be conducted in full conformance with principles of the "Declaration of Helsinki", Good Clinical Practice (GCP) and within the laws and regulations of the country in which the research is conducted.

PUBLICATION POLICY

Following completion of the study, the paper will be submitted for publication in a scientific journal. Presentations may also be made at conferences. A copy of the results will be sent to any participants who are interested in knowing the outcome of the study.

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Annex 3

## Focus site specific study: Newcastle site only

Title: Rumination, paranoia, and social functioning.

Background:

Rumination is a powerful process. Rumination is a method of 'coping with negative mood that involves self-focussed attention' (Lyubomirsky & Nolen-Hoeksema, 1993). It is important in understanding depression and anger, and it seems to share many similarities with worry which is closely linked to anxiety. Recent research on worry in psychosis indicates that worry is a causal factor in paranoia in that there is a dose response between levels of worry and paranoia, worry predicts paranoia in the general population and treating worry can actually reduce paranoid ideation (Freeman et al., 2015). Rumination or dwelling shares many similarities with worry and may also play an important role in maintaining psychotic symptoms and particularly paranoid ideation. In non-clinical participants paranoia is associated with high levels of rumination (see Simpson et al., 2012). Also if rumination is experimentally manipulated it is seen to maintain heightened levels of paranoia whereas distraction and mindfulness both reduce it (see Martinelli et al, 2013; McVie et al., under review). The next step is to investigate if similar findings are demonstrated with clinical participants, initially by considering if there is evidence that rumination is important in the maintenance of clinical levels of paranoid ideation. If this is demonstrated, in time, this knowledge may help develop brief targeted interventions to interrupt or disrupt rumination to see what impact this has on levels of paranoid ideation.

This work will explore three key areas. First it will examine if measures of rumination are particularly important in relation to paranoia or is more generally associated with other symptoms of psychosis. Second it will examine the relationship between how

people use their time, levels of rumination and functional outcomes. It would be predicted that there will be a strong relationship between the least functionally active and higher levels of rumination. Finally, it is anticipated that those people with the highest levels of rumination at follow up will also show the poorest response to treatment.

Participants: Participants recruited in the FOCUS trial (see trial protocol for inclusion criteria). In the North east there are close to 90 participants enrolled in the study. Around 60 may be available for the follow up assessments from this time onwards.

Measures:

*The Perseverative Thinking Questionnaire (PTQ, Zetsche, Ehring, & Ehlers, 2011)*

The PTQ is a 15-item self-report measure that comprises three items for each of the assumed process characteristics of repetitive negative thinking: (a) repetitive, intrusive, and difficult to disengage from, (b) unproductive, and (c) capturing mental capacity. The PTQ shows excellent internal consistency and satisfactory test-retest reliability but has not been used with this group as of now. Participants will be asked to rate each item on a scale ranging from '0'= never to '4'= always.

*Ruminative Response Scale (RRS, Treynor, Gonzalez, and Nolen-Hoeksema (2003)*

The Ruminative Response Scale is 22-item self-report measure "describing responses to depressed mood that are self-focused, symptom focused, and focused on the possible consequences and causes of the mood'' (Nolen-Hoeksema et al., p. 1064, 1999). Respondents rated each item on a scale from 1 (almost never) to 4 (almost always). The RRS was initially developed as a subscale of the Response Style Questionnaire (RSQ, Nolen & Marrow, 1991). The original RSQ consisted of four sub scales, out of which the Ruminative Response Scale was found to be highly correlated to several psychological problems such as anxiety, worry, and depression. It also have excellent psychometric properties

*Intolerance of Uncertainty Scale- Short Form (IUS-12, Carleton, Norton, & Asmundson, 2007)*

The IUS is a short 12-item version of the original 27-item Intolerance of Anxiety Scale which measures responses to uncertainty, ambiguous situations, and the future. The 12 items are rated on five point Likert Scale ranging from 1 (not at all characteristic of me) to 5 (entirely characteristic of me). It has a strong correlation with the original scale and has been shown to have two factors (prospective IU and inhibitory IU), both having high internal consistency (α= .85).

Procedure:

At the 21 months follow up participants will be asked at follow up to complete the additional measures of self-reported levels of rumination and intolerance of uncertainty.

Design:

The main analysis will use a single group design and consider relationships between rumination and other symptoms, social functioning and impact of treatment.