Avon and Wiltshire NHS
Mental Health Partnership NHS Trust

University of BRISTOL

STUDY PROTOCOL

A feasibility study of eye-movement desensitization and reprocessing (EMDR) in people with an at-risk mental state (ARMS) for psychosis

Contents

List of abbreviations

AE	Adverse Event
ARMS	At risk mental state
AWP	Avon & Wiltshire NHS Mental Health Partnership Trust
BRTC	Bristol Randomised Trials Collaboration
CBT	Cognitive Behavioural Therapy
EI	Early Intervention
EMDR	Eye-movement desensitisation and reprocessing
PIS	Participant Information Sheet
PTSD	Post-traumatic stress disorder
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Events
TAU	Treatment as usual

ADMINISTRATIVE INFORMATION

Study title:

A feasibility study of eye-movement desensitization and reprocessing (EMDR) in people with an at-risk mental state (ARMS) for psychosis

Short title:
Trauma-focused therapy in people at risk of psychosis

Funding

This study is funded by the University of Bristol's NIHR Biomedical Research Centre (BRC)

BACKGROUND AND RATIONALE

Psychotic illnesses are one of the leading causes of disability with more than 21 million people affected worldwide (World Health Organization, 2017). People with psychotic disorders, such as schizophrenia, experience significant functional impairment and are at greater risk of premature mortality (Saha, Chant, & McGrath, 2007).

The core features of psychotic illnesses are delusions and hallucinations. The onset of psychosis is usually preceded by a prodromal phase which is characterized by a series of non-specific or attenuated psychotic symptoms and behavioural changes. Studies show that about 70% of all patients with psychosis present prodromal symptoms which may last from a few months to 5 years (Hafner et al., 1998; Hafner, Maurer, Loffler, & Riecher-Rossler, 1993; Alison R. Yung, 2007). While the peak age of onset of psychosis is age 20-25, a sharp increase in incidence occurs from about age 15 (Kirkbride et al., 2012).

The most well-known criteria for identifying people with a particularly high risk of developing a psychotic illness (said to have an at-risk mental state (ARMS)) were developed by Yung et al in 2004 (A. R. Yung et al., 2005). The criteria state that to be identified as at high risk, the individual must present at least one of the following:

1. Attenuated psychotic symptoms within the last year, at least a few times per week, lasting for at least one week but no more than 5 years
2. Brief intermittent psychotic symptoms (BLIPS) which remit spontaneously within 7 days
3. Strong genetic vulnerability to psychosis (first degree relatives have a diagnosis of psychotic disorders) accompanied by a decline in psychosocial functioning

Not everybody identified as being at risk will develop psychosis. Approximately 22% of ARMS individuals will make a transition to psychosis within 1 year and 36% of them within 3 years, although transition rates vary over time and with the age of the patient and the treatment received (Fusar-Poli et al., 2012).

Various interventions for the prevention of psychosis have been employed including supportive counselling, CBT, family therapy, intensive community support, omega 3 fatty acids and olanzapine. Despite this there is still limited evidence on the effectiveness of interventions, and reliable recommendations are missing. A recent meta-analysis of randomized controlled trials comparing psychological, pharmacological and nutritional interventions with treatment as usual showed that there is moderate quality evidence for the effectiveness of CBT, very low quality evidence for omega 3 fatty acids and low to very low evidence for integrative therapies in preventing transition to psychosis within a year (Stafford, Jackson, Mayo-Wilson, Morrison, & Kendall, 2013). NICE guidelines currently recommend CBT as a first-line treatment (National Institute for Health and Care Excellence, 2014) for people with ARMS.

Research investigating the environmental risk factors for psychosis show that trauma plays a major role in the development of psychosis (Grubaugh, Zinzow, Paul, Egede, & Frueh, 2011; Morrison, Frame, & Larkin, 2003). Recent meta-analyses (Kraan, Velthorst, Smit, de Haan,

& van der Gaag, 2015; Matheson, Shepherd, Pinchbeck, Laurens, & Carr, 2013) showed that trauma is significantly more prevalent in people with ARMS and people with psychosis than in controls. For example, the mean prevalence of childhood trauma in psychosis high-risk samples is 86.8%, while in people not at high risk it ranged from 42.7 to 60% (Kraan et al., 2015).

It has been suggested that one of the core features of schizophrenia, namely hallucinations, represent a re-living of the traumatic experiences (Morrison et al., 2003). A survey on auditory hallucinations in people with schizophrenia (N = 199) showed that in 39% of the people voices were replays of previous memories. Of these, 23% were identical and 71% were similar replays (McCarthy-Jones et al., 2014). Research into the mechanisms which mediate the relationship between trauma and psychotic symptoms has proposed that poor contextual integration of traumatic memories and high dissociative tendencies may be some of the factors responsible for this association (Geddes, Ehlers, & Freeman, 2016; Steel, 2015).

Post-traumatic stress disorder (PTSD) symptoms, such as re-experiencing of the traumatic event in the form of flashbacks or nightmares, avoidance of reminders of the trauma and hyper-arousal, are common in psychotic populations, although not always recorded in patients' clinical notes. For example, a systematic review showed that the mean prevalence of undetected PTSD in psychotic populations was 28% (95% CI 19-37%) (Zammit et al., in press). Despite strong evidence showing that trauma is a key factor in the development of psychosis (Hardy, 2017), no studies have yet investigated whether a trauma focused therapy could prevent or at least delay the onset of psychosis in people at high risk.

Eye movement desensitisation and reprocessing (EMDR) is a trauma-focused therapy in which memory representations of traumatic life experiences are processed in order to decrease the distress and change the dysfunctional beliefs related to the traumatic event. This is done through an eight-phase treatment which aims to address past memories, present triggers and future templates. Typically, an EMDR session lasts from 60 to 90 minutes and, depending on trauma severity and life circumstances, treatment is likely to be between 8 and 12 sessions, or more in severe and multiple trauma.

EMDR has a strong evidence base as a trauma-focused therapy and NICE guidelines recommend either EMDR or trauma-focused CBT (TF-CBT) for the treatment of PTSD (National Institute for Health and Care Excellence, 2005). Early meta-analyses comparing the efficacy of CBT versus EMDR in PTSD showed that these therapies yield comparable results (Benish, Imel, & Wampold, 2008; Bisson & Andrew, 2007; Seidler & Wagner, 2006; Watts et al., 2013). More recently it was found that EMDR was slightly superior to trauma-focused CBT on total PTSD symptoms (SMD = -0.43, 95%CI -0.86, -0.01, z=1.00, p=0.05), intrusion and arousal scores, but was comparable to CBT on avoidance symptoms (Chen, Zhang, Hu, & Liang, 2015).

A recent randomized controlled trial comparing EMDR with treatment as usual in patients with chronic psychosis showed that EMDR significantly reduced paranoid delusions post treatment but not auditory hallucinations (de Bont et al., 2016). However, this RCT did not

specifically focus on reducing psychotic symptoms, and as such the EMDR protocol was not tailored for psychotic experiences.

In ARMS populations, a meta-analysis showed that there is limited evidence for the use of CBT in preventing psychosis (Stafford et al., 2013). There was low to moderate quality evidence that CBT had a moderate effect on transition to psychosis at 12 months follow-up (RR 0.64, 95% CI 0.44, 0.93). However, this effect was no longer significant in sensitivity analysis at 18 months follow-up (RR 0.55, 95% CI 0.25, 1.19).

Although EMDR has comparable efficacy to TF-CBT, the two forms of therapy are different While TF-CBT seeks to directly identify and restructure negative beliefs about the self and the consequences of trauma, EMDR does this indirectly, relying more on the integration of emotional, cognitive, sensory, physical, and contextual information to allow adaptive processing of traumatic memories to occur (though re-structuring of negative beliefs is also a key element of EMDR). Unlike TF-CBT, EMDR does not require patients to give a detailed description of the trauma, which may be distressing for patients, and this may make EMDR more acceptable than TF-CBT in patients with ARMS. In comparison with TF-CBT, EMDR does not involve any homework, which may be more suitable for people with a disorganized lifestyle, such as those with ARMS. Moreover, people with depression have described homework as the most challenging aspect of CBT because it triggered negative memories of school homework and brought back challenges with regards to discrete completion of homework tasks (Barnes et al., 2013). Indeed, studies in ARMS population showed that some patients did not like the homework and the structure of CBT (Addington et al., 2011), and that up to 50% of people with psychosis did not engage with CBT in clinical services (RCPsych, 2014). In light of the evidence showing the impact of trauma in psychosis and the limitations of CBT in people with ARMS, and the effectiveness of EMDR in people with PTSD, it would seem that EMDR might be potentially beneficial to patients with ARMS.

Aims and Objectives

The overarching aim of this study is to establish whether it would be feasible to conduct a large multi-centre RCT to evaluate the clinical and cost-effectiveness of EMDR to prevent the onset of psychosis in people with an at-risk mental state.

Objectives:

1) To explore patients' and therapists' views of EMDR as a treatment for ARMS
2) To investigate patients' and therapists' views of the study design and study materials
3) To estimate the rate of recruitment and retention to inform the large-scale RCT
4) To refine the eligibility criteria, screening and recruitment procedures
5) To optimize the EMDR protocols and learn about the factors which affect the implementation of EMDR
6) To understand what treatment as usual (TAU) consists of for patients with ARMS

As the study developed, to address challenges with recruitment, additional objectives were incorporated. These were:

1) To explore how potential ARMS patients are identified and managed in primary and secondary care services
2) To identify referral routes in primary and secondary care
3) To explore other researchers' experiences of recruiting ARMS patients to research studies in the UK

METHODS: PARTICIPANTS, INTERVENTIONS, OUTCOMES

Study design

The study consists of a feasibility trial with a nested qualitative study. This is a single arm feasibility trial where all participants will be offered EMDR. Outcomes will be collected at 4, 8 and 12 months after the baseline assessment.

Study setting

Recruitment will take place in the Avon and Wiltshire Mental Health Partnership NHS Trust (AWP). The intervention will be delivered within primary or secondary care services in AWP, or private clinical premises. People with ARMS are usually referred to these services by their GPs for an initial assessment and/or treatment.

Participants

Inclusion criteria

- Those aged 16 years or over who are at risk of psychosis (as defined in the Comprehensive Assessment of At-Risk Mental States (CAARMS) (A. R. Yung et al., 2005) and present at least one positive symptom (perceptual abnormality, unusual thought, non-bizarre ideas or disorganised speech) scored ≥3 on CAARMS
- History of traumatic experience as defined in ICD-10 F43.1, occurring prior to onset of first positive symptom
- Presence of 1 or more symptoms of re-living, avoidance, hyper-arousal, or cognitive distortions in relation to the traumatic experience (assessed using the PTSD Checklist for DSM-V (PCL5) during the last month (Bovin et al., 2016))

Exclusion criteria

- People with past history of treated or untreated psychotic illness or learning disability
- Current use of antipsychotics
- Currently receiving psychological therapy
- Completed a trauma-focused psychological therapy in the last 2 years
- Insufficient fluency in English
- Lacking mental capacity to provide valid informed consent

Recruitment

Patient identification

Participants will be identified via two routes:

1. Early Intervention services
2. Everybody included

1. Early intervention services

The research team will present the project at face-to-face meetings with health professionals from the Early Intervention Teams, within the Avon and Wiltshire Mental Health Partnership NHS Trust (AWP). The researchers will explain the aims and design of the study, and inform clinicians about the study's inclusion/exclusion criteria. Clinicians working in the Early Intervention Services routinely screen for ARMS using the CAARMS tool.

Researchers will identify clinical teams who would be willing to take part in the study and ask them to identify potential participants via three routes: a) during routine clinic appointments, b) invitations by mail sent out by clinicians, and c) invitations by mail sent out by CSO.

a). At the end of the initial consultation, clinicians will introduce the study to patients who have been identified with ARMS within the past 12 months using a very short information sheet. Those patients willing to hear more about the study will be asked to complete Section 1 of the Expression of Interest (EOI) form, and provide their contact details. Completed EOI forms will then be either collected by researchers or returned to them by fax. On receiving a completed EOI, a member of the research team will phone the individual, describe the study, answer any questions they have and, if the individual is willing to take part, agree a time and place for the researcher to meet with them to complete the eligibility assessment and sign the consent form. Following the telephone call, the researcher will post the individual a full participant information sheet and a letter confirming the time and place that has been agreed. For individuals who agree to meet with the researcher, standard recruitment procedures will be implemented (see the standard recruitment procedures below).

Individuals who do not want to hear more about the study will be asked to complete section 2 of the EOI form, which asks for information on age, gender, reasons for nonparticipation and willingness to take part in a short interview. Those who agree will be interviewed at their earliest convenience. Interviews with decliners will provide valuable information on the acceptability of EMDR and will also highlight concerns and potential misunderstandings about the study. As in previous situations where the ethics committee approved studies which explored patients' reasons for declining to take part in randomised controlled trials (Barnes et al., 2012), this information will help us identify ways to improve recruitment to this study and any future full-scale RCT.

b). Sometimes patients are not informed about their diagnosis at the end of the assessment but are called after the appointment by a member of the clinical team who informs them of the outcome of the assessment, and are also sent a letter detailing their diagnosis. In this case, in addition to the letter informing individuals of their diagnosis, for those meeting the

ARMS criteria, clinicians will also enclose a brief information sheet about the study and an EOI form. Individuals who are willing to hear more about the study are invited to return the EOI form by post.

Clinicians will also be given the option of discussing the study with the patient over the telephone using the Brief Information Sheet. If the patient is interested in hearing more about the study, the clinician will ask the patient for permission to share their contact details with the research team. The clinician will then fill in the "Cl_Phone permission to contact" form, and will send it to the research team by fax or by a secure NHS email address.

On receiving a completed EOI or permission to contact form, a member of the research team will telephone individuals who want to hear more about the study, describe the study in more detail and answer any questions they have. As above, following the telephone call, the researcher will post the individual a full participant information sheet and a letter confirming the time and place that has been agreed. For individuals who agree to meet with the researcher, standard recruitment procedures will be implemented (see the standard recruitment procedure below). Patients who do not reply will be followed up with a phone call by the CSO within a week of receiving the documents. As described under section a), we will also recruit decliners for interview.

c). NIHR Clinical Studies Officers (CSO) will pre-screen patients using the patient record system (RIO) and liaise with the care team about suitable patients. CSO or another member of the clinical team will post suitable patients a cover letter, the EOI and a brief information sheet. A member of the research team will telephone individuals who want to hear more about the study, describe the study in more detail and answer any questions they have. If the individual is willing to take part, a convenient time and place will be agreed to meet with the researcher to complete the eligibility assessment and sign the consent form. Following the telephone call, the researcher will post the individual a full participant information sheet and a letter confirming the time and place that has been agreed. For individuals who agree to meet with the researcher, standard recruitment procedures will be implemented (see the standard recruitment procedure below). Patients who do not reply will be followed up with a phone call by the CSO within a week of receiving the documents. If the patient is willing to hear more about the study but has not returned the EOI by post, the CSO will take permission to contact over the phone using the "CRN_Phone permission to contact" form. The CSO will then return the form to the research team who will contact the patient to discuss the study in more detail.

As described under section a), we will also recruit decliners for interview.

2. "Everyone included" within AWP

'Everyone Included' is a standard approach to research in AWP, whereby service users are routinely informed about relevant research opportunities by post, unless individuals have expressed a preference not to receive such information. As is standard practice, potential participants will be identified via an automated search of the electronic patient record system (RiO) based on the study's inclusion/exclusion criteria. The search will be authorized and

requested by a member of AWP Research and Development (R&D), who are part of the clinical team and conducted by information analysts within AWP.

The AWP R&D department will send a 'Research Opportunity Letter' on behalf of the research team to potential participants briefly explaining what this study is about and what it involves. The 'Research Opportunity Letter' will be reviewed by independent members of the Everyone Included Review Panel (includes service users, carers, clinicians and researchers), who decide whether the study is appropriate.

The letter does not contain any disclosing information (e.g. personal references to diagnosis) and invites individuals to make contact with the Everyone Included team if they are interested in participating. The letter explains how to contact the Everyone Included team (by post using a free post reply slip) and is signed by the Director of Research & Development. If individuals do not respond, nothing further will happen. If they respond, their expression of interest form will be passed to the research team, who will contact potential participants via their preferred method of communication and provide them with full information about the study via the Participant Information Sheet. This will be followed up with a phone call within a week of receiving the documents. If individuals agree to meet with the researcher, standard recruitment procedures will be implemented (see below).

Standard recruitment procedure, eligibility and baseline assessment

Individuals interested in taking part will be invited to a face-to-face appointment with a researcher to establish eligibility, answer questions about participation, and seek written informed consent.

In order to establish eligibility for the study, patients will be asked to complete the following scales:

- The Life-events Checklist for DSM-5 (Gray, Litz, Hsu, & Lombardo, 2004)
- The Childhood Trauma Questionnaire (Bernstein & Fink, 1998)
- The PTSD Checklist for DSM-5 (PCL5) (Bovin et al., 2016)

In addition to completing these questionnaires, patients recruited via the Everyone Included route who have not been seen by a clinician for more than a month, will also be administered the CAARMS tool to establish eligibility for the study. The CAARMS tool will be administered by clinical staff, CSOs and members of the research team.

Those who are eligible will be asked for written informed consent for their participation in the trial. Those consenting will be asked to provide details of their sociodemographic data (education, occupation, home ownership) and baseline data will be collected using the following quantitative measures:

- Severity of psychotic symptoms: the CAARMS (A. R. Yung et al., 2005), the Negative Scale of the PANSS (Positive and Negative Symptoms Scale) (Kay, Fiszbein, & Opler, 1987), the Positive Symptom Rating Scale (PSYRAT) (Haddock, McCarron, Tarrier, & Faragher, 1999), and the Community Assessment

of Psychotic Experiences (CAPE-42) (Stefanis et al., 2002)

- Severity of depression and anxiety: the Patient Health questionnaire (PHQ-9) for depression (Kroenke, Spitzer, & Williams, 2001) and the Generalized Anxiety Disorder Questionnaire (GAD-7) for anxiety (Spitzer, Kroenke, Williams, & Lowe, 2006)
- Impaired functioning: Work and Social Adjustment Scale (WSAS) (Mundt, Marks, Shear, & Greist, 2002)
- Health status: EQ-5D-5L (Herdman et al., 2011)
- Drug use: The Drug Abuse Screening Test (DAST 10) (Skinner, 1982)

Data will also be collected on medication use via self-report measures.

Individuals who do not meet the inclusion criteria will be thanked for their time and interest in the study, and will be explained why the study is not suitable for them.

Consent

The process of consenting young people (16 and 17 years old) to this study will follow the DoH Reference Guide to Consent and the GMC Guidelines, which provide the guide that all health professionals need to take into account in obtaining consent. Although young people may be more vulnerable than adults, they are presumed to be able to give consent to their treatment, similarly to adults. As for adults, if young people decline to take part in the study their decision will be fully respected and accepted.

Researcher will make clear that participants have the right to withdraw from the study at any point without giving any reasons. However, it will also be mentioned that should they choose to withdraw, any feedback on their experiences in study participation would be greatly appreciated as this will inform research team on future design of the full-scale RCT.

METHODS: ASSIGNMENT OF INTERVENTIONS

This is a single arm trial where all participants in the study will be offered EMDR.

Randomisation scheme

We originally planned to randomise all consented participants to one of the two groups: 1) EMDR or 2) TAU. Randomization took place by means of a computerized service administered by the Bristol Randomised Trials Collaboration (BRTC). This ensured that allocations were concealed from the recruiting researcher. Randomization was minimized by psychotic symptom severity and patients were categorized based on the positive symptoms of CAARMS (i.e, sum of Unusual Thoughts, Non-Bizarre Ideas, Perceptual Abnormalities and Disorganised Speech Global Ratings scales), with cut-off at 11 on this scale. Participants were notified of their group allocation within 48 hours of the baseline assessment.

Given the change in study design from a randomised controlled trial to a single arm trial, all eligible consenting participants will now be offered EMDR.

Blinding

The main outcome of the study is transition to psychosis at 1 year follow-up. The diagnosis of psychotic illness during the follow-up period will be made by the clinical team. Although independent of the study, it is possible that the clinicians would not have been blind to patients' treatment allocation. To avoid bias in outcome measurement, we had planned that researchers extracting data on psychotic illness diagnosis from clinical records would be blind to patients' treatment allocation and had planned to judge the success of blinding by asking researchers extracting data to record whether they thought the participant was allocated to EMDR or TAU therapy. Given that all participants in the study will now receive EMDR, it will not be possible to blind the researchers who will carry out the follow-up assessments.

EMDR

Participants will receive up to 12 sessions of manualized, weekly, face-to-face EMDR therapy (Logie et al, 2016). Each session will last approximately 90 minutes.

Therapeutic sessions will take place at the Early Intervention Services, GP Surgeries, or other NHS/private clinical premises. The first 2-4 sessions of EMDR focus on establishing the therapeutic alliance, preparation for EMDR and stabilization techniques, assessment and identification of targets, cognitions, emotions and bodily sensations. The following 8-10 sessions will focus on desensitisation, installation of positive cognitions and body scan for past, present and future stressful situations.

Treatment has been manualized by clinicians from the Lancaster NHS Trust and individualized to target psychotic symptoms. Therapeutic sessions will be delivered by EMDR UK & Europe trained therapists who will receive training based on the Lancaster manual for the study. All EMDR therapists will have at least one year of experience, and monthly supervision with an EMDR consultant will be in place. Written permission will be sought for recording therapeutic sessions. 10% of the sessions will be randomly sampled for fidelity and evaluated by accredited EMDR therapists independent of the study, using the EMDR fidelity checklist (Leeds et al, 2016).

OUTCOMES

The primary outcome is transition to psychosis which will be assessed at 12 months after the baseline assessment from clinical records or, if patients have not been kept on Early Intervention (EI) team's caseload or dropped out of the EI, at the 12 months follow-up assessment, researchers will establish via the CAARMS whether patients have transitioned to psychosis. The secondary outcomes are severity of psychotic symptoms, PTSD, depression, anxiety, impaired functioning, health status and medication use which will be

assessed at baseline, 4, 8 and 12 months after the baseline assessment. Resource use will be assessed at 4, 8 and 12 months after the baseline assessment. There will be face-to-face appointments and data will be collected by the research team.

Primary outcome

- Transition to psychosis: ICD-10 diagnosis of psychotic disorder from clinical records or via the CAARMS

Secondary outcomes

- Severity of psychotic symptoms: CAARMS, PSYRAT, the negative scale of the PANSS and CAPE-42
- Severity of PTSD symptoms: PCL-5
- Severity of depression and anxiety: PHQ-9 and GAD-7
- Impaired functioning: Work and Social Adjustment Scale (WSAS)
- Health status: EQ-5D-L
- Drug use: DAST 10
- Medication use
- Resource data use – we will ask questions about resource use including information on: a) use of primary care and community care services (GP visits, use of community health care services), b) secondary care services (number of out-patient visits, reason for visit; inpatient admissions, length of stay and reason), c) use of social services and disability payments received, d) time off school or work, d) personal expenditure (private healthcare and therapies, over-the-counter medication, travel costs associated with health visits); productivity loss due to time off work or study.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Sample size

In the initial protocol we planned to recruit up to 40 patients with ARMS and randomly allocate them to EMDR or TAU in a 1:1 ratio. The initial sample size was informed by literature guidelines (Teare et al., 2014) and pragmatic reasons concerning potential difficulties accessing this population. We were proposing to collect data on outcomes that will be used to design a future RCT. The feasibility study would not be powered to detect important clinical differences between EMDR and TAU groups but would provide estimates of the completion and retention rates that would further assist in planning the recruitment for a future RCT. Based on the original sample size, if 70% of those randomised to EMDR completed the intervention, the 95% confidence intervals would be 45% and 88%. Similarly, if 75% of those randomised were followed up to 1 year, the 95% confidence intervals for the retention rate would be 58% to 87%.

We had estimated, based on the numbers provided by AWP in 2016, that over 13 months (which was our original recruitment period), there would be 143 ARMS patients in AWP (across the 6 EI teams). The EI teams were also expecting (and were told they would be receiving) funding to increase their capacity to take on ARMS patients and increase referrals of possible ARMS patients from GPs in 2016 following the publication of the "Implementing the early intervention in psychosis access and waiting times standard: guidance". A recently conducted scoping study in AWP showed that 24 out of 30 referrals (80%) to the EI services had a history of trauma occurring prior to the onset of their psychotic experiences. Based on this and previous reports in the literature, we estimated that 75% of ARMS patients would be eligible for the study. Of these, based on recruitment rates from psychological therapy trials in ARMS patients, we estimated that 50% of eligible patients would be willing to take part, allowing recruitment to be completed in 13 months. However, when we started recruitment, we found that the number of ARMS patients was much lower than we expected.

Given the challenges with recruitment, we have modified our study design (from RCT to single arm trial) and have therefore revised our target sample size to have reasonable precision around estimates of percentages completing the intervention and follow-ups. This will provide data to inform the design of the future RCT. For example, if 70% of those who started EMDR complete the intervention, the 95% confidence intervals would be 45% and 88%. Similarly, if 75% of those who started EMDR are followed up to 12 months, the 95% confidence intervals for the retention rate would be 50% and 91%. We estimate that there will be approximately 51 patients with ARMS referred to the EI services in AWP over the extended recruitment period (12 months).

Quantitative data collection

Data will be collected via clinician-rated measures administered face-to-face by clinicians, researchers or CRNs, self-report questionnaires, and electronic clinical record searches as mentioned above. This information will assist with the planning of a future RCT.

Baseline and follow-up assessments will be conducted face-to-face at the Early Intervention Services, GP surgeries or other NHS premises, University of Bristol premises, or at participants' homes. If the appointment takes place at people's homes, researchers will abide by the lone workers policy within the University of Bristol. The eligibility/baseline assessment session will last about 90 minutes, and the follow-up session will last about 60 minutes. Data will be collected by the research team.

Qualitative data collection

We will conduct in-depth individual interviews with all the therapists and patients who participated in the trial. Up to 10 "decliners" will be interviewed. To encourage participation, and because well-planned interviews can gather the same material as those conducted face-to-face (Sturges et al, 2004), therapists, study participants and decliners will be given the choice of being interviewed in person or over the telephone.

Therapists will be interviewed after they have finished delivering the intervention within the study. The interviews will explore their views and experiences of delivering EMDR to participants in the study, how they think this treatment could be better tailored to this patient group, and what support, training and resources they think therapists would need if the intervention was evaluated in a large scale RCT. The interviews will also be used to explore their views of the training and supervision they received, and their views on the study materials and the design of a future RCT. The interviews will last up to an hour.

Interviews with patients who completed treatment or stopped early will explore patients' views and experiences of EMDR, identify how treatment delivery could be refined to increase its acceptability, and learn how study materials and procedures could be improved. Patients who adhered to therapy will be interviewed after they have completed at least 9 therapy sessions, and those who stopped early will be interviewed within a month of doing so in order to minimize difficulties with recall. The interviews will last up to an hour.

Interviews with 'decliners' will be conducted at patients' earliest convenience (see the Standard recruitment, eligibility and baseline assessment section). Interviews will explore decliner's views of the study and EMDR, and their reasons for declining to take part. This will help us identify way to improve recruitment to this study and any future full-scale RCT. These interviews will last about 15 minutes. They will be conducted early on in the study, as their findings may indicate how the patient information sheets or recruitment process for the feasibility study could be modified to improve recruitment.

Topic guides will be developed for each set of interviews, to ensure consistency across data collection. The therapist and study participant guides will be developed in parallel to ensure key areas are discussed with both practitioners and patients. This will allow their views to be triangulated, increasing the confidence with which study conclusions can be drawn. With interviewee consent, the interviews will be audio-recorded and fully transcribed.

Additional qualitative work to address issues with recruitment and explore treatment options in ARMS populations

The intention was to recruit 40 ARMS patients over a 13 month period. Recruitment to the study has been much lower than expected, i.e. we have only recruited 6 patients for now, having predicted we would have recruited 40 by now. It appears that one key reason for low recruitment is because the number of ARMS patients referred by GPs to Avon and Wiltshire Partnership NHS Trust (AWP) services is much lower than expected based on data which had been given to us from the Trust prior to the study starting.

We therefore would like to expand the qualitative element of the study to 1) better understand how ARMS patients are managed in primary and secondary care settings, in order to identify possible reasons for why recruitment to the study has been much lower than expected and 2) consider how best to recruit ARMS patients to future research studies.

We would like to conduct in-depth interviews with GPs and clinicians from secondary care services to explore how potential ARMS patients are identified in primary and secondary care, how they are managed, and the facilitators and barriers of referral to secondary care early intervention services. We are hoping that these interviews will give us insights that we can then use to improve recruitment to studies of ARMS patients. We would also like to interview UK researchers with experience of recruiting ARMS patients to their studies.

Thus, the qualitative components of the study will entail:

a. Interviews with GPs, clinicians from Primary Care Liaison Services and other secondary care services
b. Interviews with patients who did not participate in the interventional part of the study but who have been identified as ARMS by the EI teams we are recruiting from
c. Interviews with researchers who have been involved in recruiting ARMS patients to research studies in the UK

Group 1: GP interviews

Inclusion criteria:

1. GPs contacted by the CRN who are working within the general practices in Bristol, South Gloucestershire, North Somerset, Bath, Swindon and Wiltshire purposefully sampled to take part in the study.
2. Willing to give informed consent to take part in an interview
3. Able to understand and communicate in English.
4. If they wish to complete the interview over the telephone: have access to a land-line or mobile telephone over which an interview can be held.

Group 2: Clinicians

Inclusion criteria:

1. Clinicians working within the AWP Primary Care Liaison Services and other secondary care services involved in the assessment of ARMS patients.
2. Willing to give informed consent to take part in an interview.
3. Able to understand and communicate in English.
4. If they wish to complete the interview over the telephone: have access to a land-line or mobile telephone over which an interview can be held.

Recruitment of GPs:

GP practices working within Clinical Commissioning Groups in Bristol, North Somerset, South Gloucestershire, Bath, Wiltshire and Swindon will be informed about the study via the Local Clinical Research Network (LCRN). The LCRN will then inform the researcher about which GP practices are willing to support the study. From this list, the research team will identify practices that vary in size and in terms of the socio-demographic characteristics of their patient populations. The research team will then contact the GP practices by telephone or email, and arrange a follow up visit to attend the practice team meeting to further explain the study, answer any questions GPs might have, and provide invitations and information sheets to the GPs. Following this meeting, GPs who are willing to be interviewed will be asked to email the researcher directly, or let the practice manager know, who will subsequently pass the contact details of interested GPs to the researcher.

GPs who express an interest in the study will then be contacted by the researcher by telephone or email to arrange a convenient time and date for the interview. Once an interview date and time have been agreed, the researcher will post the GP a letter confirming the date and time and a consent form to read in advance. The interview will take place within GP's working hours. The GP practice will be reimbursed £40 for each interview.

Recruitment of secondary care practitioners

The research team will approach the team managers of Primary Care Liaison Services (PCLS) and other secondary care services within AWP who are involved in the assessment of ARMS patients. Contact will be made by telephone or email. The researcher will briefly introduce the study to the team managers, and then attend practice team meetings to discuss it further with individuals interested in supporting the study. Those interested will be provided with an invitation and information sheet. Following this meeting, clinicians who are willing to be interviewed will be asked to email the main researcher directly.

Clinicians who express an interest in the study will then be contacted by the researcher by telephone or email to arrange a convenient time and date for the interview. Once an interview date and time have been agreed, the researcher will post the clinician a letter confirming the date and time, and a consent form to read in advance. The interview will take place within clinicians' working hours. The PCLS and other secondary care services will be reimbursed £40 for each interview.

Interviews with GPs

GPs will be given the choice of either a telephone interview or a face to face interview at the primary care practice. Those interviewed in person will be asked to complete and sign a consent form immediately prior to interview. For the telephone interviews, consent will be taken verbally. This will entail the researcher reading aloud the consent form which will have already been sent to the GP, and checking that the GP is happy to give consent to each of the points listed. Once consent has been obtained, the researcher will sign and date the

consent form and keep it on file. This consent process will be audio-recorded. The interview will then take place.

A topic guide will be used to ensure consistency across the interviews. Interviews with GPs will explore how potential ARMS are identified and managed in primary care, their treatment and referral pathways, and facilitators and barriers in referring potential ARMS patients to the Early Intervention teams.

We aim to interview up to 15 GPs. The final number will depend on when data saturation has been reached. The interviews will last about 30 minutes. The GP practice will be reimbursed £40 for each interview.

Interviews with secondary care clinicians

Clinicians will be given the choice of either a telephone interview or a face to face interview at the primary care practice or secondary care service. Depending on the method of interview, consent to take part will be taken from clinicians immediately prior to the interview as described above.

A topic guide will be used to ensure consistency across the interviews. Interviews with clinicians will explore how potential ARMS are triaged and managed, their treatment and referral pathways, and facilitators and barriers in referring potential ARMS patients to the Early Intervention teams.

We aim to interview up to 10 clinicians. The interviews will last about 30 minutes. The PCLS and other secondary care services will be reimbursed £40 for each interview.

Group 3: ARMS patients

Given the low referral/recruitment we want to understand more about pathways into secondary care, and therefore we want to interview anyone with ARMS identified through AWP who has not yet been approached to take part in the interventional part of the study. Interviews with ARMS patients will explore what treatment as usual is for them, their views on the current treatment options, and whether a trauma focused therapy such as EMDR would be relevant and of interest in this population.

Inclusion and Exclusion criteria:

1. Patients aged 16 years who are at risk of psychosis (as defined in the CAARMS).
2. ARMS patients who have not been invited to participate in the feasibility study.
3. Willing to give informed consent to take part in an interview.
4. Able to understand and communicate in English.
5. If they wish to complete the interview over the telephone: have access to a land-line or mobile telephone over which an interview can be held.

Recruitment of ARMS patients

The research team will inform the EI team managers about the aims of this qualitative work. A follow up visit will be arranged with those team managers who wish to support this work in order to further explain the study and discuss recruitment strategies. Participants will be identified via two routes:

1. At the end of a consultation, clinicians will introduce the study to patients who have been identified with ARMS using a very short information sheet. Those patients willing to hear more about the study will be asked to complete the Expression of Interest (EOI) form. Clinicians will also be given the option of discussing the study with the patient over the telephone. If the patient is interested in hearing more about the study, the clinician will ask the patient for permission to share their contact details with the research team. The clinician will then fill in the "ARMS_Cl_Phone permission to contact" form.

Completed EOI or permission to contact forms will then be either collected by researcher, returned by fax or by a secure NHS email address. On receiving a completed EOI, the researcher will phone the individual, describe the study, answer any questions they have and, if the individual is willing to take part, agree a time and place to do the interview. Following the telephone call, the researcher will post the individual a full participant information sheet and a letter confirming the time and place that has been agreed. Face-to-face interviews will take place on NHS premises, at patients' home or over the telephone, depending on the patient's preference.

2. CSOs will pre-screen patients using the RiO and liaise with the care team about suitable patients. CSO or another member of the clinical team will post eligible patients a letter, the EOI and a brief information sheet. Those patients willing to hear more about the study will be asked to complete the EOI form, and return it to the research team using a prepaid envelope. A member of the research team will telephone individuals who want to hear more about the study, describe the study in more detail and answer any questions they have. If the individual is willing to take part, a convenient time and place will be agreed to do the interview. Following the telephone call, the researcher will post the individual a full participant information sheet and a letter confirming the time and place that has been agreed.

Patients who do not reply to the initial letter, will be followed up with a phone call by the CSO within a week of receiving the documents. If the patient is willing to hear more about the study but has not returned the EOI by post, the CSO will take permission to contact over the phone using the "ARMS_CRN_Phone permission to contact" form. The CSO will then return the form to the research team who will contact the patient to discuss the study in more detail.

Interviews with ARMS patients

Patients will be given the choice of either a telephone interview or a face to face interview. Those interviewed in person will be asked to complete and sign a consent form immediately prior to interview. For the telephone interviews, consent will be taken verbally. This will entail the researcher reading aloud the consent form which will have already been sent to the patient, and checking that the patient is happy to give consent to each of the points listed. Once verbal consent has been obtained, the researcher will sign and date the consent form and keep it on file. This consent process will be audio-recorded. The interview will then take place.

A topic guide will be developed to ensure consistency across the interviews. Interviews with patients will explore patients' referral pathways in primary and secondary care, what TAU consists of in primary and secondary care, patients' views on the available treatment and trauma focused therapy as an alternative to current treatment options.

We aim to interview around 15 patients. The interviews will last about 30 minutes. Patients will be offered a £10 voucher to reimburse them for their time.

Group 4: Researchers

Inclusion and Exclusion criteria:

1. Researchers in the UK who have recruited ARMS patients to research studies
2. Willing to give informed consent to take part in an interview.
3. Have access to a land-line or mobile telephone over which an interview can be held.

Recruitment of researchers

Researchers who have recruited ARMS patients to research studies in the UK and who are known to our research team or have published in the area will be contacted by the lead researcher by email. The email will introduce the study using the "Researcher invitation letter", and will be accompanied by an information sheet. Researchers who are willing to be interviewed will be asked to reply to the email indicating this. The lead researcher in our team will then telephone or email those researchers who are willing to be interviewed to arrange a convenient time and date for the interview. Once an interview date and time have been agreed, the lead researcher in our team will send a letter confirming the date and time of the interview, and a consent form to read in advance.

Interviews with researchers

Researchers will be interviewed by telephone. Verbal consent to take part will be taken immediately prior to the interview. A topic guide will be used to ensure consistency across the interviews. Interviews with explore researchers' experiences of recruiting ARMS patients to research studies in the UK, and facilitators and barriers to recruiting patients with this condition.

We aim to interview up to 10 researchers. The interviews will last about 30 minutes.

Timing of Data Collection (see Schedule of Events and Gantt Chart)

Data Analysis

All interviews will be fully transcribed and anonymised. Data collection and analysis will proceed in parallel, so that insights from earlier data can shape later data collection, and enable the team to establish when data saturation has been reached. The data gathered will be analysed thematically. This approach will entail members of the research team to read and re-read transcripts in order to gain an overall understanding of the participants' views and experiences, identify emerging themes and develop a coding frame. Transcripts will be independently coded by different researchers, who will then meet to discuss their coding and interpretation of the data. This will help to control for researcher bias and may lead to the coding frame being revised, with new codes being added and existing codes being removed or defined more clearly. Transcripts will then be imported into the software package NVivo to allow electronic coding and retrieval of data. Once all the transcripts have been coded, data will be analysed using a framework approach. Using this method, data pertaining to each code will be summarised in tables. Comparisons will then be made within and across the interviews to identify thematic patterns and deviant cases, and to highlight the views participants hold toward specific issues. For the interviews with patients and therapists, two preliminary coding frames will be developed. Where possible, similar codes will be used for the three datasets, as this will assist with triangulation of patients' and therapists' views.

Quantitative data will be analysed in Stata. For this feasibility study, we will calculate: (1) the proportion of patients consenting to take part in the study; (2) the proportion completing the baseline assessment and agreeing to take part in the study; (3) the number of EMDR sessions attended and the proportion completing 8 or more sessions (i.e. regarded as an adequate dose of therapy); (4) the proportion completing the follow-up assessments. Feasibility outcomes such as recruitment and retention rates will be calculated with 95% confidence intervals using the exact binomial method.

We will also report the proportion of individuals who transitioned to psychosis at 12 months, and the confidence intervals for the effect size will be calculated to assist the planning of the future RCT. We will also compare the continuous outcomes such as the severity of psychotic symptoms, depression, anxiety, PTSD symptoms and quality of life to show the frequency of data completion, mean and standard deviation for the two time points.

Data management

Completed questionnaires will be stored securely in compliance with University of Bristol Data Security policies and the Data Protection Act 1998. All data will be entered onto a secure database by a member of the research team. Personal details and administrative data will be entered onto a secure database held on the University of Bristol server, and non-

identifiable data will be entered onto a secure web-based database (REDCap) via a secure internet link maintained by University of Bristol Information Services. The Clinical Trials Unit (BRTC) database team will develop and set-up the databases.

Data collected on paper or questionnaires will be identifiable only by Patient Identification Number (PIN). This data will be stored in a secure locked cabinet in a locked room with limited access. Information capable of identifying individuals will be held on the database with passwords restricted to authorised study staff only.

Data will be analysed by the research team. All members of the research team are based at the University of Bristol. However, participants will be asked, when consenting to take part in the study, whether anonymised data can be made available to other researchers, working outside of the research team, for the purpose of secondary analysis and synthesis. Researchers are increasingly being asked to place data in public archives and to make it available to others for future research projects. After the study has ended, the electronic study data will be transferred to the University of Bristol Research Data Storage Facility (RDSF). The RDSF provides secure, long-term storage for research data.

METHODS: MONITORING

Safety assessments and monitoring

Adverse Events (AE)

In this study we will use the recommendations for defining and reporting adverse events and harm as outlined by Parry, Crawford and Duggan (2016).
An Adverse Event refers to:

- A significant episode during or shortly after treatment (e.g. suicide, suicide attempts, mental health related hospital admissions) which if related to or directly caused by treatment amount to harm or severe harm
- A sustained and clinically significant deterioration i.e. a worsened mental state after therapy is complete, which can include the emergence of new symptoms.
- A report of a negative experience of the EMDR sessions and perceived harm on the part of the participant when interviewed for the nested qualitative study.

Serious Adverse Events (SAE)

A serious adverse event is any untoward occurrence that:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Anything the investigator deems to be of clinical significance

This study will monitor closely any serious adverse events which may occur whilst patients participate in the trial.

Participants, researchers and clinical staff should notify any adverse event which they believe may have occurred as a result of the trial intervention or the research process. On notification of such an adverse event which may be related to the research process or intervention, a researcher or member of site staff should complete an adverse event report form within 5 working days, paying specific attention to information regarding the nature and timescale of events i.e. when the event started, were there any specific changes to medication or behaviour preceding the event. Further information should be requested from the participant, clinical team or GP as necessary. A completed form should be securely sent to the Chief Investigator for review and assessment of relatedness and expectedness as follows:

1. Confirmation of seriousness (whether the adverse event is an AE or SAE)
2. Causality – i.e. relatedness of the event to the study intervention, according the following definitions:

Unrelated – where an event is not considered to be related to the study intervention
Possibly – although a relationship to the study intervention cannot be completely ruled out, the nature of the event, the patient's underlying condition, concomitant medication or temporal relationship make other explanations possible
Probably – the temporal relationship and absence of a more likely explanation suggest the event could be related to the study intervention
Definitely – Known effects of the study intervention suggest that study intervention is the most likely cause.

3. Expectedness of the event. Is the event an anticipated event even if the research had not been taking place?

Serious Adverse Event reporting

All SAEs will be reported to the Chief Investigator within 24 hours of awareness of the SAE. All SAEs that occur in relation to the intervention must be recorded, together with data including date of onset and resolution, outcome, severity and causality for the intervention.

All SAEs of a related and unexpected nature will require onward reporting to the main REC, and this will be facilitated by the Chief Investigator, in accordance with any procedures of the Sponsor.

Related and unexpected SAEs will be immediately reported to the Sponsor. In addition, all investigators will be notified, and the TSC will be notified in accordance with Sponsor procedures and timeframe. SAEs which after review are not thought to be treatment related will be brought to the TSC's attention at their next scheduled meeting. The numbers and details of AEs and SAEs will be reported to the Trial Management Group and Trial Steering Committee regularly.

ETHICAL AND REGULATORY CONSIDERATIONS

Peer review

This study has been reviewed by the NIHR Biomedical Research Centre.

Approval will be sought from NHS REC and HRA. Confirmation of Capacity and Capability will be sought from Avon and Wiltshire Partnership NHS Trust.

Insurance

The University of Bristol has arranged Public Liability insurance to cover the legal liability of the University as Research Sponsor in the eventuality of harm to a research participant arising from management of the research by the University.

Sponsorship

University of Bristol will act as a sponsor for the study.

Amendments

Protocol amendments will be presented to the Study Steering Committee for consideration and will be implemented only when approved by the NHS Research Ethics Committee.

Confidentiality

Consented patients will be assigned a Participant Identification Number (PIN) which will help researchers to identify patients throughout the study without disclosing patient identity. PINs will replace personal identifiable data in all research related documents. Any personally identifiable information (consent forms) and PIN allocation will be kept separately from the collected data and will be stored securely in a place with limited access. Any personally identifiable information will be transferred from the NHS to the University on an encrypted USB or digitally via nhs.net.

Audio recordings of interviews will be password protected. Audio recordings of therapeutic sessions will be taken from NHS premises only via secure electronic means or encrypted USBs, and destroyed immediately once the supervision is completed. All local databases are password protected.

Protocol compliance

Protocol deviations will be clearly documented and reported to the Sponsor (see the Standard Operating Procedures around patient safety)

Notification of serious breaches to GCP and/or the protocol

The sponsor will be notified immediately of any situation where a breach to the protocol has taken place. The sponsor will further notify the licensing authority in writing of any serious breach of the protocol within 7 days of becoming aware of the breach.

Reimbursement

Participants will be reimbursed for their travel expenses. ARMS patients will also be given a £10 voucher as a thank you for their time at the 4, 8 and 12 month follow-up assessments.

Patient and public involvement

Public and patient involvement (PPI) played an important role in this study. This research idea was initially presented in February 2016 at a PPI event which gathered together people with lived experiences of psychosis, their carers, clinicians, academics, commissioners, and service providers. Further on, this idea was presented at the Hearing Voices Network, a support group for people who hear voices and their families.

Service users have given important feedback on the research questions, recruitment strategies, and the measures used in this study. PPI will continue to be a key component of the feasibility study. In particular, we anticipate that the PPI group will: (i) ensure that the views of patients who have had a psychotic illness are heard at every stage of the study; (ii) inform any developments of the intervention to make sure these are acceptable to the target population, (iii) ensure patient documentation is easy to understand to maximise response and retention rates; and (iv) help interpret and disseminate study findings among patients and the public. PPI involvement will also benefit this research by ensuring that the study's protocol meets the needs and expectations of individuals at high risk of, or with psychosis.

Dissemination policy

The results of this study will be disseminated through publications and conferences. Findings from this feasibility trial will be published in psychiatry journals compliant with NIHR Open Access policy. The results of this trial will also be presented at relevant conferences such as the Royal College of Psychiatrists International Congress, the UK Psychological Trauma Society Conference and the IEPA Early Intervention in Mental Health Annual Conference.

The findings of the protocol will also be presented to clinical staff at one of the quarterly Early Intervention Services Network meetings, and to the Trauma Clinical Network and the Psychological Therapies Service within AWP NHS Trust. The results of this trial will also be presented at the Bristol Health Partners Psychosis Health Integration Team annual meeting, which is attended by people who experience psychosis and their families, academics, mental health professionals, commissioners and service providers. Findings will also be presented to relevant Clinical Commissioning Groups.

The PPI group will assist with disseminating findings to their own contacts including the Early Intervention Service users group, and the Hearing Voices Network. Findings will also be sent

to patients and therapist who took part in the study.

Appendix

Schedule of events

Activity/Event	Completed by	Baseline	4 month follow-up	8 month follow-up	12 month follow-up
Screening for ARMS	Clinician				
Eligibility Assessment	R or CRN				
Informed Consent	R or CRN	√			
Demographics	P	√			
The Life-Events Checklist	P	√			
The Childhood Trauma Questionnaire	P	√			
CAPE-42	P	√	√	√	√
CAARMS	Clinician or R or CRN	√	√	√	√
PANSS	R or CRN	√	√	√	√
PSYRAT	R or CRN	√	√	√	√
PCL-5	P	√	√	√	√
PHQ-9	P	√	√	√	√
GAD-7	P	√	√	√	√
WSAS	P	√	√	√	√
EQ-5D-5L	P	√	√	√	√
Medication use	P	√	√	√	√
Qualitative Interviews with patients who took part in the interventional part of the study	R		√		
Additional qualitative interviews with GPs, clinicians, ARMS patients and researchers	R	√			
Adverse events	P, R, CRN		√	√	√

C = Clinicians; R = Researcher; CRN=Clinical Research Network; P=Participant

References

Addington, J., Epstein, I., Liu, L., French, P., Boydell, K. M., & Zipursky, R. B. (2011). A randomized controlled trial of cognitive behavioral therapy for individuals at clinical high risk of psychosis. *Schizophr Res, 125*(1), 54-61. doi:10.1016/j.schres.2010.10.015

Barnes, M., Sherlock, S., Thomas, L., Kessler, D., Kuyken, W., Owen-Smith, A., . . . Turner, K. (2013). No pain, no gain: depressed clients' experiences of cognitive behavioural therapy. *Br J Clin Psychol, 52*(4), 347-364. doi:10.1111/bjc.12021

Barnes, M., Wiles, N., Morrison, J., Kessler, D., Williams, C., Kuyken, W., . . . Turner, K. (2012). Exploring patients' reasons for declining contact in a cognitive behavioural therapy randomised controlled trial in primary care. *Br J Gen Pract, 62*(598), e371-377. doi:10.3399/bjgp12X641492

Benish, S. G., Imel, Z. E., & Wampold, B. E. (2008). The relative efficacy of bona fide psychotherapies for treating post-traumatic stress disorder: a meta-analysis of direct comparisons. *Clin Psychol Rev, 28*(5), 746-758. doi:10.1016/j.cpr.2007.10.005

Bernstein, D. P., & Fink, L. (1998). *Childhood Trauma Questionnaire: A retrospective self-report manual*. San Antonio: TX: The Psychological Corporation.

Bisson, J., & Andrew, M. (2007). Psychological treatment of post-traumatic stress disorder (PTSD). *Cochrane Database Syst Rev*(3), Cd003388. doi:10.1002/14651858.CD003388.pub3

Bovin, M. J., Marx, B. P., Weathers, F. W., Gallagher, M. W., Rodriguez, P., Schnurr, P. P., & Keane, T. M. (2016). Psychometric properties of the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (PCL-5) in veterans. *Psychol Assess, 28*(11), 1379-1391. doi:10.1037/pas0000254

Chen, L., Zhang, G., Hu, M., & Liang, X. (2015). Eye movement desensitization and reprocessing versus cognitive-behavioral therapy for adult posttraumatic stress disorder: systematic review and meta-analysis. *J Nerv Ment Dis, 203*(6), 443-451. doi:10.1097/NMD.0000000000000306

de Bont, P. A., van den Berg, D. P., van der Vleugel, B. M., de Roos, C., de Jongh, A., van der Gaag, M., & van Minnen, A. M. (2016). Prolonged exposure and EMDR for PTSD v. a PTSD waiting-list condition: effects on symptoms of psychosis, depression and social functioning in patients with chronic psychotic disorders. *Psychol Med, 46*(11), 2411-2421. doi:10.1017/S0033291716001094

Fusar-Poli, P., Bonoldi, I., Yung, A. R., Borgwardt, S., Kempton, M. J., Valmaggia, L., . . . McGuire, P. (2012). Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch Gen Psychiatry, 69*(3), 220-229. doi:10.1001/archgenpsychiatry.2011.1472

Geddes, G., Ehlers, A., & Freeman, D. (2016). Hallucinations in the months after a trauma: An investigation of the role of cognitive processing of a physical assault in the occurrence of hallucinatory experiences. *Psychiatry Res, 246*, 601-605. doi:10.1016/j.psychres.2016.10.081

Gray, M. J., Litz, B. T., Hsu, J. L., & Lombardo, T. W. (2004). Psychometric properties of the life events checklist. *Assessment, 11*(4), 330-341. doi:10.1177/1073191104269954

Grubaugh, A. L., Zinzow, H. M., Paul, L., Egede, L. E., & Frueh, B. C. (2011). Trauma exposure and posttraumatic stress disorder in adults with severe mental illness: a critical review. *Clin Psychol Rev, 31*(6), 883-899. doi:10.1016/j.cpr.2011.04.003

Haddock, G., McCarron, J., Tarrier, N., & Faragher, E. B. (1999). Scales to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales (PSYRATS). *Psychol Med, 29*(4), 879-889.

Hafner, H., Maurer, K., Loffler, W., an der Heiden, W., Munk-Jorgensen, P., Hambrecht, M., & Riecher-Rossler, A. (1998). The ABC Schizophrenia Study: a preliminary overview of the results. *Soc Psychiatry Psychiatr Epidemiol, 33*(8), 380-386.

Hafner, H., Maurer, K., Loffler, W., & Riecher-Rossler, A. (1993). The influence of age and sex on the onset and early course of schizophrenia. *Br J Psychiatry, 162*, 80-86.

Hardy, A. (2017). Pathways from Trauma to Psychotic Experiences: A Theoretically Informed Model of Posttraumatic Stress in Psychosis. *Front Psychol, 8*, 697. doi:10.3389/fpsyg.2017.00697

Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., . . . Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res, 20*(10), 1727-1736. doi:10.1007/s11136-011-9903-x

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull, 13*(2), 261-276.

Kirkbride, J. B., Errazuriz, A., Croudace, T. J., Morgan, C., Jackson, D., Boydell, J., . . . Jones, P. B. (2012). Incidence of schizophrenia and other psychoses in England, 1950-2009: a systematic review and meta-analyses. *PLoS One, 7*(3), e31660. doi:10.1371/journal.pone.0031660

Kraan, T., Velthorst, E., Smit, F., de Haan, L., & van der Gaag, M. (2015). Trauma and recent life events in individuals at ultra high risk for psychosis: review and meta-analysis. *Schizophr Res, 161*(2-3), 143-149. doi:10.1016/j.schres.2014.11.026

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med, 16*(9), 606-613.

Matheson, S. L., Shepherd, A. M., Pinchbeck, R. M., Laurens, K. R., & Carr, V. J. (2013). Childhood adversity in schizophrenia: a systematic meta-analysis. *Psychol Med, 43*(2), 225-238. doi:10.1017/S0033291712000785

McCarthy-Jones, S., Trauer, T., Mackinnon, A., Sims, E., Thomas, N., & Copolov, D. L. (2014). A new phenomenological survey of auditory hallucinations: evidence for subtypes and implications for theory and practice. *Schizophr Bull, 40*(1), 231-235. doi:10.1093/schbul/sbs156

Morrison, A. P., Frame, L., & Larkin, W. (2003). Relationships between trauma and psychosis: a review and integration. *Br J Clin Psychol, 42*(Pt 4), 331-353. doi:10.1348/014466503322528892

Mundt, J. C., Marks, I. M., Shear, M. K., & Greist, J. H. (2002). The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *Br J Psychiatry, 180*, 461-464.

National Institute for Health and Care Excellence. (2005). Post-traumatic stress disorder: management. Retrieved from https://www.nice.org.uk/guidance/cg26

National Institute for Health and Care Excellence. (2014). Psychosis and schizophrenia in adults: prevention and management. Retrieved from https://www.nice.org.uk/guidance/cg178/chapter/1-recommendations#preventing-psychosis-2

RCPsych. (2014). Report of the Second Round of the National Audit of Schizophrenia (NAST). Retrieved from http://www.rcpsych.ac.uk/workinpsychiatry/qualityimprovement/nationalclinicalaudits/nationalschizophreniaaudit/reports.aspx

Saha, S., Chant, D., & McGrath, J. (2007). A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry, 64*(10), 1123-1131. doi:10.1001/archpsyc.64.10.1123

Seidler, G. H., & Wagner, F. E. (2006). Comparing the efficacy of EMDR and trauma-focused cognitive-behavioral therapy in the treatment of PTSD: a meta-analytic study. *Psychological Medicine, 36*(11). doi:10.1017/s0033291706007963

Skinner, H. A. (1982). The drug abuse screening test. *Addict Behav, 7*(4), 363-371.

Spitzer, R. L., Kroenke, K., Williams, J. B., & Lowe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med, 166*(10), 1092-1097. doi:10.1001/archinte.166.10.1092

Stafford, M. R., Jackson, H., Mayo-Wilson, E., Morrison, A. P., & Kendall, T. (2013). Early interventions to prevent psychosis: systematic review and meta-analysis. *BMJ, 346*, f185. doi:10.1136/bmj.f185

Steel, C. (2015). Hallucinations as a trauma-based memory: implications for psychological interventions. *Front Psychol, 6*, 1262. doi:10.3389/fpsyg.2015.01262

Stefanis, N. C., Hanssen, M., Smirnis, N. K., Avramopoulos, D. A., Evdokimidis, I. K., Stefanis, C. N., . . . Van Os, J. (2002). Evidence that three dimensions of psychosis have a distribution in the general population. *Psychol Med, 32*(2), 347-358.

Teare, M. D., Dimairo, M., Shephard, N., Hayman, A., Whitehead, A., & Walters, S. J. (2014). Sample size requirements to estimate key design parameters from external pilot randomised controlled trials: a simulation study. *Trials, 15*, 264. doi:10.1186/1745-6215-15-264

Watts, B. V., Schnurr, P. P., Mayo, L., Young-Xu, Y., Weeks, W. B., & Friedman, M. J. (2013). Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. *J Clin Psychiatry, 74*(6), e541-550. doi:10.4088/JCP.12r08225

World Health Organization. (2017). Schizophrenia. Retrieved from http://www.who.int/mental_health/management/schizophrenia/en/

Yung, A. R. (2007). Identification and treatment of the prodromal phase of psychotic disorders: perspectives from the PACE Clinic. *Early Intervention in Psychiatry, 1*(3), 224-235. doi:10.1111/j.1751-7893.2007.00033.x

Yung, A. R., Yuen, H. P., McGorry, P. D., Phillips, L. J., Kelly, D., Dell'Olio, M., . . . Buckby, J. (2005). Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Aust N Z J Psychiatry, 39*(11-12), 964-971. doi:10.1080/j.1440-1614.2005.01714.x

Zammit, S., Lewis, C., Dawson, S., Colley, H., McCann, H., Piekarski, A., . . . Bisson, J. (in press). Systematic review of undetected post-traumatic stress disorder in secondary care mental health services. *The British Journal of Psychiatry*.