**COGNITIVE BIAS MODIFICATION FOR PARANOIA**

**RESEARCH PROTOCOL**

**AIMS AND OBJECTIVES**

This study investigates a potential new therapeutic procedure, ‘Cognitive Bias Modification for paranoia’ (CBM-pa) which has arisen from laboratory research into cognitive biases in paranoia61. A single session of CBM-pa has reduced paranoid beliefs, and the distress associated with an ambiguous real-life social situation, in people with paranoid traits. A six session version has been developed, with input from service-users interested in paranoia. The main aim of the current proposal is to demonstrate that the intervention has patient benefit and would be feasible as a targeted therapeutic intervention in outpatients who experience significant paranoia associated with their disorder. We propose to compare CBM-pa to a text-reading control, both delivered in addition to treatment-as-usual (TAU), an individualised combination of medication, care co-ordination, and psychological treatments, as appropriate. This design is methodologically rigorous and directly evaluates the hypothesized ‘active ingredient’ of CBM-pa (bias manipulation). Our hypothesis is that the biases which CBM-pa manipulates are a maintaining mechanism for patients’ delusional paranoid beliefs. Reducing these biases should reduce paranoid beliefs and associated distress.

Objectives are:

1. Selection of primary outcomes. We will test three domains of potential outcome measures: paranoid beliefs, clinical symptoms and stress/distress.

2. Testing data collection instruments. Several potential measures are self-report and some are lengthy (see supplementary material). Comprehensibility and suitability of these, and information sheets/consent forms will be examined.

3. Sample size. Data collected will provide estimates of population variance on key outcomes to inform sample size calculations for a subsequent trial.

4. Recruitment, consent, dropout and follow-up. Rates will be measured to determine whether current local sources suffice.

5. Integrity of protocol. The combination, length and feasibility of the current protocol will be assessed. This factor has been significant in CBM trials for other disorders1.

6. Intervention Acceptability. We will assess acceptability using 8 qualitative interviews, including views on training content, delivery format (eg. use of audio/visual) and engagement

7. Randomisation. Acceptability of randomisation will be examined, including the best way to explain double-blinding. The necessary with-holding of information about group assignment is likely to be a significant issue, because heightened suspiciousness is an inherent feature of clinical paranoia.

In line with the guidelines of Lancaster and colleagues2,3 endorsed by NIHR, we do not propose hypothesis testing on outcomes. Nevertheless we would expect to observe a pattern of means consistent with reduction in delusional beliefs, clinical symptoms and stress/distress, in the CBM-pa group including clinically important (20% reduction) treatment effect sizes. Manipulation checks for the intervention (experimental measures of belief change) will be examined using hypothesis driven tests and these data will be potentially publishable in clinical experimental psychology journals. The study will provide essential proof-of-concept data, alongside service-user opinion, to support a funding application to either NIHR's HTA Programme, or the MRC's EME stream (given the intervention's focus on underlying mechanism and its laboratory origins). The primary outcome for RCT will be selected by steering group consensus after considering observed effect sizes and views arising from qualitative interviews.

**PLAIN ENGLISH SUMMARY**

Many people with psychosis continue to have paranoid beliefs, despite the best treatments available. We will examine a new computer therapy, ‘Cognitive Bias Modification for paranoia’ (CBM-pa). CBM encourages people to develop alternative ways of interpreting difficult thoughts (i.e. “someone is watching me”), leading participants to change their understanding of what these situations might mean. CBM is used in anxiety62,21 , but has not been appropriately applied to other disorders. Our version, CBM-pa, was developed with service-user input. It is based on new research into the biases that people with paranoia have when interpreting events61. It involves participants reading stories on a computer screen, completing missing words and answering questions about each story in a way that encourages more helpful beliefs about themselves and others. After one session of CBM-pa, people with paranoia displayed a range of helpful effects, including significant belief change, and less distress in ambiguous social situations. This study will test whether, in addition to usual treatment, six sessions of CBM-pa produces significant benefit for patients (for example by reducing symptoms and distress) immediately, and at 1 and 3 month follow-up, compared to reading passages of text alone. Eight participants will be interviewed in more depth about their experiences. The overall aim is to test whether CBM-pa could be an effective treatment for paranoia. If so, CBM-pa would have a number of potential advantages over other approaches, including, minimal effort to complete, no homework, no therapist, and portability.

**SCIENTIFIC ABSTRACT OF RESEARCH**

**Background**

Mental illness accounts for 23% of disease burden but currently receives only 13% of NHS resources4. Paranoia is associated with a range of mental health conditions, including psychosis. The lifetime rate of psychotic disorders is 3.5%5, meaning in London alone 287,000 people will be afflicted during their lifetime. Psychosis is one of the most disabling mental health conditions6, associated with distress and impairment in work, family and social functioning (Schizophrenia Commission, 2012). Persecutory delusions, the most common form of psychotic delusion, are also prevalent in other disorders and present in around 10-15% of the general population63. Recent advances favour targeted interventions, focussing on specific symptoms or mechanisms 58, 9. This study proposes to test feasibility of one such intervention, ‘Cognitive Bias Modification for paranoia' (CBM-pa). CBM-pa is a self-administered psychological procedure that has been developed by combining basic research on biases in paranoia61 with established CBM techniques. CBM-pa is computerised and involves reading text inviting paranoid interpretations, but then generating responses reflecting an alternative, non-paranoid interpretation. Several other psychological interventions target cognitive processes in psychosis/paranoia64-66, but none focus specifically on biased interpretations of emotional ambiguity, or can offer the easy-access flexibility that CBM techniques do. Preliminary work shows that CBM-pa manipulates paranoid biases toward more adaptive processing, as expected. After one session paranoid beliefs are reduced, as is the distress associated with an ambiguous real-life social situation, in people with paranoid traits. A six session version has been developed, with input from service-users.

**Aims**

Our aim is to examine whether CBM-pa, in outpatients experiencing paranoia, has patient benefit, would be feasible as a targeted therapy, and to provide justification for a randomised controlled trial (RCT). We will examine acceptability; select outcomes; obtain variance estimates; measure recruitment, retention and follow-up rates and test protocol feasibility. We will gather qualitative interview data on patients’ experience using CBM-pa, focussing on acceptability and promoting engagement.

**Question to be addressed**

We hypothesize the biases CBM-pa manipulates are a maintaining mechanism for patients’ paranoia. Reducing them should reduce paranoia and associated distress.

Specific questions include:

1) Which symptom measure should be the RCT primary outcome

2) What sample size this requires

3) Whether the protocol requires any modifications

**Plan of investigation**

We will randomize 60 stabilised outpatients presenting persistent distressing paranoia to either CBM-pa or text-reading control, both in addition to TAU. All participants will receive TAU in the form of individualised combinations of medication, care co-ordination and psychological treatments. This design directly evaluates the hypothesized ‘active ingredient’ (bias reduction) by using the control condition to match all other aspects of the adjunct intervention. CBM-pa is delivered on computer, set up by researchers, and once running is a self-directed, automated package involving participant input only. Experimental measures serve as manipulation checks for CBM-pa and confirm intervention integrity. Participants will be able to ask questions after each session and upon completion of follow-up full debriefing will be given. Each participant will attend the IoP, or other convenient location, receiving one 40min session per week, for 6 weeks, with 1 and 3 month follow-ups. Assessments (symptoms and bias level) will be conducted at each session to enable investigation of dose effects. Qualitative interviews will be held, after quantitative data collection, with 8 patients who were randomised to CBM-pa.

**BACKGROUND AND RATIONALE**

Paranoia is associated with a range of mental health conditions, including psychosis and the most common form of psychotic delusion, persecutory delusions8. Persecutory delusions are prevalent in a range of disorders and present in 10-15% of the general population6. Patients with the most common diagnosis (Schizophrenia) are estimated to occupy a quarter of all psychiatric hospital beds, account for one half of all psychiatric admissions7 and cost England £11.8 billion annually4. The Schizophrenia Commission reported patients have to battle for services, suffer considerable distress, low self-confidence and loss of control4. Employment rates are low (8%) and 87% service-user suffer stigma and discrimination. A significant proportion continue to experience distressing symptoms despite pharmacotherapy. The Commission report NICE-recommended psychological treatment for psychosis, Cognitive Behavioural Therapy (CBT), is received by only 1 in 10 of those who could benefit. We propose a feasibility test of a potential new low-cost easy-access targeted psychological intervention, developed by combining basic research on paranoia and biased cognition 61 with established Cognitive Bias Modification (CBM) techniques15. Persecutory delusions are sustained by underlying paranoid beliefs which are themselves maintained by biased cognitive and emotional processes6,9,10. An intervention targeting these biases therefore offers potential benefits to society across a variety of mental health conditions. Our study will test an intervention, ‘Cognitive Bias Modification for Paranoia’ (CBM-pa) which has arisen directly from laboratory research into cognitive biases underlying paranoid beliefs. ‘Cognitive bias’ refers to selective processing of information matching the content of the core pathology of a disorder, for example interpreting ambiguous information negatively. Evidence shows that cognitive biases are mechanisms underlying pathological beliefs across a range of disorders11. These biases help cause and maintain psychopathology12. Cognitive treatments can work by changing underlying biases so that these maintaining mechanisms are no longer present and, ideally, patients instead acquire biases that promote well-being13,14. As a result symptoms resolve15. However CBT for psychosis has shown only moderate effect sizes for delusions58, potentially because treatment is too generic. We have been working to identify the specific biases supporting paranoid beliefs, so that they can be targeted more effectively.

The CBM technique is an exciting theory-driven treatment development that uses a computerised task to manipulate biases toward more adaptive processing. Two high impact articles alert to CBM’s potential as a novel treatment15,17. CBM is efficacious in reducing pathological beliefs, symptoms and stress vulnerability in anxiety and depression21. It has been used in a psychosis sample in 2 small studies18,19. Both aimed to reduce comorbid anxiety, rather than targeting paranoid beliefs directly, as we propose here. In addition both were methodologically limited, in one case by a small single case series, in the other by a small sample size and the absence of an external control group. The application of CBM to paranoid beliefs remains unexplored, perhaps because the biased mechanisms themselves have been under researched, but now these data are available61, the potential benefit for patients needs to be evaluated. We already have evidence that paranoid biases can be manipulated using CBM-pa and that benefits result in individuals with high levels of trait paranoia. Participants were randomised to one of two versions of CBM-pa: a training condition encouraging paranoid interpretations, or training encouraging benign/positive interpretations. Results showed CBM-pa significantly reduced paranoid interpretations of new hypothetical situations. It also significantly reduced internal attributions and distress about a real life ambiguous social event suggesting that effects are generalizable beyond the laboratory.

CBM-pa has moved beyond the development phase of MRC guidelines20. There is already appropriate theory and an evidence base, including - for its application to other disorders- a systematic review21. Feasibility testing for application to patients with paranoid beliefs is now needed. In this study we will collect data providing justification for a randomised controlled trial (RCT) of CBM-pa. This will examine integrity and acceptability of the intervention; feasibility/acceptability of proposed instruments; selecting primary outcomes; variance estimates; recruitment, retention and follow-up rates; testing the protocol and randomisation procedures. Following MRC guidelines, we propose a mixed methods (qualitative and quantitative) design.

**Rationale**

Among those psychological treatments available, CBT has only modest effect sizes58, and Cognitive Remediation Therapy (CRT) does not have any impact on symptoms66. That only 1 in 10 patients actually receive CBT59 is partly because it requires highly skilled therapists, partly inability to commit to lengthy treatment (minimum 6mths) and partly difficulty engaging in active aspects of the treatment, such as homework67. As a result new treatments for delusions have been briefer, focusing on targeting specific causal factors, such as reasoning deficits64,65. However none focus specifically on manipulating the biased interpretations of emotional ambiguity, or can offer the low-cost, easy access potential that CBM techniques do. CBM-pa is self-administered, can be conducted remotely, and is likely to be less demanding. It is brief, requires no insight or homework, and personal beliefs are not discussed. Subject to the appropriate evidence base, and further funding for development, CBM-pa could be offered through the internet or using a smart phone. These platforms would provide a low-cost, flexible approach. For patients, this could reduce stigma often attached to traditional interventions, because delivery is subtle and convenient.

The research is important because the size and nature of clinical problems posed by paranoid beliefs is considerable. Paranoia is closely linked to clinical symptoms of persecutory delusions8, which are the most frequent type of delusion22 and one of the most common clinical symptoms of schizophrenia23. Schizophrenia currently accounts for half of all psychiatric admissions7 and costs the NHS £11.8 billion per annum4. Persecutory delusions are associated with significantly more distress than other types of delusion24, are the delusion most likely to be acted upon25 and are a strong predictor of hospitalisation26. Persecutory delusions have also been reported in depression27, bipolar disorder28 posttraumatic stress disorder29 and anxiety30. Over one third of all UK psychiatric patients suffer from persecutory delusions31. By targeting paranoid beliefs CBM-pa has potential benefits across a wide variety of disorders. Although NICE recommends CBT and Family Intervention for people with a diagnosis of Schizophrenia, only 1 in 10 eligible patients actually receive it. With the pilot stage of IAPT for Serious Mental Illness currently underway the NHS is seeking interventions which could be made more widely available to complement existing psychological interventions. CBM-pa has the potential to provide a low intensity option which could be used by a large number of clients. Work in anxiety32 suggests 4 sessions of CBM can produce effect sizes equivalent to lengthier psychological interventions. We will evaluate 6 sessions including an analysis of dose effects. CBM-pa could be widely disseminated at minimal cost (subject to the appropriate evidence base). Patient insight is not required and engagement in the therapy may be easier, further improving service uptake. In sum, CBM-pa could provide a new low-cost, targeted intervention increasing patient choice, accessibility and flexibility.

We propose to evaluate CBM-pa as a ‘low-intensity’ intervention to complement other psychological treatments (including CBT). New low intensity interventions are required because CBT effect sizes for delusions are modest60, a significant proportion of patients do not respond fully and resource limitations restrict availability59. This has been recognised by the advent of the IAPT-SMI programme (Increasing Access to Psychological Therapies for Severe Mental Illness) for which our Trust is one of two national demonstration sites. The development of an evidence-base for ‘low-intensity’ psychological treatments is seen as a priority for IAPT- SMI and the evaluation of CBM-pa will contribute to these developments. Further, current recommendations for the development of new psychological treatments for delusions are that they should be targeted at specific causal factors60, such as the cognitive biases which CBM-pa manipulates.

**RESEARCH PLAN**

**Design**

**Quantitative.** We will randomize 60 stabilised outpatients with persistent distressing paranoid symptoms to treatment as usual (TAU) plus CBM-pa or TAU plus a text reading control. We propose to compare CBM-pa to a text reading control, with both conditions delivered in addition to TAU as this design is methodologically rigorous and directly evaluates the hypothesized ‘active ingredient’ of CBM-pa. It overcomes one of the main current criticisms of designs where a new intervention is directly compared to Cognitive Behavioural Therapy, namely the inability to isolate the crucial component which the new treatment offers. The active arm will comprise 6, weekly sessions of computerised CBM-pa (interpreting ambiguous text in a non-paranoid way: 40mins/ 50 items per session). The control arm will comprise 6 sessions of computerised text reading (reading neutral passages of text). Six sessions are chosen because preliminary work suggests that 4 sessions produces effect sizes equivalent to other psychological therapy in anxiety32, and our more severe patient group may be more resistant to change. Optimal number of sessions will be determined by measuring clinical symptoms and level of bias at each session and analysing change over time (dose effects). Researchers will be trained by the applicants (who together cover the necessary expertise). They will take consent, deliver the intervention and perform assessments. Assessments will be conducted at baseline, post-treatment and 1 and 3 month follow-up. TAU will include any standard care delivered by local services and may include pharmacotherapy and/or psychological therapies. Those receiving psychological therapy specifically targeting the same psychological mechanisms as CBM-pa (paranoid beliefs) during the study period are excluded to avoid uncontrolled confounds and patient confusion.

**Qualitative.** Eight purposively sampled patients receiving the intervention will be recruited to participate in qualitative interviews after quantitative data collection. Researchers will be trained by the lead applicant in qualitative methods and conduct 4 interviews each, together with a service-user researcher.

**Participants.** As recommended by service-users, eligible participants will be outpatients with distressing paranoid symptoms, irrespective of primary diagnosis. This is appropriate because CBM techniques are designed to target transdiagnostic functional mechanisms, rather than individual diagnoses. Casenote diagnoses will be recorded and the MINI35,36 diagnostic interview will be conducted during baseline assessment. Participants will be recruited from a range of local sources, including: a research register maintained by Prof Shergill; PICuP (Psychological Intervention Clinic for outpatients with Psychosis); Prof McGuire's clinical networks; SURF, MHRN and McPin networks. Recruitment will be supplemented as necessary through local Community Mental Health Teams (CMHT) and Clinical Academic Groups ('Promoting Recovery' pathway). Patients will be screened and selected by researchers according to the criteria below.

***Inclusion criteria:***

1. Any diagnosis featuring clinically significant persecutory or paranoid symptoms, present for at least the preceding month

2. Above threshold (>2 on item 6) on the paranoia item of the PANSS 37;

3. Displaying a baseline interpretation bias, as measured by the SST33;

4. Stable on medication for at least the last 3 mths and expected to be so for study duration

5. Age 18-65 years

6. Capacity to consent

***Exclusion criteria***:

1. Severe cognitive impairment

2. Illiteracy

3. Major physical illness (cancer, heart disease, stroke)

4. Major substance or alcohol misuse

5. Currently receiving, or soon due to receive, a psychological intervention targeting the same psychological mechanisms as CBM-pa (paranoid beliefs), or having done so in the last 3 mths

**Recording other therapies**: Both patient self-report and casenote review will be used to enhance validity of this information. We will record details of TAU, including pharmacotherapy, received during the study, for all participants, including uptake/adherence plus any changes, using a standardised template. We will also record histories of receiving CBT. Information recorded will allow post-hoc assessment of these potential confounds, as well as the need for stratification on these variables in a full trial.

**Procedures**

Participants will attend the Institute of Psychiatry for six sessions and receive postal/ telephone 1 and 3 month follow-up. Remote follow-up is preferred to reduce costs and minimise attrition. All participants will be reimbursed for completing assessments (£10 per each session attended), and travel, in line with local norms.

**Recruitment, consent and retention rates**. Experience of the applicant team shows that patients meeting similar criteria can be recruited at the rate of 1 per week from the sources listed. This will require 15 months to recruit 60 patients. Recruitment and testing are now specified separately in the Gantt chart, with corresponding milestones, to demonstrate feasibility within the proposed timescale. Figures on recruitment and retention (drop-out) rates will be recorded. These will be used, alongside sample size calculations, to evaluate the need for multiple sites in the full trial.

**Feasibility of screening procedures**. Some screening measures will require investigation to determine feasibility and optimum delivery method. This includes establishing PANSS item 6 score and baseline cognitive bias. Both are crucial to successful recruitment to full trial, because the intervention is specifically targeted at a) those with presenting clinical levels of paranoia (irrespective of primary Axis 1 diagnosis) and b) those with pre-existing cognitive biases.

**Baseline assessment** completed prior to randomisation, at the start of session 1, will include measures listed as outcomes plus the following socio-demographics: age, gender, IQ38, educational/employment history, previous computer use, urban/rural home environment. Groups should be equalized on the expectation of benefit and this will be assessed using the Credibility and Expectancy Questionnaire57. A short semi-structured clinical interview, the MINI35,39, designed for use by trained non-clinical researchers, will capture DSM-IV primary diagnosis and comorbidities.

**Randomisation**. To meet objective 7 (randomisation feasibility), we will conduct this study following CONSORT guidelines47. The King's Clinical Trials Unit will conduct double-blind randomisation. CBM-pa is self-administered, allowing researchers to be blind to condition, as demonstrated in a recently published RCT1. Control and intervention are procedurally identical and previous studies' debriefing indicates participants cannot correctly guess their assigned condition. Here, participants and researchers will be asked to guess assigned condition to evaluate double-blinding. Minimisation will be piloted on key participant characteristics (age, gender, medication type, severity of baseline paranoia, primary diagnosis).

**Interventions** **CBM-pa:** CBM-pa is available as six sessions of 50 trials (@40 minutes plus midpoint break). PPI input indicated i) several additional sources of item content to broaden coverage and ii) unsuitability of some items. Consequently we plan a further service-user content review over three meetings, coordinated by Dr Kabir. This should maximise acceptability, validity and match to the content of paranoid beliefs of most concern and frequency for service-users.

**Text-reading control:** A computerised text-reading control will be given to those randomised to this condition. The experience is identical, but content omits the active ingredient: resolution of an ambiguous situation in a benign/non-paranoid manner. Instead control participants read and respond to factual material. For example: ‘You turn the kettle on and wait for the water to boil. You get a teabag out of the tin, which you put into a mug, and pour the boiling water onto the teabag. Next, you add the m- - k (milk). Have you made a cup of tea?(correct answer: Yes)' Dose Effects To evaluate optimum number of sessions assessments at each session comprise clinical symptoms and bias level, using the provisional primary outcomes (see below). This will inform decisions about optimum number of sessions for full trial.

**Outcomes**

We will test three domains of outcomes, endorsed by our service-user focus group: paranoid beliefs, clinical symptoms and stress/distress. For each we will collect information on a) comprehensibility and suitability (Objective 2) and b) variance estimates (Objective 3). In each domain we have chosen one provisional primary outcome, but will assess secondary variables as potential primary outcomes by calculating standardised treatment effect sizes (Cohen’s d) and their confidence intervals.

Process for deciding the subsequent RCT primary outcome is given under ‘progression criteria’.

**1) Paranoid beliefs**

*Provisional primary outcome: Ambiguous passages task*. This is the standard test used to measure the effects of CBM. It is an experimental measure of belief change and serves as a manipulation check for the intervention. It appears similar in form to the intervention, but contains important differences in content and measurement. A set of previously unseen ambiguous passages are presented, without any resolution of the ambiguity they contain (unlike the intervention where participants are 'taught' to resolve ambiguity in a given direction). Later, participants give ratings of different possible meanings which indicate the spontaneous interpretation they have made of the previous passages. Six parallel versions will be used, in Latin-square counterbalanced order across CBM-pa sessions. This will be the basis for concluding that belief change using the intervention has been achieved and that the basic manipulation has transferred successfully to the patient sample.

*Scrambled sentences task33,34 (SST).* This task requires participants to unscramble 20 sentences, each of which has at least two possible grammatically correct versions (eg. from 'winner am born I loser a': 'I am a born winner' or 'I am a born loser'). It is most sensitive when given with cognitive load (ie. participants must remember a number while performing the task).The SST is reliable, directly related to the cognitive mechanisms CBM-pa targets and a known predictor of symptoms33.

*Cognitive Bias Questionnaire for Psychosis40 (CBQP).* This self-report measure comprises 30-items rated on a 3-point scale (1 = absent, 2 = present with qualification, 3 = present) and produces an overall score (/90) with three subscales (anomalous perceptions, emotion-based reasoning, threatening events). Items describe common experiences and participants choose one of three possible explanations.

**2) Clinical symptoms**

*Provisional primary outcome: PANSS*37. This widely used clinical outcome in psychosis research is a researcher-administered semi-structured interview. It provides a total score, plus subscales reflecting positive and negative symptoms. One specific item (item 6) can be used in isolation to evaluate degree of clinical paranoia.

Secondary outcomes are: *Paranoia Scale41, Paranoid Thoughts Scale42, Peter’s Delusions Inventory43*. The latter includes subscales reflecting clinically important elements of delusions: degree of delusional conviction, frequency of delusional thoughts and degree of associated distress.

Symptoms of depression/anxiety will be assessed using the HADS69.

**3) Stress/distress**

Vulnerability to stress will be assessed using two measures: i) *the laughter task* (provisional primary outcome in this domain)44; ii) *Visual analogue scale* measure of anxious mood while watching a video clip of an underground train journey and imagining oneself in the situation45.

**Cost effectiveness** is likely to be a major benefit of CBM-pa. We will pilot collecting, from participants themselves, and from their treating clinicians, information on the frequency and type of service contact, therapy use and the prescription and use of medication.

**Sample Size** We require a sample size sufficient to estimate variance, for each group separately, of the pre-post difference scores on our measures (see formula above). This will provide robust variance estimates for effect size estimation on optimum outcome measures, allowing a power analysis for an RCT48,49. Sample size guidelines range between 20-40 participants2,49. We have opted for 30 per group, allowing for some drop out. As outlined earlier, we will also examine the integrity of the intervention using the standard CBM manipulation check (Ambiguous passages task) to confirm whether the intervention has manipulated target beliefs as intended. This is a key progression criterion for full trial. A Group x Target Type (2) x Direction (2) within –between interaction (4 levels of repeated measurement) is required. Previous data 14 suggest a large effect size on this interaction (f=0.4). Therefore requiring 80% power, setting alpha =.05 and using a random effects analysis, a total sample size of 52 would suffice50. Thus the proposed sample size, 60, will have sufficient power.

**Statistical methods** Analyses will be conducted using STATA 13. The variance observed in this sample will be used for sample size calculation for the future RCT. As recommended by Brown48 and Lancaster and colleagues2 the 80% upper one-sided confidence limit of the variance estimate rather than the variance estimate itself will be used. The final effect size for sample size calculations will be obtained by dividing the minimum clinically important difference by this variance estimate. We define a clinically important difference as a symptom score drop of >=20%. The three factorial within and between group design will be analysed using random effects model51.

**Qualitative Interviews** Qualitative interviews will be conducted after the end of quantitative data collection, using a purposively selected subsample of 8 active-arm patients. The aim is to explore acceptability, barriers to participation, promoting engagement and optimum delivery method. The draft topic guide, which has been reviewed and amended by service-users, will be further reviewed by our PPI group. The lead applicant is experienced in conducting qualitative research, having done so on previous occasions, leading to high impact publications52,53.

Purposive selection will represent sample variation in age, gender, ethnicity, socioeconomic status and severity of paranoia. To reduce interview anxiety patients will be invited to bring a friend/family member, using McPin’s ‘patient preference form’. Interviews will last around one hour, with participants receiving £30 per interview. Interviews, using a topic guide, will be administered by study researchers, after training from Yiend. PPI group members will be invited to assist with interviews, which may help reduce anxiety on the part of interviewees and elicit richer, more meaningful data. One service-user will be invited to co-deliver each interview after they have received appropriate training, which will comprise BRC service-user researcher training day, individual training from Yiend, and support from McPin. Interviews will take place at the Institute of Psychiatry in dedicated, bookable interview rooms and will (with appropriate specific consent) be audio recorded. Data will be transcribed by study researchers, in line with accepted methodology, and free text comments entered into NVivo for thematic analysis. The PPI group will be involved in identifying themes and codes, supported by McPin’s previous similar experience. Data will be analysed using the principles of grounded theory and framework analysis54-56 which seeks ‘the discovery of theory from data’54. In this approach, categories or themes emerge naturally from the data during an iterative process of coding and revision that can identify recurrent patterns of views/experiences. This approach, if implemented rigorously, can elicit findings of considerable worth. Results and conclusions will be disseminated alongside quantitative results and form recommendations for future CBM-pa development in terms of improving acceptability, uptake, reducing participation barriers, and improving patient engagement. Where discrete factors are identified which may influence patient benefit, these will be included within existing quantitative analyses post hoc. For example, if CBM-pa is found at interview to be more acceptable to one or other gender, then post hoc analyses of study data will specifically report on the influence of gender on study outcomes.

**PROJECTED OUTPUTS AND DISSEMINATION**

**Dissemination**

The study website will substantially aid dissemination (including 'easy read' versions, reviewed by service-users) and enable participants to update on progress whenever they choose. Locally, NHS Trust newsletters will feature results. We will present at SURF. National organisations will provide further vehicles for dissemination (eg. MHRN, SANE; Rethink Mental Illness; McPin). The Institute of Psychiatry holds frequent national and international events (eg. Trust and CAG workshops) for dissemination which we will utilise. International dissemination will include high impact open-access peer-review publication (e.g. top specialist journal Clinical Psychological Science68) and international conferences (eg. WCBCT).

**Progression criteria to full trial:**

**a) Recruitment rate:** 4 patients per month. Applicants have professional links with psychosis services in Oxford, East Anglia and Sussex should additional sites be required for subsequent full trial.

**b) Integrity of the intervention:** the ambiguous passages task is a robust test of whether the intervention has manipulated the target beliefs as intended. Demonstrable belief change is an essential prerequisite to the measurement of clinically relevant outcomes. The 95% confidence interval should include a 20% reduction in paranoid beliefs on this measure.

**c) Acceptability and retention:** at least 66% participants completing all sessions AND finding procedures acceptable as is, or subject to specified and feasible modification.

**d) Clinically important treatment effects** (20% reduction) observed on one or more outcome.

**Primary outcome decision process.** We define a provisional primary outcome in each domain (above). The final primary outcome for the subsequent trial will be selected based on consensus after presentation of results to the steering group. This decision will be informed by a) observed effect sizes and b) opinions on most important outcome from qualitative interviews.

**EXPECTED OUTPUT OF RESEARCH/IMPACT**

**Short term**

Our short term aim is to conduct an RCT of CBM-pa. An immediate output of this research will therefore be an application to either EME or HTA using the trial design proposed here, subject to identified revisions. The trial would answer the same question: whether introducing CBM-pa as an addition to TAU could offer significant patient benefit to outpatients presenting persistent distressing paranoia. The trial would include a full cost effectiveness evaluation, incorporating a health economist on the team. An RCT of CBM-pa would meet current recommendations for the development of new psychological treatments for delusions, which suggest targeting at specific causal factors60, such as the cognitive biases which CBM-pa manipulates.

**Long term**

In the long term CBM-pa offers significant benefits over existing ‘low intensity’ psychological interventions64-66 in that it is self-administered, flexible to deliver and the first technique to specifically target biased interpretations of emotional ambiguity. There will be potential cost savings, which will have downstream benefits for the NHS and its patients. After further development, including a corresponding evidence base, it could be delivered over the internet or using a smart phone 'app'.

Long term aims are:

1. Provide an appropriate evidence base from full clinical trial to evidencing efficacy to NICE

2. Implement CBM-pa (if shown efficacious) through our local trust IAPT-SMI demonstration site. The development of an evidence-base for ‘low-intensity’ psychological treatments is seen as a priority for IAPT- SMI and CBM-pa could make a significant contribution to this. Our local NHS trust, SLAM, has a track record of implementation of novel interventions and the PICuP clinic (coapplicant Peters is Director) has a history of testing, implementing and disseminating new interventions.

3. Secure funding to develop a bespoke web/app platform allowing widespread, cost-effective national use.

**ETHICAL ISSUES**

Participants will take part in addition to receiving treatment-as-usual. Capacity to consent is assessed via a standard written protocol used routinely within Dr Shergill's lab and approved by ethics committees for previous studies. Participants will be fully informed about the study using approved consent procedures, after eligibility and suitability checks by the clinical psychologist team member and researchers. Procedures for explaining randomisation will be adapted from those used by a recently complete RCT lead by Yiend, subject to ethical approval in the context of the current study. The measure involving a real life social situation can be perceived as mildly stressful for those experiencing paranoia. To address this, the nature of the task, including the option to withdraw, will be described in writing (information sheet) and verbally immediately prior to the relevant session. Mood state will be assessed before leaving and follow-up contact with a clinician on the team (Shergill/ Peters) offered if necessary. Patients currently receiving or soon due to receive a psychological intervention thought to target the same cognitive mechanisms will not be invited to participate (see exclusion criterion).

**RESEARCH TIMETABLE**

**The first milestone** (3 months, M1) will be achieved when all approvals are in place (Ethics, R&D, Research Passports) and all induction/training is complete for service-user representatives.

**The second milestone** (6 mths, M2) will be achieved on completion of one successful dry run for each study arm and to have resolved all procedural and methodological questions.

**The third milestone** (15mths, M3) will be achieved when all 60 participants have been recruited to the study. An average recruitment rate of 1 participant per week is necessary to achieve this milestone. (18mths, M3)

**The fourth milestone** (18 mths, M4) corresponds to 50% of data (30 full datasets) collected and entered. The final patient recruited to the study will require 6 weeks testing plus 3 months follow-up, meaning data collection will be complete 18 weeks following end of recruitment.

**The fifth milestone** (27 mths, M5) is the completion of trial data entry and qualitative interview data collection.

**The sixth milestone** (33 mths, M6) is completion of all data analysis (qualitative and quantitative) with corresponding summary of main results.

**The seventh milestone** (36 mths, M7) is completion of a draft final report, proposed publication plans, and corresponding presentation to the steering group.

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