1. THE EFFECTS OF REDUCING WORRY IN PATIENTS WITH PERSECUTORY DELUSIONS: FINDING OUT IF WORRIES CAN BE REDUCED BY BRIEF COGNITIVE THERAPY.

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"I believe that all of my very close friends are out to get me. I worry all the time about them." David

"I worry that there is something paranormal, maybe the devil, coming to get me or my child. I hate worrying and would like to enjoy life and make the most of it." Susie

2. BACKGROUND

2.1 Existing research

Schizophrenia, the core psychotic illness, falls into the top ten medical disorders causing disability worldwide. It contains a heterogeneous collection of symptoms that cluster into many separate factors (e.g. Peralta and Cuesta, 1999). Studying single symptoms has emerged as a way of making progress with the complex problem of schizophrenia spectrum diagnoses. One of the key symptoms is persecutory delusion. This is the unfounded belief that others are deliberately trying to harm the person (Freeman & Garety, 2000). In psychosis, persecutory delusions are very frequent (e.g. Sartorius et al, 1986), particularly distressing for patients (e.g. Appelbaum et al, 1999), are often acted upon (e.g. Freeman et al, 2007), and are a predictor of admission to psychiatric hospital (e.g. Castle et al, 1994). Paranoid thinking is associated with increased rates of suicide attempts (Freeman, McManus et al, in press) and cause particular problems for carers (e.g. Onwumere et al, 2008). Persecutory delusions are a key clinical symptom for which improvements in treatment are greatly needed. Many patients do not respond to neuroleptic medication, relapse is common, and adherence to these treatments is problematic (see review by Bebbington et al, 2008); while the first generation of generic cognitive behavioural (CBT) approaches only show weak-moderate effects (e.g. NICE update, 2010) and have not been shown to change key causal factors (Garety et al, 2008). In the last ten years there have been considerable advances in understanding persecutory delusions but these have not yet been translated into treatment.

The lead applicant and colleagues have developed a cognitive model of persecutory delusions (Freeman et al, 2002; Freeman, 2007). Delusions arise from a number of interacting factors, but worry and associated processing are given a central role in the model. The connection is plausible - worry brings unlikely and distressing ideas to mind and keeps them there – and has been established empirically. It has been shown that worry is extremely common in individuals with persecutory delusions, that it is especially associated with more distressing persecutory delusions, and that it is a predictor of symptom persistence (e.g. Freeman & Garety, 1999; Freeman et al, 2001; Startup et al, 2007; Morrison and Wells, 2007; Bassett et al, 2009). Other studies have also shown that worry is associated with non-clinical paranoia and predicts its occurrence (Freeman et al, 2008; Freeman, Pugh et al, 2010; Freeman, Brugha et al, 2010; Freeman, McManus et al, in press). Furthermore, in a new longitudinal study of over two thousand people taking part in the British Psychiatric Morbidity Survey, worry was shown to

predict the new occurrence of paranoid thinking over an 18 month period (Freeman et al, in prep.); examining individuals with no paranoid thinking at baseline, high worriers were 8 times more likely to subsequently report paranoid thinking than low worriers. Drawing upon the theoretical literature for generalised anxiety disorder, we have shown that worry in individuals with persecutory ideation is associated with catastrophising (characterized as the worrier posing internal, automatic questions of the form 'what if this bad thing happens?') and positive and negative meta-cognitive beliefs (Freeman & Garety, 1999; Startup et al, 2007; Freeman et al, 2008).

On the basis of this work we have completed a pilot study examining the impact of a brief cognitive-behavioural worry intervention for patients with persecutory delusions (Foster, Startup, Potts & Freeman, 2010). The aim was to treat the clinical problem of worry in patients with delusions but also to examine the subsequent impact on persecutory delusions. This is known as an interventionist-causal model approach; `it [the interventionist-causal approach] connects causation with the practical interests of psychiatry, defining causation in terms of "what would happen under interventions", a question of key interest to those of us whose interest is ultimately in intervening to prevent and treat illness' (Kendler and Campbell, 2009). 24 patients with persistent persecutory delusions were recruited. Half were randomised to the intervention in addition to their standard psychiatric care and half were randomised to the control group (standard psychiatric care). Assessments were carried out at baseline, end of treatment (one month), and at follow-up (two months). There was a large effect size reduction in worry (Penn State Worry Questionnaire effect size = 1.05) and also in the persecutory delusions (Psychotic Symptoms Rating Scale – Delusions effect size = 1.35). One in three patients showed a 25% or greater reduction in worry and the delusion. Changes in worry were associated with changes in persecutory delusions. However the trial assessments were not carried out blind and the sample size is small. A more rigorous evaluation is now required. Using Medline searches for worry and psychosis (or schizophrenia), a search of the current controlled trials register, and from knowledge gained at attendance at scientific meetings on psychosis, we are confident that there is no comparable work being carried out. This is unsurprising – the work on worry and delusions has been pioneered by our group.

2.2 Risks and benefits

Worry is present in many patients with persecutory delusions at a level comparable to generalised anxiety disorder. Therefore it should be targeted in its own right with successful worry treatments. But of even more import the evidence also indicates that these interventions will reduce persecutory delusions. This will lead to less personal distress for patients, reduce the social avoidance that typically accompanies these problems, and lead to less service use, especially lengthy inpatient stays which are expensive. Patients with psychosis often fear losing control of their mental state and this intervention will enable them to increase their sense of control and lower their levels of anxiety and depression. It is also notable that we propose a brief treatment that can be provided by all types of mental health professional i.e. it is a treatment that can be implemented in practice. We anticipate few risks for patients entering this trial. Participation in the trial does not change existing treatment receipt, so there is no disadvantage in taking part. The main potential problem is the addition of burden for participants with the additional assessments; however most trials with this patient group show even a modest symptom benefit of entering the control condition in a therapy trial, most likely due to the additional monitoring and sensitive manner of the research assessors (e.g. Kuipers et al, 1998).

2.3 Rational for current study

In summary, worry has been hypothesised as an important contributory factor in the occurrence of paranoid thinking, and this has been supported by experimental and epidemiological studies. Importantly, worry is a manipulable factor, meaning that reducing it should lead to reductions in the delusions. In a small randomised controlled pilot study we have shown that a targeted CBT intervention does lead to substantial decreases in worry and persecutory delusions. Needed

now is a larger and methodologically robust examination of targeting worry in people with persecutory delusions. This is the principal purpose of the proposed research.

3. RESEARCH OBJECTIVES

The project has three objectives:

1. Clinical outcome: To test the clinical efficacy of a brief cognitive-behavioural intervention for worry for patients with persecutory delusions.

2. Explanatory mechanisms: To determine how the worry treatment reduces persecutory delusions.

3. Theory: To develop the theoretical understanding of worry in patients with psychosis.

The first two objectives will be achieved upon completion of the randomised controlled trial. The third objective will be achieved at the completion of recruitment of patients into the trial, since a theoretical study is built into the baseline assessments. The theoretical study addresses the question: How does worry interact with psychotic processes? The theoretical study is described in this protocol in a separate section after the main trial. The theoretical study is complementary to the clinical trial and in no way interferes with or detracts from the running of the main trial.

4. RESEARCH DESIGN

The trial is a randomised controlled evaluation. Patients with persecutory delusions will be randomised to the worry intervention in addition to standard psychiatric care or to standard psychiatric care. A psychological intervention control group is not included in the design. We will instead examine how the treatment works by including repeated measures of worry and associated processes. Non-specific therapist factors will also be assessed (Horvath & Greenberg, 1989). A two group design makes the successful completion of the trial much more feasible, while the addition of a third group would not add value in this instance. Randomisation will be carried out independently, via an on-line system, by the Mental Health & Neuroscience Clinical Trials Unit, using randomised permuted blocks. Stratification will be by centre. Rater assessments will be blind. All patients will be informed of allocation by a trial therapist to prevent the research assessors becoming unblinded. Precautionary strategies will include: therapists being encouraged to consider room use and diary arrangements in the light of potential breaks of masking; patients being reminded by the assessors not to talk about treatment allocation; and, after the initial assessment, the assessors will not look at the patient's clinical notes until the last of their ratings have been collected. The success of the blinding will be monitored and where there are breaks of blind another assessor will be used. The reliability of the raters on the key interviewer measures will be formally assessed. Embedded within the design will be measures that elucidate how the treatment works and the mechanisms underlying worry in psychosis. The trial does not have formal stopping rules; although the Data Monitoring and Ethics Committee (DMEC) will monitor the progress of the trial, and will consider all reports of adverse events, it is very unlikely that this would lead to any decision about closure. The study will be registered (an ISRCTN will be obtained). We will follow the MRC Guidelines for Good Clinical Practice in Clinical Trials (1998) in the running of the trial. The Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement, and the extension for nonpharmacologic treatment (Boutron et al, 2008), will be followed for reporting the trial.

5. STUDY POPULATION

Patients will be recruited from two mental health NHS Trusts. The inclusion criteria are: a current persecutory delusion as defined by Freeman and Garety (2000); scoring at least 3 on the conviction scale of the PSYRATS (Haddock et al, 1999); that the delusion has persisted for

at least three months; a clinical diagnosis of schizophrenia, schizoaffective disorder or delusional disorder (i.e. diagnosis of non-affective psychosis (F2) in the International Classification of Diseases and Diagnostic and Statistical Manual IV); a clinically significant level of worry, as indicated by scores above 44 on the Penn State Worry Questionnaire (see Startup and Erickson, 2006); aged between 18 and 65; and where major changes in medication are being made, entry to the study would not occur until at least a month after stabilisation of dosage. It should be noted that we will be seeing patients when the main treatment for delusions, neuroleptic medication, has generally been tried at length and their delusions are relatively stable (persistent). It is increasingly recognized that the action of neuroleptic medication occurs rapidly. As a meta-analysis in the *Archives of General Psychiatry* reports: 'This analysis rejects the commonly held hypothesis that antipsychotic response is delayed. Rather, these findings suggest that the antipsychotic response starts in the first week of treatment and accumulates over time. Furthermore, greater improvement occurs in the first 2 treatment weeks than in the subsequent 2 treatment weeks.' (Agid et al, 2003). The effects of antipsychotic treatment are rapid and then plateau. Emsley et al (2006) report that among these patients who respond to medication the response was achieved in '23.3%, 23.3%, 18.5%, and 12.5% at weeks 1, 2, 3, and 4, respectively, after treatment initiation'. We anticipate that the overwhelming majority of patients in the trial will have held their persecutory delusions despite medication for much longer than three months, and their standard care will be generally stable. It should also be noted that the criterion that patients reach a sufficiently high score on the worry measure excludes very few people with persecutory delusions (only one patient out of 25 referrals in the pilot study). Criteria for exclusion are: a primary diagnosis of alcohol or substance dependency; organic syndrome or learning disability; a command of spoken English inadequate for engaging in therapy; and currently having individual CBT (though previous CBT experience is not an exclusion). A patient may withdraw from the trial at any point that they request. Therapists will consult with the patient and the clinical team about continuation in the trial if there is any symptom deterioration.

6. PLANNED INTERVENTIONS

The worry intervention will be provided in six sessions over eight weeks. This is an increase in the number of sessions used in the pilot, since the patients asked for extra sessions. The eight week window will allow some flexibility for appointment times and the extension of intervals between the final two sessions. The additional change is that we will present the main content of the sessions via a laptop computer with the patient and therapist working through the content together; this is a format popular with patients, will standardise the intervention further, and subsequently enable the intervention to be used very easily by other mental health professionals. The intervention is designed to provide clear and simple messages for patients to take into their day-to-day lives. The worry reduction strategies included are indicated in the anxiety literature to be effective at reducing worry and do not challenge or review the delusion itself. Key influences from the generalised anxiety disorders literature were Butler et al (1987), Borkovec et al (1998), Dugas & Ladouceur (1998), Wells, (1997) and Leahy (2006). The main techniques are psychoeducation about worry, reviewing of positive and negative beliefs about worry, increasing awareness of the initiation of worry and identification of individual triggers, learning to 'let go' of worry, use of worry periods, substituting problem-solving in place of worry, and relaxation exercises. Homework exercises are set between sessions. Written information is provided for patients in a leaflet called 'Winning against Worry'. Sessions will be taped for assessment of adherence and for competence (Young and Beck, 1980); when the purpose is clearly explained we have found that 80% of patients with paranoia agree to recordings of sessions. Patients will also be asked to complete an assessment of the therapist's empathy (Burns & Nolen-Hoeksema, 1992). Standard care is delivered according to national and local service protocols and guidelines. During hospitalisation standard care usually involves prescription of anti-psychotic medication, and to some extent occupational therapy activities and exercise groups. Following discharge, the level of standard care varies according to the needs of the individual. However, this usually consists of prescription of anti-psychotic medication, visits from a community mental health worker and regular outpatient appointments with a

psychiatrist. A strong indication of what standard care will consist of is provided by a dataset of ours of over 200 patients with psychosis, who will be very comparable to the study sample. In this dataset, over six months, 95% were being prescribed neuroleptic medication, 75% had seen a community mental health nurse, 60% had seen a psychiatrist, 26% had seen an occupational therapist, 25% had an inpatient admission, 25% had seen a social worker, and 21% had attended a daycare centre. Service use will be measured using the Client Service Receipt Inventory (CSRI; Beecham & Knapp, 1992). The CSRI covers services provided by the National Health Service, other health and social care agencies, the criminal justice system and informal carers. Antipsychotic medication data will be extracted from medical records and dosages converted into chlorpromazine equivalents.

7. Proposed outcome measures

The key outcome measures will be levels of worry as assessed by the Penn State Worry Questionnaire (PSWQ; Meyer et al, 1990) and levels of persecutory delusions as assessed by the Psychotic Symptoms Rating Scale - Delusions (PSYRATS; Haddock et al, 1999). These are the best available measures of worry and delusions, with established psychometric properties. Secondary outcome measures will be a service user-led outcome measure (Greenwood et al, 2010), a quality of life measure (EQ-5D; Brooks et al, 2003), the Paranoid Thoughts Scale (Green et al, 2008), the Perseverative Thinking Questionnaire (Ehring et al, 2010), and the Positive and Negative Symptom Scale (PANSS; Kay, 1991). We will also record service use (including medication consumption), adverse events, and hospital admission data using the CSRI (Beecham & Knapp, 1992). For examination of mediation we will include: the Beck Anxiety Inventory (Beck et al., 1988), the catastrophising interview (Vasey & Borkovec, 1992; Startup & Davey, 2001), the Meta-Cognitions Questionnaire (Cartwright-Hatton & Wells, 1997), the stop rule checklist (Davey, 2006) and the Intolerance of Uncertainty Questionnaire (Freeston et al, 1994).

8. Assessment and follow up

8.1 Assessment of efficacy/effectiveness

The outcome measures will be completed before therapy (0 weeks), at the end of therapy (8 weeks) and at a follow-up (24 weeks). At baseline we will also ask participants to complete assessments of intellectual functioning (WAIS; Wechsler, 1999), illicit drug use (MAP; Marsden et al, 1998) and illness and treatment representations (Weinman et al, 1996). These can be completed in a single session with a research assessor. The majority of assessments are self-report measures; the interviewer rated PSYRATS and PANSS will be taped for reliability purposes. Paper copies will be kept of all assessments and data entered onto the electronic database within one day of the assessment. All the data entry for the two main outcomes will be double checked. The baseline assessment must be completed before randomisation. The end of therapy assessment must be carried out after therapy has been completed. We will endeavour to have the repeat assessments carried out at exactly the timings specified, but will allow a two week window for the post therapy assessment and a one month window for the follow-up assessment. Participants will be paid £15 for each assessment session, and travel expenses will also be paid.

8.2 Assessment of safety

The following events in trial patients are considered as adverse events: 1. All deaths. 2. Suicide attempts. 3. Serious violent incidents. 4. Admissions to secure units. 5. Formal complaints about therapy. We will also scrutinise any instances of patients being admitted to psychiatric hospital in the period of the therapy. These adverse events are likely to come to the attention of the assessor or therapist but we will also check medical notes at the end of a participant's time in the trial. The responsible clinical team, the trial management committee and the Data Monitoring and Ethics Committee (DMEC) will be informed of any adverse event. The responses to an adverse event will be determined on a case by case basis.

9. Proposed sample size

Recruitment will be split equally across centres. In a conservative fashion we power the study to detect moderate effect sizes (see below) but we anticipate large effect sizes for several reasons: our sample is far less heterogeneous than typical CBT for psychosis trials (i.e. our group is selected for one key problem: distressing persecutory delusions) and this means that variance in the repeated outcome variable is substantially reduced leading to larger standardised effect sizes if change is shown; rates of engagement with active therapy will be higher because our patient sample rate themselves as worriers which is the focus of the intervention and the delusion is not disputed (i.e. there are fewer 'insight' issues which can hinder engagement in standard CBT for psychosis); and we focus the intervention on changing a key causal factor for persecutory delusions (which has not been the case with generic CBT therapies for psychosis). In the pilot study the effect sizes were large: worry (PSWQ mean difference=10.00 SD=9.50)=1.05; persecutory delusion (PSYRATS Mean difference=2.91 SD=2.15)=1.35. These effect sizes are not a 'one off'. For instance we have recently completed a pilot trial focussing on treating insomnia in people with persecutory delusions and achieved an effect size reduction of insomnia of 2.6 and an effect size reduction in the delusions of 1.1 (Myers, Startup, Freeman, in prep). Persecutory delusions are threat beliefs, which have similarities to anxiety disorders, and we aim to produce treatments for delusions that are a significant advance on generic CBT and that have effect sizes that begin to approach those seen for anxiety disorders. A simple two-tailed t-test with 60 people per group would provide 90% power to detect an effect size of 0.60 at a significance level of .05. It would have 80% power to detect an effect size of 0.52. In practice, further power would be gained by use of multiple regression. Drop-out from the assessments in the pilot was low: 13%. The intervention is brief and the time in the trial will be relatively brief (6 months). In the much more intensive PRP Trial involving 300 patients with psychosis, we achieved follow-up rates of 82% over 12 months. Therefore conservatively allowing for 20% drop-out, 150 people will need to be recruited to enable full data to be obtained from 120 participants (60 in each condition).

10. Statistical analysis

A full statistical analysis plan will be written prior to starting the trial. All main analyses will be carried out at the end of the last follow-up assessments (i.e. there will be no interim analyses) and will be based on the intention-to-treat principle, with due consideration being given to potential biases arising from loss to follow-up. Random effects regression models will be fitted to the repeated measures to estimate treatment effects for outcomes, controlling for treatment centre, in-patient status and the corresponding baseline assessment for the outcome under investigation. We will allow for the presence of missing outcome data under the assumption that the data are Missing At Random (MAR), using the terminology of Little and Rubin (2002), with the possible addition of inverse probability weighting to adjust for the possible role of nonadherence to allocated treatment and other intermediate outcomes as predictors of future loss to follow-up (Dunn *et al*., 2005). *Stata* will be used for these main analyses. Secondary analyses to investigate putative meditational mechanisms, but also the effect of receipt of an adequate dose of treatment (CACE estimation), will be carried out using methods similar to those of Baron and Kenny (1986) but also the newer approach of instrumental variables analysis (to allow for the omitted variables problem i.e. hidden confounding) (see Dunn et al. 2005; Maracy & Dunn, 2010; Emsley, Dunn & White, 2010). *MPlus* and *Stata* will be used for these analyses.

THEORETICAL STUDY: THE EFFECT OF STATE WORRY ON PSYCHOTIC PROCESSES

A theoretical study, using experimental manipulation to determine a causal role, will be carried out at the baseline assessment stage of the trial. The results can be used to refine future treatment. The study will take only 15-20 minutes in the baseline assessment before randomisation. It is also of note that the extra psychotic processes assessed can later be included in a moderation analysis for the trial.

Background and aims

In our theoretical model, persecutory delusions arise from an interaction of emotional processes and psychotic processes. In this study we will examine the effect of state worry on three key processes associated with psychosis: jumping to conclusions, working memory difficulties, and anomalies of experience. There is consistently replicated evidence that: individuals with delusions 'jump to conclusions' (JTC) (see reviews by Garety & Freeman, 1999; Freeman, 2007; Fine et al. 2007); that working memory deficits are common in people with psychosis (see reviews by Lee and Park, 2005; Barch, 2005; Joyce & Huddy, 2004); and anomalies of experience (e.g. perceptual disturbances, hallucinations) have repeatedly been found to be associated with clinical and non-clinical delusional ideation (e.g. van Os et al, 2000; Bunney et al, 1999; Freeman et al, 2008). The aim of this study is to test the effect on these established psychotic processes of a period of worry. It is hypothesized that psychotic processes are exacerbated when a person engages in a period of worry: that they find it harder to reason and process information and that they feel in a more subjectively odd state. The effect of state worry on psychotic processing has not been examined before. However two previous studies have found jumping to conclusions to be increased by an anxiety induction (Ellett et al, 2008; Lincoln et al, 2009), other research indicates anxiety is a trigger of anomalies of experience (e.g. Delespaul et al, 2002), while research in nonpsychotic populations has shown that state worry restricts working memory capacity in high worriers (e.g. Hayes et al, 2008).

Design

Participant will complete the tasks assessing jumping to conclusions, working memory and anomalies of experience. They will then be randomly allocated to one of three groups: worry induction, worry reduction, neutral control. Participants randomized into the worry induction experimental group will participate in a procedure already shown in previous experimental work by our group to induce a state of worry (Southgate, 2009). With the worry induction procedure we have shown a mean increase of worry on a 0-100 scale of 24.8 (SD = 20.2) (n = 49), compared with a change of -6.2 (SD = 16.0) (n = 48) with a neutral control condition, $t = 8.4$, $p < .001$. These effects persisted for at least 6 minutes with the induction. Worry reduction will use a brief mindfulness relaxation exercise (see Ellett et al, 2008) and positive mood induction using music (see Martin, 1990). Participants in the neutral control group will engage in a neutral reading task. Concerning the ethics of the worry induction condition it is important to note that this is a group already reporting worrying and we will be assessing a process that they are doing routinely everyday. Following the induction, participants will repeat the tasks, with 'top ups' of the mood inductions.

Measures

Jumping to conclusions will be assessed with a probabilistic reasoning task, 'the beads task' (Garety et al, 2005). Two versions will be used, differing in their difficulty. Working memory will be assessed with the digit span and letter number subtests of the WAIS III (Wechlser, 1997). The presence of anomalies of experience will be assessed with a state version of the Cardiff Anomalous Perception Scale (Bell et al, 2006) and appropriate state items of the Cambridge Depersonalisation Scale (Sierra & Berrios, 2000). Levels of worry, anxiety and paranoia will be assessed with visual analogue scales.

Hypotheses

Primary

1. Jumping to conclusions, working memory difficulties and anomalies of experience will all be greater in people with persecutory delusions who are currently worrying than individuals with persecutory delusions who are not currently worrying. It is predicted that the presence of these difficulties will be greatest in the worry induction group and least in the worry reduction group.

Secondary

1. Levels of anxiety and paranoia will be higher after the worry induction.

2. Changes in levels of paranoia will be mediated by changes in the psychotic processes.

Analysis and power calculation
The difference in jumping to conclusions between an anxiety-provoking condition and control condition in the study of Ellett et al (2008) was of an effect size of 0.78. Hayes et al (2008) found a difference in performance on a cognitive task related to working memory of effect size 0.65 between a worry induction condition and positive mood induction – a direct assessment of working memory, as in the proposed study, would likely produce larger effects. A sample size of 40 in each group will have 80% power to detect an effect size of 0.63 using a two group t-test with a 0.05 two-sided significance level. For the primary hypothesis, analysis of covariance will be used to evaluate the effect of the manipulation (i.e. group allocation) on the measures of jumping to conclusions, working memory and anomalies of experience, allowing for pre-manipulation performance. The secondary mediation analysis will be carried out using the methods employed in the clinical trial.

11. Ethical arrangements
Ethical approval for the study will be obtained from the NHS Research Ethics Service. The consultants of the clinical teams will be approached to give general permission for approaching patients within their care. We will then visit clinical team members asking for potentially suitable participants. How to best approach the patient will be agreed with the responsible clinical team member. Information sheets are provided to participants and informed consent obtained before entry into the trial. Individuals will be given a minimum of 24hrs to consider their decision (and usually much longer). Participants are free to withdraw at any stage without providing a reason. It should be highlighted that capacity to consent is actually infrequently an issue with people with schizophrenia; incapacity is most likely to occur when patients are just admitted to a psychiatric ward at the acute stage of illness, which is not a group we will be approaching for this trial. The main ethical issue may be the increased burden for participants in completing the assessments. We take care to inform participants exactly what is involved, allow for as many breaks as needed, and handle the assessments sensitively. Most participants in our studies report finding the assessments helpful. We also have procedures to ensure confidentiality. Patient's details are entered anonymously onto the database, and the raw data are stored in a locked cabinet in a secure room. The study will be conducted in accordance with the principles of the Declaration of Helsinki. Oxford University (the sponsor) has arrangements in place to provide for harm arising from participation in the study for which the University is the Research Sponsor. NHS indemnity operates in respect of the clinical treatment which is provided. There will be no post-study access for the therapy for patients in the treatment arm, since they will have received all the designed intervention if they had wished. For control participants we offer a one-session intervention after their participation in the trial, since this is the maximum available from the research funding.

12. Research governance
Oxford University is the research sponsor. NHS ethical and R&D approvals will be obtained before commencement. For trial management we will follow the MRC Guidelines on Good Clinical Practice in Clinical Trials (1998). A Trial Steering Committee (TSC) will be formed, which will include an independent chair and two other independent members, including a service user. The main trial investigators will also attend the TSC. A Data Monitoring and Ethics Committee will be formed, which will have a clinician as independent chair and a further clinician and statistician. The chair of the DMEC will also be a member of the TSC. Graham Dunn, the trial statistician, and Dr Helen Startup, trial co-ordinator, will also attend the DMEC as appropriate. For independent membership we will approach a number of experienced trialists, for example, Professor John Geddes (Oxford), Professor Max Birchwood (Birmingham), Professor Christine Barrowclough (Manchester) and Professor John Norrie (CTU, Glasgow). For service user involvement we have a number of local contacts but may also approach MIND. Relevant trial documentation will be kept for at least five years after publication of the trial results.

13. Project timetable and milestones

Before start of funding:
October 2010: Decision of EME Board.
November 2010: NHS Ethics and R&D application submitted (decision within 60 days).
December 2010: Approach potential TSC and DMEC members.
February 2011: Recruitment adverts appear for main trial staff.
April 2011: Interview applicants for positions.
April 2011: For successful applicants obtain contracts with NHS Trusts (including CRB checks)
Jan – April 2011: Further development of intervention materials (e.g. putting materials onto computer), writing of standard operational procedures, and completion of data analysis plan.
April 2011: Meeting of Trial Steering Committee.
May 2011: Meeting of DMEC.
April – June 2011: Applicants make contact with clinical teams and attend team meetings.

Trial funding (30 months) (June 2011):
Start of Month 1: Staff begin in posts.
Months 1-2: Staff training, including formal teaching (concerning assessments for the research workers and the intervention for the clinicians), learning the trial standard operational procedures, taking on pilot cases, and meeting clinical teams.
Month 3: Trial begins.
Recruitment will be taking place in two large mental health NHS trusts. The Oxfordshire and Buckinghamshire NHS Foundation Trust covers a population of 1.1 million. Hampshire Partnership NHS Foundation Trust covers a population of 1.3 million. We will have two full-time research workers for recruitment, given active support in recruiting from the two part-time clinical psychologists and trial clinicians. Recruitment rates tend to start low and increase as the trial attracts greater attention, the benefits of being in the trial are seen, and the researchers become more confident in their roles. Typically, at least three names have to be suggested by a clinical team to get one study participant (one person normally does not meet entry criteria, one may be suitable but does not agree to take part - though we expect to have a higher consent rate given the nature of the intervention - and one person is suitable and agrees to take part). In our pilot study (Foster et al, 2010), one part-time researcher recruited the 24 patients in 8 months (equivalent to 6 people a month full-time). In the longitudinal study of Startup et al (2007), one part-time researcher recruited 30 patients with persecutory delusions in 7 months (equivalent to 8 people per month full-time). In a current project this year, a PhD student has recruited 25 patients with persecutory delusions in the first 6 months (4 patients per month). We will enhance recruitment further in the current study by: seeking the active consent of clinical teams who will ‘sign up’ to take part in the study and agree to help facilitate the recruitment process; by using the clinical psychologists and trial therapists to assist the research workers; and by using the MHRN. Overall, in previous studies, we have typically obtained an average rate of 4 patients per month per full-time research worker. Therefore with full-time research workers, we expect a recruitment rate of at least 4 patients a month per centre, though we build in an initially slower rate.

Month 3: Recruit 4 patients (2 per month per centre)
Months 4-5 (i.e. 2mths): Recruit 12 patients (3 per month per centre)
Months 6-12 (i.e. 7mths): Recruit 54 patients (4 per month per centre)
End of first 12 months: 70 patients in total recruited
Month 13: DMEC and TSC meetings.
Months 13-18: Recruit 48 patients (4 per month per centre)
Months 19-22: Recruit 32 patients (4 per month per centre)
End of month 22: 150 patients in total recruited. Recruitment complete.

Months 23-24:	Final checking of all baseline data entry.
Months 23-28:	Write introduction, method and description of sample for trial paper.
Months 23-30:	Write theoretical study paper.
End of month 24:	8 weeks assessments complete.
Month 25:	DMEC and TSC meeting.
Months 25-26:	Checking data entry for the 8 weeks assessment point.
Months 23-28:	The last patients entered into the trial complete therapy and follow-ups.
End of month 28:	All follow-ups finished. Data collection complete.
Month 29:	Final data-checking and completion of data file.
Months 29-30:	Trial data analysis.

Post trial funding:

Month 32:	TSC and DMEC meetings to share results.
Months 31–36:	Completion and submission of paper for publication.

14. Gantt chart summarizing trial timetable (in months).

				Month of Trial														
	Task	**Start**	**End**	**1-2**	**3-4**	**5-6**	**7-8**	**9-10**	**11-12**	**13-14**	**15-16**	**17-18**	**19-20**	**21-22**	**23-24**	**25-26**	**27-28**	**29-30**
1.	**Staff Training**	**1**	**2**															
2.	**All Recruitment**	**3**	**22**															
	70 patients	**3**	**12**															
	48 patients	**13**	**18**															
	32 patients	**19**	**22**															
3.	**Baseline assessments**	**3**	**22**															
4.	**Check baseline data**	**23**	**24**															
5.	**Write initial parts of paper**	**23**	**28**															
6.	**Intervention**	**3**	**24**															
7.	**8 week assessments**	**5**	**24**															
8.	**Check 8 week data entry**	**25**	**26**															
9.	**Follow-up assessments**	**9**	**28**															
10.	**Check follow-up data entry**	**29**	**29**															
11.	**Trial analysis**	**29**	**30**															

15. Expertise

The Mental Health & Neuroscience Clinical Trials Unit at the Institute of Psychiatry will provide on-going consultancy concerning the management of the trial. The main trial team will meet monthly to assess the progress of the trial. Daniel Freeman will be the main lead of the trial, and take particular responsibility in Oxford, with David Kingdon leading the research in Southampton. Graham Dunn will take the responsibility for the trial analysis. Helen Startup will be the trial co-ordinator: she will supervise the research workers and clinical psychologists together with either Daniel Freeman or David Kingdon (depending on location). Daniel Freeman, Helen Startup and David Kingdon will provide training and supervision in the therapy. Chloe Foster, the original pilot therapist, will be a collaborator. She will provide teaching and contribute to supervision of the intervention. The research workers will work very closely with their local clinical psychologists, who will have a supervisory role under the direction of the applicants.

16. Service users

During the pilot we obtained feedback from the participants, which was one reason that we increased the number of sessions to six. We will consult further with service users on the study procedures, informed consent process and modifications to the worry intervention materials. We have previously done this in other studies, where it is helpful to learn what is unclear or should be added. There are a number of patients from a local specialist psychological intervention service for people with psychosis that are happy to be consulted, and we would provide suitable payment for their time. We will also have a service user representative on the TSC.

17. References

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18. Flow Diagram for Worry Intervention Trial

