***The SlowMo trial is supported by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership.***

# 1. PROTOCOL FULL TITLE: A randomised controlled trial to evaluate the outcomes and mechanisms of a novel digital reasoning intervention for persecutory delusions.

## Protocol Short Title/ Acronym:

SlowMo trial: a digital therapy for people who fear harm from others.

### Trial Identifiers

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| **ISRCTN:** | 32448671 | | |
| **REC Number:** | REC Reference: 16/LO/1862; IRAS: 206680. | | |
| **UKCRN Number:** | **CPMS ID: 32154** | | |
| **Protocol Version Number:** | 1.1 | Date: | 13/03/2017 |

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## 2. Study Synopsis

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| **TITLE OF CLINICAL TRIAL:** | A RANDOMISED CONTROLLED TRIAL TO EVALUATE THE OUTCOMES AND MECHANISMS OF A NOVEL DIGITAL REASONING INTERVENTION FOR PERSECUTORY DELUSIONS. |
| **Protocol Short Title/ Acronym:** | SlowMo trial: a digital therapy for people who fear harm from others. |
| **Study Phase If Not Mentioned In Title:** | This is a late phase II/early phase III trial. |
| **Sponsor Name:** | Kings College London (Co-Sponsor: South London and Maudsley NHS Foundation Trust) |
| **Chief Investigator:** | Professor Philippa Garety |
| **UKCRN Number:** | CPMS ID: 32154 |
| **REC Number:** | REC Reference: 16/LO/1862 |
| **Medical Condition Or Disease Under Investigation:** | Psychosis (specifically paranoia/ fears about harm from others) |
| **Purpose Of Clinical Trial:** | We aim to test the clinical efficacy of SlowMo, our new therapy, and determine the mechanism through which it reduces paranoia severity, over 24 weeks, and to identify participant characteristics that moderate its effectiveness (either by moderating the degree of change in the mechanism, or by influencing adherence to the intervention). |
| **Primary Objective:** | The main research questions are as follows:<br>1. Is SlowMo efficacious in reducing paranoia severity over 24 weeks, when added to treatment as usual (TAU), in comparison to TAU alone?<br>2. Does SlowMo reduce paranoia severity by improving fast thinking (reducing belief inflexibility and jumping to conclusions)?<br>3. Do participant characteristics (i.e. their cognitive capacities, specifically working memory and thinking habits; and their symptoms, specifically negative symptoms) moderate the effects of the intervention?<br>4. Does outcome differ by adherence to the intervention and is adherence predicted by the participants' beliefs about their illness and about the intervention?<br>5. Does the SlowMo digital therapy platform have acceptable rates of usability, acceptability and adherence? |

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| | 6. Does SlowMo reduce worry? |
| **Secondary Objective(s):** | N/A |
| **Trial Design:** | A parallel-group randomised controlled trial, with 1:1 allocation and blinded assessors, to test the efficacy of the SlowMo intervention in reducing paranoia severity when added to standardised Treatment As Usual (TAU). |
| **Endpoints:** | Assessments will be made at baseline, after treatment at 12 weeks, and at 24-week follow-up. Trial aims to commence in January 2017 and will proceed for a total of 31 months. |
| **Sample Size:** | 360 people (2 groups):<br>Intervention (SlowMo) plus Treatment as Usual (TAU); n=180<br>TAU only; n=180 |
| **Summary Of Eligibility Criteria:** | Inclusion criteria: aged 18 years and over, persistent (3+ months) distressing paranoia (as assessed using clinical interview (SCAN) and score >29 on Green Paranoid Thoughts Scale (GPTS; Green et al., 2008), Part B persecutory subscale), diagnosis of schizophrenia-spectrum psychosis (F20-29, ICD 10: Present State Examination, version 10), capacity to provide informed consent, sufficient grasp of English to participate in informed consent process, assessments and interventions.<br>Exclusion criteria: Profound visual and/ or hearing impairment; inability to engage in the assessment procedure; currently in receipt of psychological therapy for paranoia; primary diagnosis of substance abuse disorder, personality disorder, organic syndrome or learning disability. |
| **Intervention (Description, frequency, details of delivery)** | SlowMo consists of eight individual, face-to-face sessions (delivered weekly on average), delivered by trained therapists, and assisted by a website with interactive stories and games. SlowMo supports people to find out how fast thinking habits can contribute to upsetting thoughts, and try out tips to learn what helps them slow down their thinking and cope with worries. Personalised session content is synchronised with a mobile app to support people to make use of strategies learnt in their daily life. |
| **Comparator Intervention:** | Treatment as usual (TAU) only:<br>N.B All participants will receive TAU. We define usual care with reference to best practice guidance, specifically NICE guidance on community mental health treatment for people with psychosis and the standards of community care required by the Care Quality Commission. Participation will not alter normal treatment decisions about medication and additional psychosocial interventions which remain the responsibility of the clinical team. |
| **Maximum Duration Of Treatment Of A Subject:** | Time taken to complete the 8 sessions- typically period between randomisation and 12-week follow up. |

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| **Version And Date Of Final Protocol:** | Version 1.1; 13/3/2017 |
| **Version And Date Of Protocol Amendments:** | Version 1.0; 26/09/2016- Amended on 13/3/2017 (Version 1.1) |

# 3. Revision History

| Document ID - (Document Title) revision X.Y | Description of changes from previous revision | Effective Date |
|---|---|---|
| Version 1.0; 26/09/2016- Amended on 13/3/2017 | Inclusion criteria added (18 years old and use of SCAN). Further detail on screening and stratification by paranoia severity. Time-points specified on Table 1 (previously missing.) | 13/3/2017 |
| | | |

# 4. Protocol Contents

# 5. Background & Rationale

*'Every day, I think they are following me and am terrified that they will kill me.'*

'Ben' believes he is in danger. When someone looks at him in the street he decides he is under attack. He rushes home and avoids going out. People often experience distressing fears about other people intentionally causing harm, which is also known as paranoia (Freeman et al., 2005). Paranoia severity lies on a continuum, and can range from fleeting ideas that someone on the street might be laughing at us, to more elaborate and persistent beliefs (sometimes called persecutory delusions) such as that the secret services are trying to have us killed. Paranoia is one of the most common symptoms of schizophrenia-spectrum disorders and is associated with significant distress and disruption to the person's life. This results in increased use of services, including inpatient admissions and high costs to mental health care providers. Developing effective interventions for paranoia is therefore a clinical priority. NICE (2014) recommend cognitive-behavioural therapy for psychosis (CBTp), including paranoia. However, there are significant challenges to access, engagement, adherence and effectiveness (Freeman et al., 2013; Haddock et al., 2013). CBTp has relatively high training and delivery costs, which limits access, and even when available, people can struggle to understand, remember and apply strategies learnt during therapy. Recent meta-analytical studies of CBTp have found small- to medium-sized beneficial effects on paranoia, and a pressing target of research is therefore to improve outcomes (van der Gaag et al., 2014). Our new therapy, SlowMo aims to address these identified challenges, specifically in terms of improving the appeal, ease of use and clinical effectiveness for people who fear harm from others.

Our research group has adopted an interventionist causal approach to improving therapy effectiveness, which involves developing tailored interventions to target the specific mechanisms that research has shown to play a causal role in paranoia. These mechanisms include thinking habits, worry processes, negative self-beliefs, safety behaviours, and sleep dysfunction (Freeman, 2016). Interventions targeting each of these mechanisms are all anticipated to reduce paranoia severity, albeit it through different pathways, given the multifactorial causality of paranoia. For example, a recent randomised controlled trial of a brief intervention focused on worry processes demonstrated that reductions in this mechanism accounted for improvements in paranoia (Freeman et al, 2015). In contrast, SlowMo works by targeting a certain type of thinking habit, which can be considered *fast thinking* (Garety et al., 2015; Kahneman, 2011). Fast thinking is characterised by focusing on too little information ('jumping to conclusions') and belief inflexibility (high conviction in thoughts and a lack of consideration of alternative ideas), and has been robustly associated with paranoia (Garety et al, 2014; Dudley et al., 2015; McLean et al., 2016; So et al., 2012). When Ben feels in danger, he is sure of what is happening based on his instincts, does not look for more information or consider other possible ideas. SlowMo aims to help people like Ben by supporting them to notice their upsetting worries and fast thinking habits, and then provides tips to help them *slow down for a moment* to focus on new information and develop safer thoughts.

We have iteratively developed SlowMo over the past 10 years, and now have sufficient proof-of-concept, feasibility and acceptability evidence from four preliminary studies to test the intervention in a randomised controlled trial (Ross et al., 2009; Waller et al., 2011; Garety et al., 2014; Waller et al. 2015). In three randomised studies and one case series, we found that reductions in unhelpful fast thinking account for improvements in paranoia severity, and that the intervention is highly acceptable. Our pilot data indicate very promising large effects on paranoia severity.

SlowMo has been developed from a user-centred inclusive design approach, to address the challenges to therapy engagement and adherence for people with severe mental health problems.

It consists of an easy to use and enjoyable digital interface, thereby harnessing the potential of technology for improving health-related outcomes and reducing costs, in line with the 'NHS Five Year Forward View' (Hollis et al, 2015; NHS England, 2014). Thoughts are visualised as bubbles, with different speeds, sizes and colours, to reflect different thinking habits, levels of distress and coping tips. This simple metaphor makes it easier for people to understand thoughts are transient, and that by using coping strategies we can modify them. An interactive digital interface assists the delivery of face-to-face sessions, which are synchronised with a mobile app for use in daily life. Our design approach was informed by the Design Council's (2005) double diamond method consisting of discover, define, develop and deliver phases. As an inclusive design project, stakeholders (service users, clinicians and researchers) were involved from the outset, with iterative interviews, observation of therapy sessions, and system mapping of service contexts. This led to the development of a design brief, followed by iterative concept generation and prototype testing with service users. Feasibility testing of SlowMo has been extremely positive, with people indicating they significantly prefer the digital interface to conventional therapy materials.

Given its established evidence base and comprehensive user-centred design, SlowMo is expected to be highly acceptable and to lead to clinically worthwhile gains, reducing paranoia distress, conviction and preoccupation, enhancing wellbeing, and improving quality of life. It is anticipated to reduce service use, including inpatient admissions for the duration of the trial assessment period. The data from this study will also add significantly to our understanding of psychological mechanisms and change processes in paranoia. We will test our hypothesis that changes in fast thinking mediate changes in paranoia severity. In line with our interventionist causal approach, worry is not hypothesised to be a mediator as it is not targeted in the SlowMo intervention, but any observed effects will be explored. As well as providing valuable information for treatment development, evidence of mechanisms of action will inform the theoretical understanding of paranoia in a way that may itself shape future therapeutic initiatives. In addition, we have preliminary evidence of modifiers of treatment effects that we will investigate further. We will examine whether characteristics of participants (including working memory and negative symptoms) moderate the effects of the intervention on fast thinking, and also the effect on treatment of receipt of an adequate dose of treatment and therapy adherence. Finally, the trial will be the first to examine the usability and adherence of digital therapies in a large sample of people affected by severe mental health difficulties. The findings therefore have the potential to inform future stratified medicine approaches, and the development of more targeted therapies.

# 6. Trial Objectives and Design

## *6.1 Trial Objectives*

### Aims

We aim to test the clinical efficacy of SlowMo and determine the mechanism through which it reduces paranoia severity, over 24 weeks, and to identify participant characteristics that moderate its effectiveness (either by moderating the degree of change in the mechanism, or by influencing adherence to the intervention).

The main research questions are as follows:

1. Is SlowMo efficacious in reducing paranoia severity over 24 weeks, when added to treatment as usual (TAU), in comparison to TAU alone?
2. Does SlowMo reduce paranoia severity by improving fast thinking (reducing belief inflexibility and jumping to conclusions)?
3. Do participant characteristics (i.e. their cognitive capacities, specifically working memory and thinking habits; and their symptoms, specifically negative symptoms) moderate the effects of the intervention?

4. Does outcome differ by adherence to the intervention and is adherence predicted by the participants' beliefs about their illness and about the intervention?
5. Does the SlowMo digital therapy platform have acceptable rates of usability, acceptability and adherence?
6. Does SlowMo reduce worry?

**Hypotheses**

Primary hypotheses:

1. The intervention will reduce paranoia severity over 24 weeks.
2. Fast thinking (belief inflexibility and jumping to conclusions) will improve in response to the intervention.
3. Reductions in fast thinking will mediate positive change in paranoia severity.

Secondary hypotheses:

4. Poorer working memory and more severe negative symptoms will negatively moderate treatment effects.
5. Therapy adherence will moderate the effects of treatment on outcome and adherence will be predicted by beliefs about mental health problems.
6. Worry will not mediate reductions in paranoia severity

### *6.2 Follow-ups/ endpoints*

Outcomes will be assessed over 24 weeks (first follow-up occurs at 12 weeks).

### *6.3 Trial Design*

***Design:*** A parallel-group randomised controlled trial, with 1:1 allocation and blinded assessors, to test the efficacy of the SlowMo intervention in reducing paranoia severity when added to standardised Treatment As Usual (TAU). Independent randomisation (King's Clinical Trials Unit) will use randomly varying permuted blocks, stratified by site and baseline paranoia severity. Stratification by paranoia severity will be based on a split into above/ below 62 of the screening GPTS: Part B (Green et al., 2008) - this value is based on data from a recent trial targeting worry in paranoia (Freeman et al., 2015). Research workers will be blind to therapy allocation, to facilitate completion of unbiased and objective assessments. Adherence to the blindness procedure will be supported by the research co-ordinator and therapists having responsibility for the randomisation process, and informing participants of randomisation outcome. Further, the blinding procedure will be explained to participants and they will be reminded not to inform research workers of therapy allocation. Breaks in blinding will be monitored and recorded.

### *6.4 Trial Flowchart*

Please refer to Appendix 1 for trial/ recruitment flow-chart and Section 11.1 for details of assessment at each visit.

## 7. Trial Intervention

### *7.1 Therapy/Intervention Details*

***Intervention:*** SlowMo consists of eight individual, face-to-face sessions, delivered by trained therapists, assisted by a website with interactive stories and games (see Figure One for examples on the session content). SlowMo supports people to find out how fast thinking habits can contribute to upsetting thoughts, and try out tips to learn what helps them slow down their thinking and cope with worries. Personalised session content is synchronised with a mobile app to support people to make use of strategies learnt in their daily life (see Figure Two for examples of the app content). The first two sessions involve learning that worries about others and fast thinking are

common, and developing an individualised understanding of the person's thoughts and thinking habits. The concepts of 'thinking fast' and 'thinking slow' are introduced. It is explained that everyone thinks fast at times, and this can be helpful although at other times thinking fast can mean we feel worried when we do not need to be. Participants learn that thinking slow can be helpful in dealing with stress and worries about other people. This key principle frames the remaining 6 sessions where people are supported to find out about and try out tips to *slow down for a moment*, such as the impact of mood and past experiences on paranoia.

Figure One. Examples of the website content to support delivery of face-to-face sessions.

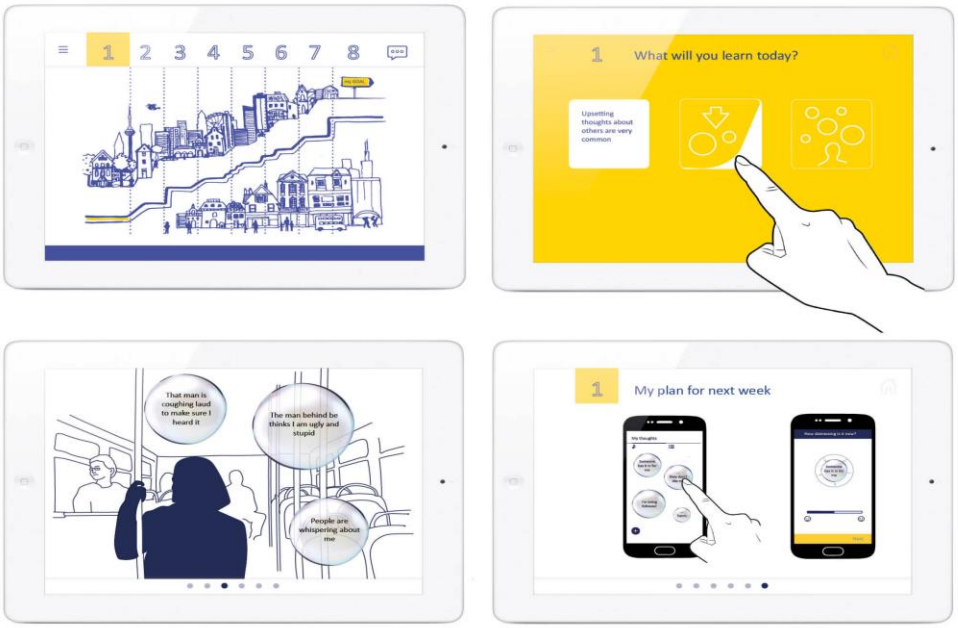



Figure Two. Examples of the app content to support self-management in daily life.


There is an emphasis throughout the intervention on practicing using the skills inside and outside of sessions. Participants build confidence in being able to manage paranoia, feeling safer in their daily life and working towards a valued goal. Security and privacy of information stored on the app has been considered throughout its development, with the functionality only allowing sharing of information with people's informed consent and no personally identifiable information being stored. If people agree, app usage can be synchronised with the digital platform and guides the subsequent sessions. The final session provides an opportunity for the participant to reflect on what has been learnt, progress made towards goals, and make plans for how they can continue to slow down their thinking and make use of coping tips in the future. The digital platform allows session-by-session monitoring of distress, conviction, preoccupation and general wellbeing which helps to monitor progress and tailor sessions according to participants' needs. Given the novelty of the digital platform therapy, usability and acceptability will be assessed through system analytics data on the use of the platform, a post-therapy assessment of participants' experience with a semi-structured interview and the User Experience Survey (adapted from Ben-Zeev et al, 2014) and a service-user led qualitative interview with a sub-sample of those receiving SlowMo (n = 20).

During the trial, therapy will be delivered by trained and experienced therapists, with expertise in working with this client group, who will attend peer supervision with the project team for the duration of the studies. The therapy will not interfere with the usual care offered through mental health services and no attempt to control the delivery of other services to either group will be made. The only exception to this will be if a person is currently receiving psychological interventions from another source, in which case we will liaise carefully with the participant and their therapist prior to randomisation to ensure that engagement in two psychological therapies is not overwhelming, confusing or unhelpful.

## *7.2 Frequency and duration of intervention*

PROCEDURE: RECRUITMENT, INFORMED CONSENT AND RESEARCH ASSESSMENTS

Potential participants will be identified by close liaison between research workers and staff in clinical teams. Potential participants will be screened for suitability to see if they meet the initial

eligibility criteria. Service users meeting these study criteria will be briefly introduced to the research by their clinician to see if they wish to give verbal consent to meet with the research worker and commence the remainder of the screening and informed consent process. Alternatively, potential participants may contact the researcher directly through responding to posters promoting the study displayed in community health team bases. If this is the case, the research worker will then complete the initial screen of the service user for suitability to participate, through discussion with the service user's clinician, before arranging to meet them to complete the screening process and commence the informed consent process. Potential participants will be given the opportunity to discuss the study and at least 24 hours to decide whether to participate. The research worker will also assess capacity to provide consent to participate. Throughout the recruitment and research process all efforts will be made to tailor to participants' needs and preferences.

Service users who consent to participate will then complete a range of self-report and interview based measures involving questions about paranoia severity, wellbeing, self-esteem, quality of life, service use, worry and mood. Assessments will be done at baseline, after treatment at 12 weeks, and at 24-week follow-up. These assessments will be administered by trained local research workers, who will be supervised by experienced research clinical psychologists. Assessments will be conducted at locations convenient for the participant (at either NHS, University or residential locations). The research worker will inform the research coordinator when the baseline assessments have been completed, and the participant will then be randomised to either the SlowMo intervention or Treatment as Usual (TAU). The research coordinator or research therapist will meet with the participant to inform them of the outcome of randomisation and remind them about not informing the research worker of the allocation during the follow-up assessments. Participants will meet with the research workers again at 12 and 24 weeks following randomisation to complete follow-up assessments.

FOR PARTICIPANTS RANDOMISED TO TAU ONLY:

N.B All participants (in both groups) will receive TAU.

We define usual care with reference to best practice guidance, specifically NICE guidance on community mental health treatment for people with psychosis and the standards of community care required by the Care Quality Commission. Participation will not alter usual treatment decisions about medication and additional psychosocial interventions which remain the responsibility of the clinical team.

FOR PARTICIPANTS RANDOMISED TO SLOWMO IN ADDITION TO TAU:

SlowMo consists of eight individual, face-to-face sessions, delivered by trained therapists, assisted by a website with interactive stories and games. It is anticipated that face-to-face sessions will mostly be conducted at a local community clinical team setting. However the intervention is portable and therefore location can be changed in line with participant preference.

## *7.3 Intervention records*

Assessments and therapy sessions will be audiotaped (after first establishing consent) to allow for assessment of adherence to the research protocol and assessment ratings. Relevant information concerning meetings with the project worker or therapist will be recorded in the participants' electronic notes system.

## *7.4 Subject Compliance.*

Compliance will be determined by the participants' attendance at sessions and by system analytic data on engagement with the digital intervention.

## *7.5 Study adherence*

Each session will be recorded and the following will be assessed:

1) Treatment adherence: sessions attended and system analytics data on website and app use.

2) Therapy adherence (including digital recording of in-session tasks and use of app for self-monitoring and exercises)

3) Therapist competence and fidelity to the manual.

### *7.6 Concomitant Medication*

Participation will not alter usual treatment decisions about medication and additional interventions which remain the responsibility of the clinical team.

## 8. Research environment

The three main University trial sites are the Institute of Psychiatry, Psychology and Neuroscience, (King's College London), Oxford University and Sussex University. Participants will be recruited from mental health services associated with each University site with similar procedures followed at each site: South London and Maudsley NHS Foundation Trust, Sussex Partnership NHS Foundation Trust, and Oxford Health NHS Foundation Trust. Two additional PICs have been identified per site to be used as required: Oxford site- Berkshire Healthcare NHS Foundation Trust and Northamptonshire Healthcare NHS Foundation Trust; London site-South West London and St George's and Oxleas NHS Trust; Sussex site- Surrey & Borders Partnership NHS Foundation Trust and Kent & Medway NHS & Social Care Partnership Trust. All measures and procedures, apart from therapy-specific assessments, will be administered by trained local research workers, who will be supervised by experienced research clinical psychologists. Assessments and therapy will be conducted at locations convenient for the participant (at either NHS, University or residential locations) and will be audiotaped to allow for reliability checks for adherence to the research protocol and assessment ratings. Please see Table One for an overview of the assessment battery.

## 9. Selection and Withdrawal of Subjects

### *9.1 Inclusion Criteria*

Aged 18 years and over, persistent (3+ months) distressing paranoia (as assessed using clinical interview (SCAN) and score >29 on Green Paranoid Thoughts Scale, (GPTS; Green et al., 2008), Part B; persecutory subscale)), diagnosis of schizophrenia-spectrum psychosis (F20-29, ICD 10: Present State Examination, version 10), capacity to provide informed consent, sufficient grasp of English to participate in informed consent process, assessments and interventions.

### *9.2 Exclusion Criteria*

Profound visual and/ or hearing impairment; inability to engage in the assessment procedure; currently in receipt of other psychological therapy for paranoia; primary diagnosis of substance abuse disorder, personality disorder, organic syndrome or learning disability.

### *9.3 Selection of Participants*

***Recruitment:*** Participants will be recruited from mental health services across three main trial sites with similar procedures followed at each site: South London and Maudsley NHS Foundation Trust, Sussex Partnership NHS Foundation Trust, and Oxford Health NHS Foundation Trust. Participants will be identified through close liaison with clinical staff. Clinicians will need to obtain verbal consent from potential participants to be contacted by a study research worker, but no further demands will be placed on their time. After clinical staff have confirmed that a potential participant is suitable to be approached (i.e. meets study criteria and no clinical contra−indications) Research Workers will meet each potential participant to discuss the study, provide written information, respond to questions and seek written informed consent.

Additional sources of recruitment:

1) Consent for Contact (C4C) provides access to existing research recruitment databases- e.g. South London and Maudsley (SLaM) Clinical Record Interactive Search (CRIS), an IT system which anonymises and provides authorised researchers with access to SLaM's 230,000 electronic health records. Sussex Partnership Trust is also currently setting up an opt-out system for consent to be contacted about research projects, scheduled to start in 2017, which should aid recruitment.

2) Patient Identification Centres (PIC) sites- two additional PICs have been identified per site to be used as required: Oxford site- Berkshire Healthcare NHS Foundation Trust and Northamptonshire Healthcare NHS Foundation Trust; London site-South West London and St George's and Oxleas NHS Trust; Sussex site- Surrey & Borders Partnership NHS Foundation Trust and Kent & Medway NHS & Social Care Partnership Trust.

3) Through direct patient approach: we intend to place recruitment posters in the main clinical areas of the specialist mental health teams. This will give details of the study. Although the poster asks participants to approach the research staff via their clinical team, we know from experience in the pilot that some will make a direct approach. Additional self-referrals are also possible as a result of interest generated through media/ public engagement events. In all such instances we will contact the relevant clinical team and discuss suitability for participation.

## *9.4 Randomisation Procedure / Code Break*

Independent randomisation (King's Clinical Trials Unit) will use randomly varying permuted blocks, stratified by site and baseline paranoia severity. Stratification by paranoia severity will be based on a split into above/ below 62 of the screening GPTS: Part B (Green et al., 2008) - this value is based on data from a recent trial targeting worry in paranoia (Freeman et al., 2015).

## *9.5 Withdrawal of Subjects*

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study in the event of clinical contra-indications. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of participants should be avoided. Should a participant decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a participant withdraw from therapy only, efforts will be made to continue to obtain follow-up data, with the permission of the patient.

## *9.6 Expected Duration of Trial.*

The participation of each person within the trial will be 6 months from assessment/ randomisation until the 24 week follow-up.

**Timescale**

The study will take 31 months in 4 stages (with an additional preparatory stage 6 months beforehand).

***Stage 0 Preparatory stage in the six months before start:*** Detailed Trial Protocol drafted; Ethics and all R&D approvals applied for and granted; digital intervention and app redesign completed by end of May 2016; identification of trust therapists; initiation of coordinator recruitment; initiation of research worker recruitment; preparation of participant recruitment; computers and digital equipment ordered.

*Milestone 1 Digital intervention and app re-design completed by end of May 2016*

***Stage 1 Months 1-3 Final set up:*** Staff recruitment completed and training completed, therapists trained and site-specific testing of digital platform completed. Participant recruitment initiated,

including publicity campaign, visits to participating teams. Trial management folder and all essential trial documentation created; protocol finalised. Staff will be in post (trial and site coordinators on day 1 and research workers by the end of month 2 (all staff recruitment having commenced in preparatory phase). Trial therapists (previously identified) will be in place from start and will be trained in the first two months.

*Milestone 2 Ethics and R&D approvals in place before start of month 1*

*Milestone 3 end month 3 Protocol submitted for publication.*

***Stage 2 Months 4-24 Participant recruitment and treatment delivery:*** Participant recruitment initiated, monitored and completed and treatment delivered without delay following randomisation. Data completion rates monitored. Participant recruitment (18 months: months 4-21) commences.

*Milestone 4 end month 4: participant recruitment commenced in three sites*

*Milestone 5 end of month 6 Statistical Analysis Plan completed*

*Milestone 6 end month 7: 72 participants recruited, min 20 in each site. If Milestone 6 target not met in any site, activate additional recruitment sites in neighbouring Trusts*

*Milestone 7 end month 13: 192 participants recruited; 90 commenced treatment. If Milestone 7 not met, activate additional recruitment sites*

*Milestone 8 end month 21: 360 recruited (End of recruitment)*

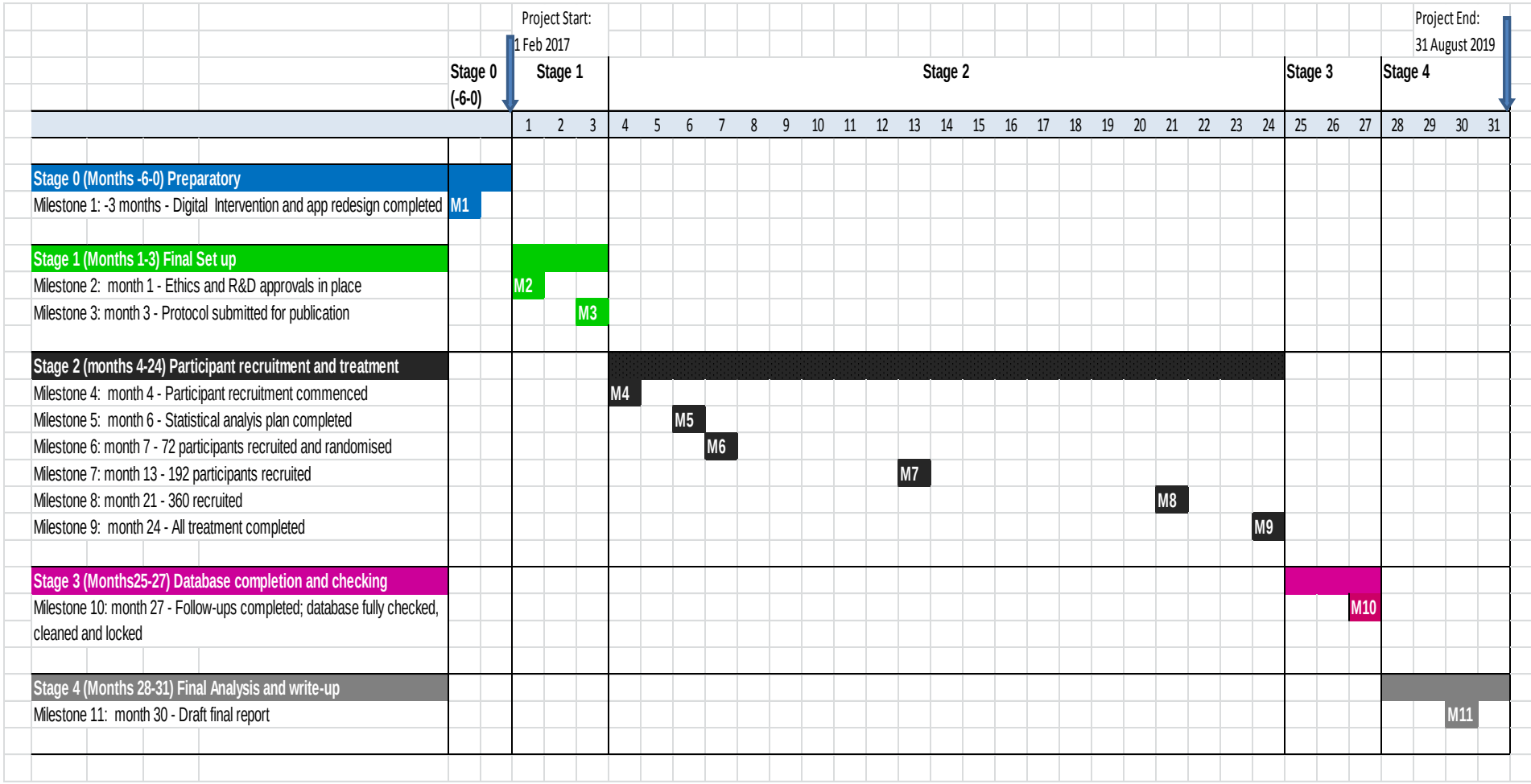
*Milestone 9 end of month 24 All treatment completed*

***Stage 3 Months 25-27 Database completion and checking:*** All follow-up data collected. All baseline, 12 week and 24 week data correctly entered, checked, cleaned and data base locked ready for analysis

*Milestone 10 end of month 27 All follow ups (24 weeks) completed; database fully checked, cleaned and locked.*

***Stage 4 Months 28-31 Final analysis and writing up.*** Data analysis, write up and initial dissemination. *Milestone 11 End of month 30 final report drafted.*

**Project Gantt Chart**:



# 10. Trial Procedures

## *10.1 By Visit*

Table One. Overview of assessment battery

| Measure type | Measure | Time-point* |
|---|---|---|
| Paranoia screening for eligibility and primary outcome | Green Paranoid Thoughts Scale (GPTS). Green et al. (2008). | Screening, 1, 2, 3 |
| Other paranoia outcome measures | The Psychotic Symptom Rating Scales (PSYRATS) – a dimensional measure of delusions. Haddock et al. (1999). Amended to include visual analogue scale ratings (0-100) of belief conviction, distress and preoccupation.<br>Persecutory delusions and ideas of reference items from Scales for Assessment of Positive Symptoms (SAPS). Andreasen (1984). | 1, 2, 3 |
| Fast thinking measures[1] | Maudsley Assessment of Delusional Beliefs (MADS): Possibility of Being Mistaken (PM). Wessely et al. (1993). | 1, 2, 3 |
| | Explanation for Experiences. Freeman et al. (2004). | 1, 2, 3 |
| | The Jumping to Conclusions Reasoning Test. Beads in ratios 60:40 and 85:15 Garety et al. (1991). | 1, 2, 3 |
| Other problems and processes | Scales for Assessment of Positive Symptoms (SAPS). Andreasen (1984). | 1 |
| | Brief Negative Symptom Scale (BNSS). Kilpatrick et al. (2011). | 1 |
| | Beliefs about Problems Questionnaire. Marcus et al. (2014). | 1 |
| | Letter Number Sequencing Test from the Wechsler Adult Intelligence Scale (WAIS). (Wechsler et al., 1997) | 1 |
| | Trail Making Task- A&B (Lezak 2004) | 1 |
| | TAPS (Thinking about Paranoia Scale); Hardy et al. (in prep) | 1, 2, 3 |
| | Penn State Worry Questionnaire (Meyer et al. 1990) | 1, 2, 3 |
| | Brief Core Schema Scales (BCSS). | 1, 2, 3 |

| | | |
|---|---|---|
| | Fowler et al. (2006). | |
| | Perception of carer criticism (adapted from Hooley et al., 1989) | 1 |
| | The Warwick-Edinburgh Mental Well-being Scale (WEMWBS). Tennant et al. (2006). | 1, 2, 3 |
| | Short Assessment of Quality of Life (MANSA, Priebe et al 1999) | 1, 2, 3 |
| | Client Service Receipt Inventory including medication, bed and crisis team days, contact with criminal justice system. Beecham (1995). | 1, 3 |

*Time-points: 1=baseline; 2=12 weeks; 3=24 weeks

### *10.2 Laboratory Tests*

N/A

## 11. Assessment of Efficacy

Participants will complete a range of self-report and interview based measures to assess the impact of the interventions on outcomes, the hypothesised mediators and other key processes implicated in paranoia and response to therapy (See Table 1 above for full details).

### *11.1 Primary outcome*

The primary outcome is change in paranoia severity over 24 weeks.

### *11.2 Secondary outcome*

Secondary outcomes include wellbeing, self-esteem, quality of life, service use, worry and standard mood and symptom assessments.

### *11.3 Procedures for Assessing Efficacy Parameters*

N/A

## 12. Assessment of Safety

### *12.1 Specification, Timing and Recording of Safety Parameters.*

Best practice, professional guideline and local NHS policies for monitoring mental state and risk will be followed throughout the participants' involvement in the trial and will be facilitated by close liaison with clinical teams.

### *12.2 Procedures for Recording and Reporting Adverse Events*

**Adverse Event (AE):** Any untoward medical occurrence in a subject to whom a therapy has been administered including occurrences which are not necessarily caused by or related to that therapy.

**Adverse Reaction (AR):** Any untoward and unintended response in a subject to a therapy which is related to any duration of therapy administered to that subject.

**Unexpected Adverse Reaction** (UAR): An adverse reaction the nature and severity of which is

not consistent with the information known about the therapy in question in the view of the investigator

**Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR)**: Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

- Results in death;
- Is life-threatening;
- Required hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect.

Reporting Responsibilities

All SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately by the Chief Investigator to the R&D office

***Safety and adverse event assessment and monitoring:*** It is an important subsidiary goal of the trial to establish the safety of the intervention, and we will also take all appropriate steps during the conduct of the trial for ensuring participant safety. The occurrence of adverse events (AEs) will be monitored actively and systematically, following guidance from the Consolidated Standards of Reporting Trials (CONSORT) with the extension for non-pharmacologic treatment, and the extension for reporting of harms. Medical Research Council Guidelines for Good Practice in Clinical Trials will also be followed to ensure good governance of the trial for integrity and participants' safety and wellbeing. AEs are defined as including deaths; self-harm; serious violent incidents; complaints about therapy; referrals to crisis care or admission to psychiatric hospital during therapy. A standard method of reporting will be employed, categorising events by severity (five grades, A-E). Investigators will also determine relatedness of an event to the intervention based on a temporal relationship, as well as whether the event is unexpected or unexplained given the participant's clinical course, previous conditions and history, and concomitant treatments, in five categories from 'not related' to 'related' (following Linden 2013). The following will be considered as serious adverse events (SAE, Categories A-C): All deaths (category A), incidents which acutely jeopardise the health or psychological wellbeing of the individual, resulting in immediate hospital admission and/or permanent disability (category B), or resulting in injury requiring immediate medical attention (category C). These SAEs will include but are not limited to: 1) Hospital admissions; 2) Home treatment team involvement; 3) Suicide attempts; 4) Any violent incident necessitating police involvement (whether victim or accused); 5) Self-harming behaviour; 6) All deaths.

Reasons for withdrawal from the study will also be recorded. Furthermore, in the event of any AEs and participant withdrawal, the trial coordinator/ site coordinators will review participant clinical notes and contact clinicians for any important additional information. In order to ensure active surveillance of harms, at each assessment point, research workers will actively check for the occurrence of specific AEs using a structured checklist. At the completion of the trial, all medical notes will additionally be checked, for the total duration of enrolment, for any previously undisclosed record of AEs. This is to ensure completeness of records and to address the possibility that the disclosure of adverse events might be greater in the active intervention condition, as a result of the therapeutic relationship. For the final reports of the trial, the numbers, types and severity of AEs by trial condition, as well as discontinuations, will be reported, using descriptive statistics (since there are no pre-specified hypotheses concerning adverse events or harms, and, given the expected low frequency of AEs, the data will not be suitable for an ITT statistical analysis).

All SAEs will be reported immediately to the Chief Investigator and Principal Investigators (for each site) and the independent chair of the Data Monitoring and Ethics Committee (DMEC). All AEs including complaints (from each site) will be pooled and reported monthly to the Trial Management Committee and at each meeting of the DMEC. All relevant protocols for reporting SAEs to the Research Ethics Committee, the research sponsor and the respective local NHS Trust will be followed. Urgent actions concerning participant and staff safety, communication with others, and clinical care will be immediately addressed by the Trial CI and PIs and reported to the Trial Management Committee. At each meeting of the DMEC, or at any time at the request of the DMEC Chair, a full report of AEs will be reviewed. The DMEC will be responsible for investigating further, if there are any concerns about unexpectedly high rates of AEs, which may include being unblinded as to trial condition or seeking further data on adverse events, and will advise the TSC on any ethical or safety reasons why the trial should be prematurely ended.

### *12.3 Adverse events that do not require reporting*

There are no AEs or SAES that do not require reporting for this trial.

### *12.4 Stopping Rules*

The trial may be prematurely discontinued by the Sponsor or Chief Investigator on the basis of new safety information or for other reasons given by the Data Monitoring & Ethics Committee / Trial Steering Committee regulatory authority or ethics committee concerned. The trial may also be prematurely discontinued due to lack of recruitment or upon advice from a Trial Steering Committee (if applicable), who will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

## 13. Statistics

Research workers will be blind to therapy allocation, to facilitate completion of unbiased and objective assessments. Adherence to the blindness procedure will be supported by the research co-ordinator and therapists having responsibility for the randomisation process, and informing participants of randomisation outcome. Further, the blinding procedure will be explained to participants and they will be reminded not to inform research workers of therapy allocation. Breaks in blinding will be monitored and recorded.

### *13.1 Sample Size*

Total n=360 (120 per site):

SlowMO plus TAU; n=180

TAU only; n=180

***Power calculation:*** Calculations used Clsampsi in Stata. A 10-point reduction in the primary outcome measure (GTPS) is clinically meaningful; based on a standard deviation of 25, this is a 0.4 effect size (Freeman et al, 2014). We account for: clustering in the SlowMo arm with an ICC=0.01 with 10 therapists (no clustering in the TAU arm), 1:1 allocation, 0.05 significance level. A simple two-tailed t-test with 150 people per group gives 90% power to detect an effect size of 0.4, and 80% for 0.35. In practice, power will be increased by using multiple regression. To allow for 20% attrition (conservatively high: our trials in this population had much lower rates: 5% Freeman et al, 2015; 4% Garety et al, 2008), we will recruit 360 patients at baseline split equally across 3 sites (120 per site, 60 per arm per site). While powering the study to detect moderate effect sizes, we anticipate larger effects: our sample is more homogeneous than in standard psychosis trials (being selected for one key problem: paranoia severity) with substantially less variance in the outcome variable and larger standardised effect sizes, giving increased power. For

mediational analyses, N= 300 has >80% power to detect a proportion mediated of 40%, and >70% power to detect a proportion mediated of 30%, corresponding to findings in pilot work (calculated using PowerMediation in R).

## *13.2 Randomisation*

Independent randomisation (King's Clinical Trials Unit) will use randomly varying permuted blocks, stratified by site and baseline paranoia severity.

## *13.3 Analysis*

### Analysis

Following CONSORT principles, we will report all participant flow and analyses will be conducted on the intention-to-treat (ITT) population: all participants randomised regardless of non-compliance with protocol or withdrawal from the study. Analyses will post-date final follow-up assessments, with due consideration of potential biases from loss to follow-up.

The primary analysis will test for a treatment effect on the primary and secondary clinical outcomes. Random effects regression models allowing for clustering by both participants and therapists will be fitted to the repeated measures, controlling for treatment site, baseline paranoia severity and the corresponding baseline assessment for the outcome under investigation. We will allow for missing outcome data under the Missing At Random assumption (Little and Rubin, 2002); we may also use inverse probability weighting to adjust for non-adherence to allocated treatment and other intermediate outcomes as predictors of future loss to follow-up (Dunn et al, 2005).

Secondary analyses will test treatment-effect mechanisms, moderation and process/adherence effects using modern causal inference methods (Emsley, Dunn & White, 2010, Dunn et al, 2015). The trial outcomes will comprise two parallel series of longitudinal data: one for the putative mediators (M) and one for the clinical outcomes (Y). For the mechanistic analysis, to test for a treatment effect on the putative mediator, we will replace the clinical outcome with the mechanistic variable as the dependent variable in the random effect models.

If we separately demonstrate a treatment effect on both the putative mediator and on the clinical outcome, we will evaluate mediation in these parallel longitudinal data sets through the use of parallel growth curve and latent change models (Cheong et al., 2003; MacKinnon, 2008). These models preserve the basic mediation model by replacing observed variables with latent constructs – the growth factors driving the temporal responses, $M_1$ to $M_p$ and $Y_1$ to $Y_p$. Importantly the mediational structure only applies to the slope growth or change factors since randomised treatments are independent of the intercept growth factors (baseline values). Growth curve and latent change models can be estimated by maximum likelihood and other methods using the software package Mplus (Muthén & Muthén, 1998-2016). The application of these methods to mechanism evaluation within EME trials is illustrated in Dunn et al (2015), Chapter 4.

The aim of these analyses is to demonstrate that the effect of treatment on the growth (change) in the clinical outcome (Y) is explained (caused) by its effect on the growth (change) in the mediator. The major challenge to a valid inference is that there may be confounding of the mediator and outcome. We will begin by allowing for baseline values of the mediator and of the clinical outcome, as in the analyses of the successful WIT EME trial (Freeman et al, 2015) and then check the sensitivity of the results to the possibility of hidden confounding (unmeasured variables) through the use of instrumental variable methods (Emsley et al, 2010; Dunn et al, 2015).

## 14. Trial Steering Committee

The Trial Steering Committee (TSC) will meet at least annually and will report to the EME Programme. Its purpose is to provide overall supervision of the trial, approving the protocol and amendments, monitoring adherence to the protocol and providing independent advice on all aspects of the trial. Prof Richard Bentall, an independent international expert in psychological treatment research will be nominated as the chair. The TSC will include two further independent clinical academics, a service user and the lead investigator. Observers from the EME Programme will be invited to all TSC meetings.

## 15. Data Monitoring Committee

A DMEC will be convened and will meet at least annually and report to the TSC. It will have access to all trial data and will receive regular reports on adverse events. Membership of the DMEC will be independent of the applicants and of the TSC. Prof Andrew Gumley, an independent international expert experienced in conducting clinical trials with this population will be nominated as chair and the group will also comprise an independent senior statistician and another independent senior clinician. The DMEC will be notified of any serious adverse events as they occur and will consider whether any interim analyses are warranted, review data and advise the TSC on any ethical or safety reasons why the trial should be prematurely ended.

## 16. Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits and REC review by providing the Sponsor(s), and REC direct access to source data and other documents as required.

## 17. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Mental Capacity Act 2005. This protocol and related documents will be submitted for review to Camberwell St Giles Research Ethics Committee (REC). The Chief Investigator will submit a final report at conclusion of the trial to the funder, the REC and the Sponsor.

## 18. Quality Assurance

The trial has been carefully designed to ensure compliance with Good Clinical Practice and scientific integrity. The research programme development, design and implementation will be managed by the Chief Investigator and the co-applicants, in consultation with service-user consultants and other expert research collaborators from within and outside of the Chief Investigator's institution. A dedicated Trial coordinator post will assist in the day-to day management of the project reporting to the Chief investigator, (CI). A trial management committee (TMC) will meet monthly, its membership will include the investigators and the Trial coordinator and site coordinators. It will be chaired by the CI and will manage the day–to-day running of the study and ensure good communication between trial sites, receiving monthly reports from each site on recruitment, therapy completion, adverse events, reviewing progress against milestones and finding solutions to problems as they arise. It will oversee the preparation of reports to the Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC). The Chief Investigator and the co-applicants are highly experienced in working clinically with service users with psychosis, and in carrying out research studies in this population.

# 19. Data Handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

Participant data will be anonymised.

- All anonymised data will be stored on a password-protected computer.
- All trial data will be stored in line with the Data Protection Act.
- and archived in line with Sponsor requirements

CONFIDENTIALITY/ DATA PROTECTION

Issues relating to confidentiality will be addressed and potential participants will be advised of the limits of confidentiality (i.e. that the researcher will have a duty to inform health professionals if the participant discloses information which highlights any safeguarding or risk issues). The potential participant will be given at least 24 hours to consider all the information provided before written consent can be obtained. Participants will provide informed consent to data being collected on the understanding that information will be confidential and stored in a secure manner (in a locked room in a locked filing cabinet) for the duration of the study, or for longer, only if specific consent has been sought and given for this. A numerical system will be used for computerised information so that individual participants will not be identifiable. After completion of questionnaires and collection of demographic and clinical data, the researcher will destroy information linking participants to their research numbers so that individuals cannot be identified from their data. Participant consent forms will be retained, kept confidential and stored securely. All data will be destroyed following a period of 7 years as determined by relevant information governance policies) after the completion of the trial. It is possible that disclosure of criminal or other acts potentially requiring action will occur during sessions. The research team will be trained in both local and national policies for dealing with such disclosures, and have access to supervisory input to ensure appropriate action is taken. The possibility of action arising from certain disclosures will be clearly noted in the information sheet for participants.

PRIVACY ISSUES RELATED TO MOBILE APPLICATION (‘APP’)

We appreciate that use of a mobile application raises potential privacy issues, which we have considered throughout the development phase and are of great importance in mobile healthcare. We have developed the platform in line with the British Standards Institute quality criteria and code of practice for healthcare apps (2015) and guidance from the National Information Board. We have established and are regularly reviewing our risk management strategy and propose setting up a risk register that would be monitored by the trial management committee and data monitoring and ethics committee. Measures to address privacy issues include the informed consent process, which will ensure potential participants are fully aware of what data are collected by the platform, and how data are stored and used. This information will also be available from the settings menu of the app, which consenting participants can access at any time. Second, all participants will have the opportunity, if they wish, to password protect the handset with a pin number or password. Third, the app does not store or transfer any personal identifiable information. Data transferred over internet transfer protocols will only contain a name (chosen by the person) and a Unique Device Identifier (UDID) which is generated automatically by the system, and will match the anonymised participant number. Any data transferred will also be secured by standard internet transfer protocol security layers. The welcome screen message does contain the participant’s chosen name, should they agree to this doing so, however this can also be left blank if they prefer. During this project, the app will run as an offline native app, and therefore will not be connected to any network. App data will be synched during therapy sessions, over secure connections and stored on a password protected, secure database. It is of

note that to date the app has been tested by service users with high levels of clinical paranoia, and all have wanted their name to be inputted onto the welcome screen.

AUDIO RECORDING

The study will adhere to the joint guidance on secure audio recording issued by King's College London and South London and Maudsley (SLaM). Assessment and therapy sessions will be recorded, with consent, using encrypted smart phone devices and data will be transferred to secure central storage as soon as possible. When not in use, devices will be stored in a locked cabinet within a locked office. Each device will be password protected. In the event of the device being lost or stolen this will be reported as a data incident to the Information Management and Compliance Team at King's College London and the Information Governance Team at SLaM. Any sensitive data on a lost/stolen device will be remotely erased.

# 20. Data Management

All data is anonymised at source. A log of contacts with participants including address and other contact details will be kept separate from all the research data. Details necessary to contact participants, and for communication with teams will be stored as above. Data will be shared through CRN, potentially with other researchers working under their auspices.

No patient identifiable information is recorded on the research assessment records and the computerised database is held centrally and managed by the KCL Clinical Trials Unit. Data from the assessments are entered into this central record by research assistants using a secure network connection. Audiorecording equipment will be used to record assessments to check fidelity to assessment protocols and allow for multiple ratings of assessments to ensure interrater reliability. The therapy sessions will be audio recorded (with participant consent) for monitoring the intervention in terms of fidelity and competence. These audio files named with a unique participant identifier will be stored as computer files on secure NHS/ University servers.

All personal data will be kept in a locked filing cabinet in a locked office at the three trial sites and will be accessible only by researchers. Therapy files will be kept in a secure office in the clinic and are not accessible to the staff collecting the research outcome data. Audio recordings of the therapy are stored as described above, are accessible to the patient's trial therapist and to the senior research clinician supervising that therapist.

# 21. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals and will be made available to participants and clinical teams in an accessible format.

# 22. Insurance / Indemnity

KCL insurance applies.

# 23. Financial Aspects

This trial is fully funded by the MRC/NIHR Efficacy and Mechanism Evaluation (EME) Programme.

# 24. Signatures

_____ 13.03.2017

Chief Investigator Date

*Print name:* Professor Philippa Garety

_____ _____

Statistician (if applicable) Date

*Print name*

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**Disclaimer:**
The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NHS, NIHR or the Department of Health.

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# 26. Appendixes

**Appendix 1: SlowMo Trial**
**Design and Recruitment Flowchart**