ExPRESS2 (Experiences of Psychosis Relapse: Early Subjective Signs) feasibility study

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Background

Around 80% of those treated for a first episode of psychosis relapse within five years, with cumulative relapse rates of 78% and 86% for second and third relapses during this period (Robinson et al, 1999). Relapses can be devastating for the individual and their family (Maclean, 2008; Appleby, 1992), may lead to a deteriorating course of illness (Wiersma et al, 1998) and frequently require hospital admission, the principal source of schizophrenia's annual direct cost to the NHS of over £3.9 billion (Mangalore & Knapp, 2007; Almond et al, 2004; Schizophrenia Commission, 2012). Given the prevalence and considerable negative consequences of relapse, it is clear that relapse prevention strategies for those with psychosis are a priority.

There is growing evidence that interventions monitoring 'early signs' can be effective in preventing relapses of psychosis (Herz et al, 2000; Lee et al, 2010; Gumley et al, 2003; Eisner et al, 2013). Such interventions work on the premise that timely prediction of relapses will allow preventative action to be taken, minimizing the chance of full relapse occurring (Birchwood, Spencer, & McGovern, 2000). The patient is assisted in identifying and monitoring early signs of relapse, and in developing concrete action plans for dealing with them (e.g. short term medication increases, stress reduction techniques, intensive psychological support). Early signs reported to emerge in the weeks before a relapse include: anxiety, dysphoria, insomnia, poor concentration, attenuated psychotic symptoms (Early Signs Scale [ESS]; Birchwood et al., 1989) and fear of relapse (Fear of Recurrence Scale [FoRSe]; Gumley et al, 2014). However, such checklists are only modestly predictive of relapse (Norman & Malla, 1995) so they could be improved by including more specific psychopathology (Eisner et al, 2013; Gumley et al, 2014).

Evidence suggests that 'basic symptoms' may be useful relapse indicators that could be added to checklists of conventional early warning signs to improve predictive power. Studies in individuals at high risk of psychosis have characterised basic symptoms as subtle, sub-clinical, qualitative disturbances in one's experience of oneself and the world which are predictive of transition to first episode psychosis (Schultze-Lutter et al, 2007; Fusar-Poli et al, 2012). Typical basic symptoms include: changes in perceptions, such as increased vividness of colour vision; mild subjective cognitive problems; impaired tolerance to certain stressors; subjective difficulty finding or understanding common words. Two retrospective studies examining service users' experiences in the run up to a recent relapse of psychosis provide preliminary evidence that basic symptoms occur prior to relapse (Bechdolf et al, 2002; Eisner et al, 2014; Eisner et al, in preparation).

Aims

The long term aim is to conduct a definitive study to prospectively investigate the predictive value of basic symptoms as early signs of psychosis relapse using a mobile phone application to monitor these within individuals' everyday lives. In line with the Medical Research Council guide for developing complex interventions (Craig et al, 2008) we will begin by conducting a feasibility study. This study has four phases (see Figure 1). In Phase 1 we will design a measure of basic symptoms, assessed via smart-phone, and adapt it as applicable following feedback from participants. Phase 2 begins with a screening interview to identify participants with at least one basic symptom; these individuals will be eligible for Phase 3 (since past basic symptoms are likely to predict future basic symptoms; Eisner et al, in preparation). Cross-sectional assessments will also be conducted in Phase 2; by comparing those with and without basic symptoms we will begin to characterise the sub-group of individuals with whom the basic symptom assessment can be used. In Phase 3 we will use a prospective, longitudinal design to investigate the feasibility of using a mobile phone application to regularly measure basic symptoms, conventional early signs and relapse over an extended period. Finally, in Phase 4, participants' experiences of using the phone application will be explored using qualitative interviews (acceptability). Detailed aims of Phases 1 to 4 are tabulated in Appendix A.

Design

The study design is summarised in Figure 1 and details of each phase, including justification of sample sizes, are given below.

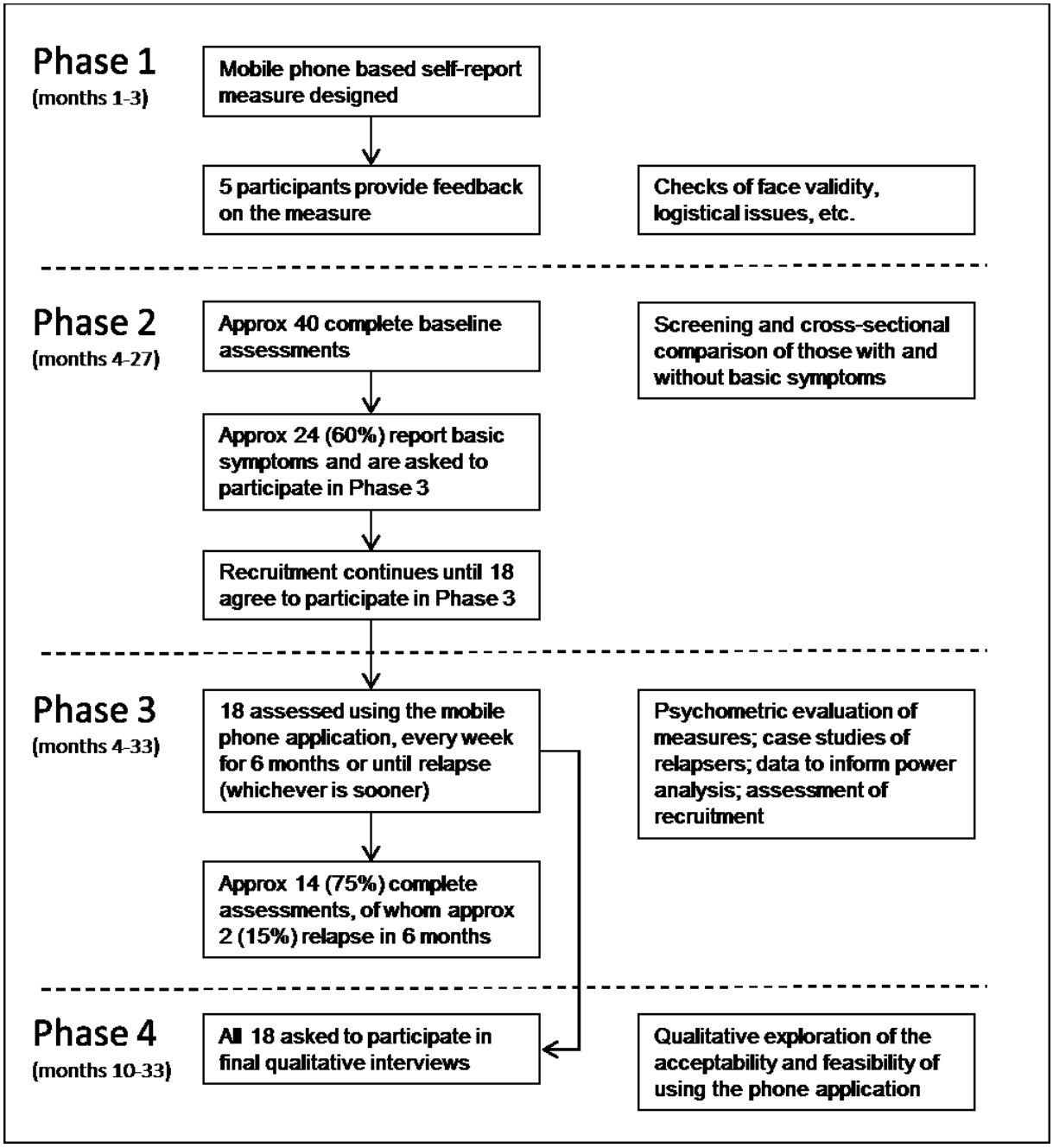

Figure 1: study design

Phase 1: Measure design

Aims

The aim of Phase 1 is to design a measure of basic symptoms that can be completed via a smart-phone app and to obtain feedback from initial participants in preparation for its use in Phase 3. Detailed aims are given in Appendix A.

Measure design

A self-report measure of basic symptoms will be designed, based on the SPI-A interview measure (Schizophrenia Proneness Index Adult version; Schultze-Lutter et al, 2007), information gathered during our previous qualitative study (Eisner et al, 2014; Eisner et al, in preparation) and Bechdolf and colleagues' (2002) study. The measure will be designed specifically to be completed via a mobile phone application (e.g. using brief questions; Ben-Zeev et al, 2013), using software adapted from an existing phone app used for the assessment of psychotic symptoms (ClinTouch; Palmier-Claus et al, 2012). Items will consist of descriptions of the basic symptom experience (e.g. "colours have seemed brighter than usual"), with participants asked to use a sliding bar analogue scale to report the extent to which they experienced the basic symptom in the past week. An example item, with an approximation of how it might appear on the phone screen is provided in Figure 2.

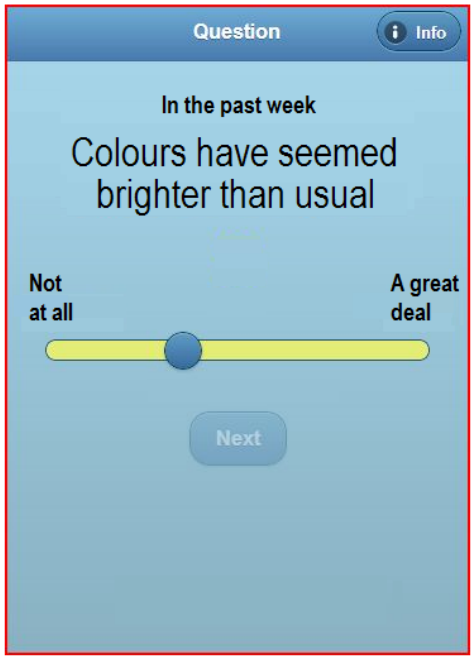

Figure 2: example phone app screenshot

A large pool of potential items will be designed but not all of these will be used by every individual; instead a sub-set of items relevant to the individual will be selected (using the SPI-A interview; see Phase 2) for ongoing monitoring. This will vary from participant to participant but is likely to be less than five per person. Descriptions of the proposed pool of items are given in Appendix B.

The newly designed measure will be used during Phase 3, along with relevant items from a phone app based version of the Early Signs Scale (Birchwood et al, 1989; see Appendix B), three items from the Fear of Recurrence Scale (Gumley et al, 2014) and five items from the PANSS (Kay et al, 1987; Palmier-Claus et al, 2012; see Appendix B). The software will automatically upload participants' responses to each of these measures to a secure server, maintained by the University of Manchester, where they will be accessible to the research team. Details regarding the security of this system are given under the heading *data protection and confidentiality* on page 17 of this protocol. The phone app is not classed as a medical device by the MHRA (2014) since it is analogous to a paper diary, being used purely to collect data rather than to make a diagnosis or prompt participants to seek help.

Participants and procedure

A small number of service users (n=5) with at least one previous episode of psychosis and experience of basic symptoms will be recruited from Mental Health Trusts in the North West of England. Following informed consent, participants will be interviewed using the SPI-A interview to identify any experiences of basic symptoms prior to previous psychosis episode(s). This is so that the researcher can personalise the questions they are asked on the app. They will then be asked to give initial feedback on the phone app based assessments. Among other things, they will be asked to check the basic symptom measure's face validity, whether there are any logistical problems with use of the application on their own or study-provided mobile phones and whether the number and wording of questions is suitable (see Appendix C for Phase 1 participant feedback form). The assessments will then be adapted as appropriate prior to their use for data collection during Phase 3. The participant information sheet and consent form for Phase 1 participants are given in Appendix D and Appendix E, respectively.

Phase 2: Screening and cross-sectional assessment

Aims

Phase 2 has three main aims:

- to inform future basic symptom screening by examining the feasibility and acceptability of using a sub-set of SPI-A screening questions and by determining which items to include in this;
- to examine the characteristics of those who do and do not report basic symptoms;
- to identify eligible participants for Phase 3 (namely, those with at least one basic symptom).

Detailed aims are given in Appendix A.

Inclusion and exclusion criteria

Between 35 and 45 service users will be recruited from Mental Health Trusts in the North West of England. To inform future studies, a log will be kept of the study recruitment rate and also the service type of service users who decline to take part.

Inclusion criteria are as follows: age over 18 years; current contact with mental health services; a current, primary clinical diagnosis of non-affective psychotic disorder (DSM-IV); at least one episode of acute psychosis in the past year (admission to crisis team or hospital; or exacerbation of psychotic symptoms lasting at least 2 weeks and leading to a change in management), or at least two episodes of psychosis in

the past 2 years, including index episode; currently prescribed antipsychotic medication; fluency in English; fixed abode (including a B&B or hostel); informed consent.

Exclusion criteria are as follows: not sufficiently stable to take part (unable to complete screening assessment); significant history of organic factors implicated in the aetiology of psychotic symptoms; current alcohol or drug dependence (SCID; First et al, 1997).

Recruitment and consent

Participants will be recruited from NHS mental health trusts in the North West of England. Clinical staff from acute inpatient units and community-based mental health teams (e.g. Community Mental Health Teams, Early Intervention Teams, Assertive Outreach Teams, Crisis Teams) will be given a verbal presentation and clinician leaflets (Appendix F) about the study. They will be asked to provide potentially eligible service users with initial information about the study, either verbally or using service user leaflets (Appendix G). If the service user consents, the clinician will pass on their contact details to the research team and provide the additional information needed to complete a risk assessment and to confirm eligibility.

Further information about the study will be provided by the researcher either face-to-face or by telephone, depending on individual preference. If the potential participant is interested in taking part, the researcher will provide a Participant Information Sheet (which covers Phases 2-4; see Appendix H) and arrange to meet them to discuss this. The meeting will be conducted at least 24 hours after the service user has received the Participant Information Sheet in order to give them time to decide whether or not to take part. During the meeting, the researcher will provide any further information required by the potential participant. If the potential participant wishes to take part in Phase 2 of the study they will be asked to give written consent (Appendix I).

In addition to recruitment directly from clinical teams, participants may be referred by other ethically approved studies (e.g. CareLoop, REC reference 14/WM/0045; Actissist, 14/WM/0118; ExPRESS study part 1, 12/NW/0091). In this case, the referring study will provide the potential participant with an ExPRESS study leaflet. If the potential participant gives permission, the referring study will pass on their contact details to the ExPRESS study researcher who will proceed as above.

Assessments

Once informed consent has been obtained, the Phase 2 assessments will be carried out. These assessments are a mixture of audio recorded interview based measures and self-report paper questionnaires (see Table 1 for details). Firstly, eligibility (DSM-IV diagnosis; absence of drug or alcohol dependence) will be confirmed using the MINI (Sheehan et al, 1998).

Having confirmed eligibility, basic symptom screening will be conducted. The subtle nature of basic symptoms means that an interview based measure (the SPI-A; Schultze-Lutter et al, 2007) is needed to *initially identify* which basic symptoms an individual has experienced. During this interview, participants will be asked whether they experienced the start or increase of any of the basic symptoms prior to their most recent relapse. Those reporting at least one such basic symptom will be eligible for Phase 3, during which

the self-report smart-phone based assessment designed in Phase 1 will be used to assess the relevant basic symptoms on a repeated measures basis. Similarly the full Early Signs Scale (ESS; Birchwood et al, 1989) will be used during Phase 2 to identify conventional early signs (e.g. sleep disturbance) that participants experienced prior to their most recent relapse; for those participating in Phase 3, the relevant sub-set of early signs will be monitored using a smart-phone based version of the ESS.

A number of other cross-sectional measures will be collected in Phase 2 (see Table 1). These assessments will be used to compare those who report basic symptoms with those who do not and will form the baseline measures for those who participate in Phase 3. The PANSS assessment will be used to assess level of insight (PANSS item G12) and whether the participant is currently in remission (remission can be defined using PANSS P1, P2, P3, N1, N4, N6, G5, G9; see Andreason et al, 2005) so that any relapses during follow-up can be defined as type 1 or type 2.

Table 1: Phase 2 assessments

To be measured	Measure	Reference	Format	Duration
DSM-IV diagnosis; drug or alcohol dependence	MINI	Sheehan et al, 1998	Interview	10 mins
Basic symptoms	SPI-A	Schultze-Lutter et al, 2007	Interview	30 mins
Early signs	ESS	Birchwood et al, 1989	Self-report	5 mins
Dissociation	DES-T	Waller et al, 1996	Self-report	5 mins
Symptoms	PANSS	Kay et al, 1987	Interview	} 30 mins
Symptoms	PSYRATS	Haddock et al, 1999	Interview	
Depression & anxiety	HADS	Zigmond & Snaith,1983	Self-report	5 mins
Fear of Relapse	FoRSe	Gumley et al, 2014	Self-report	5 mins
Substance use	4 point scale	Tarrier et al, 2006	Interview	3 mins
Medication adherence	7 point scale	Kemp et al, 1996	Interview	2 mins
Demographics	Questionnaire	Unpublished	Self-report	5 mins
			Total:	1 hr 40 mins

Abbreviations: DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, fourth edition; MINI= Mini-International Neuropsychiatric Interview; SPI-A=Schizophrenia Proneness Index Adult Version; ESS=Early Signs Scale; DES-T=Dissociative Experiences Scale – Taxon; PANSS=Positive and Negative Syndrome Scale; PSYRATS=Psychotic Symptom Rating Scales; HADS=Hospital Anxiety and Depression Scale; FoRSe=Fear of Recurrence Scale.

Phase 3: Longitudinal assessment

Aims

The overall aim of Phase 3 is to examine the feasibility of using a mobile phone app to obtain repeated measures of basic symptoms, early signs and relapse over an extended follow-up period. This will inform the design of a definitive study examining whether basic symptoms predict relapse. To this end attention will be paid to: feedback from participants during training with the app, dropout rate, percentage of items completed per week, as well as formal feedback during Phase 4 qualitative interviews. Phase 3 data will also be used to inform the sample size estimate and analysis plan for a definitive study and to validate some of the assessments. Detailed aims are given in Appendix A.

Inclusion criteria and sample size

The inclusion criteria for this phase are the same as for Phase 2, with the additional specification that participants must have participated in Phase 2 and reported at least one basic symptom (on the SPI-A) prior to a previous relapse. Figure 1 (pg. 3 of this protocol) provides an outline of likely participant flow through the study. Based on data from a previous qualitative study (Eisner et al, in preparation), we anticipate that approximately 60% of participants will report suitable basic symptoms during Phase 2 meaning that 40 Phase 2 participants would give approximately 24 eligible for Phase 3. All of these service users will be given the opportunity to participate in the Phase 3; we will continue recruiting participants to Phases 2 and 3 until 18 eligible individuals have agreed to participate in Phase 3. Assuming a 25% drop out rate and at least a 15% relapse rate (see Leucht et al, 2012) during the 6 month follow up period, approximately 14 people will complete Phase 3, of whom at least two will relapse. This will provide sufficient data to examine the feasibility of using the mobile phone app to assess changes in basic symptoms and early signs prior to relapse as well as in those who do not go on to relapse.

Consent and training

Assessments conducted during Phase 2 will serve as a baseline for the longitudinal study (Phase 3). Once Phase 2 assessments have been completed, the researcher will remind the participant what will be involved in Phase 3 and check whether they would like to participate. Separate written consent to take part in Phase 3 will be obtained (see Appendix J).

Training with the phone app can be conducted on the same day as Phase 2 assessments or on a different day depending on participant preference. On the basis of the SPI-A and ESS assessments from Phase 2, the researcher and participant will define a 'relapse signature' which includes the basic symptoms and conventional early warning signs that the service user reported having started or increased prior to their previous relapse. The researcher will program the relevant questions into the mobile phone app, either on the participant's own mobile phone (if suitable) or on a pay-as-you-go Android Smartphone (Samsung Galaxy Y) provided by the researcher. Participants will be asked when (day of the week; time of day) they would prefer to regularly fill in the assessments on the app so as not to disrupt their weekly routine. The researcher will then teach the participant how to use the phone app; this will include completion of an example set of questions. The researcher will briefly ask the participant for feedback about the app at the end of this training session, making a note of their responses on the feedback form provided in Appendix C. The training session and feedback is likely to take about 45 minutes.

Assessment procedure and relapse definition

The timeline in Figure 3 gives an overview of the routine assessments to be carried out during the 6 month follow up period. These include assessments via the phone app (PANSS items; basic symptoms items; early signs items; fear of relapse items), telephone calls with the researcher (PANSS items), case note checks (management change) and one face to face meeting. Further details of these assessments are provided below.

Remission will be defined as follows:

- Remission at baseline interview: use criteria proposed by Andreasen et al, 2005 (a decrease to 3 or below on all of P1, P2, P3, N1, N4, N6, G5, G9 PANSS items), based on the face to face PANSS interview at baseline.

- Remission during Phase 3 follow-up: use a parallel of the Andreasen et al remission criteria (decrease to 3 or below on all 4 psychotic symptoms, as assessed by the smartphone app, for two consecutive weeks).

The flow chart in Figure 4 outlines the procedure for assessing relapse during the 6 month follow up period. Criteria for relapse (adapted from Wunderink et al, 2007) are as follows:

- Symptom increase criteria for participants who have not met remission criteria: Either at least one PANSS positive subscale item ≥5 (for people with baseline PANSS positive items all below 5) or an increase of more than 1 point on at least one PANSS positive item (for people with at least one baseline PANSS positive item already at 5 or above)
- Symptom increase criteria for participants who have met remission criteria: an increase to a score of 4 or above on any psychotic symptom item or an increase of 2 panss points whichever is higher (i.e. 1-->4, 2-->4, 3-->5)
- Duration: at least 1 week
- Management consequences: medication increase, hospital admission, crisis team admission, more frequent visits. These must be for reasons related to the symptom increase, as reported in the case notes or verbally by staff.

In cases where all relapse criteria have been confirmed, the start of the relapse will be counted as either the date of the first phone app report of symptom criteria being met, or the date reported during the phone interview as when the symptom increase started (whichever is earliest). For logistical reasons the researcher assessing PANSS positive subscale items is unlikely to be blind to the basic symptom status of the participant. However, the use of case notes to confirm management consequences provides a blinded element to the relapse definition.

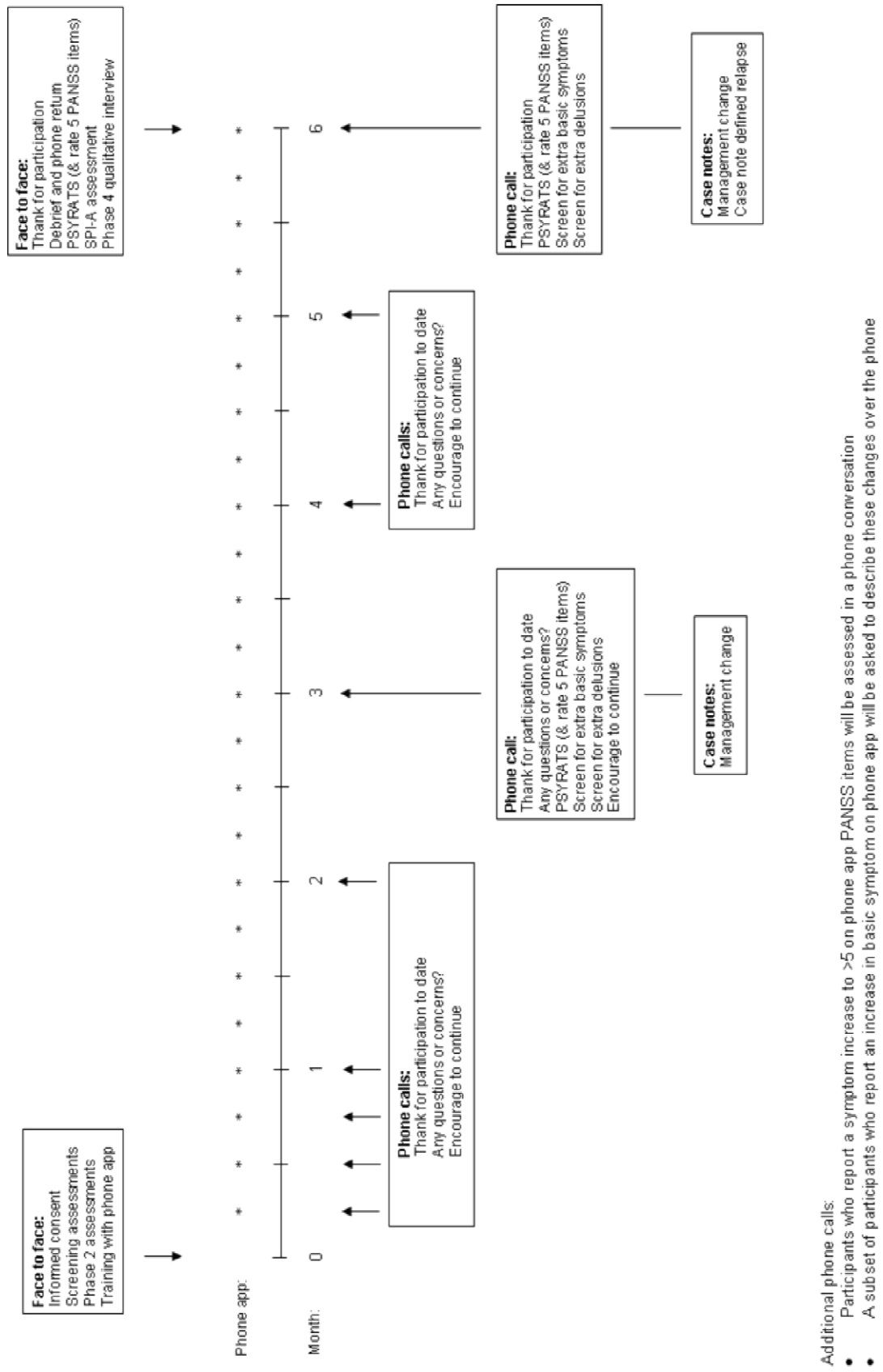

Figure 3: Overview of assessments during the Phase 3 follow up period

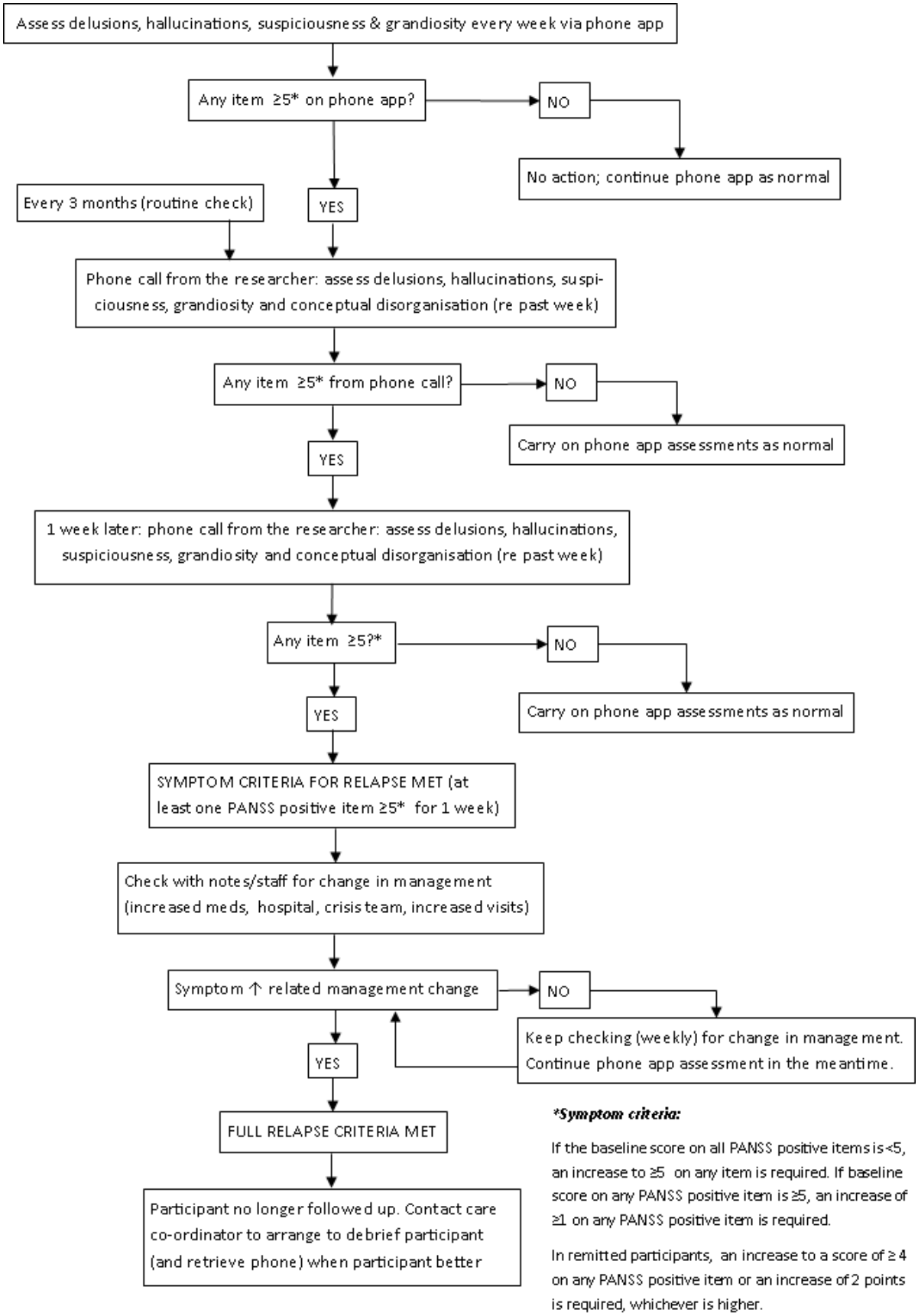

Figure 4: flow chart for determining whether relapse criteria have been met

Phone app assessments

During Phase 3, the following assessments will be conducted via self-report, using the smartphone application, every week for 6 months or until relapse (whichever is sooner):

- relevant items from the basic symptoms measure designed during Phase 1
- relevant items from the ESS
- three items from the fear of recurrence scale
- five PANSS items, including four from the positive subscale (delusions [two most distressing or strongly held; defined during phase 2], hallucinations, suspiciousness, grandiosity) and one from the general subscale (depression)

These questions will be presented as one set, unless Phase 1 participants are concerned about their length in which case they will be presented as two sets. In line with Tait and colleagues' findings (Tait et al, 2002), any occasion on which the participant does not complete the self-report assessment on the smart-phone app within 1 week of the initial alert (despite text message reminders from the researcher) will be treated as an additional putative early sign of relapse.

Telephone calls

The researcher will telephone the participant weekly for the first four weeks and monthly thereafter (i.e. 9 phone calls in total) to thank them for their participation and to encourage them to continue to complete the assessments. She will check whether the participant has any questions or concerns about the study.

During the 3 and 6 month telephone calls the researcher will also:

- rate five PANSS positive items (delusions, hallucinations, suspiciousness, grandiosity, conceptual disorganisation)
- screen for additional delusions
- screen for additional basic symptoms using the COPER (Cognitive-Perceptive) and COGDIS (Cognitive Disturbances) sections of the SPI-A interview.

These telephone calls will last 5-10 minutes each, depending on level of symptoms. They will be used to assess whether any new symptoms or symptom increases have been missed using the phone app. Additionally at 6 months the telephone call PANSS items will be audio recorded and compared to the same items assessed in a face to face meeting (within 3 days of the phone call) to validate the use of the PANSS over the phone. The order of the phone and face to face assessments will be randomised across participants.

As indicated in Figure 4, if a participant's self-report on the phone app indicates an increase to ≥5 on at least one PANSS positive subscale item (for people with baseline PANSS positive items all below 5) or an increase of more than 1 point on at least one PANSS positive item (for people with at least one baseline PANSS positive item already at 5 or above) they will receive a phone call from the researcher. During this phone call the researcher will obtain the information needed to rate five PANSS positive items (delusions, hallucinations, suspiciousness, grandiosity, conceptual disorganisation) to confirm whether the symptom increase criteria have been met. This will be repeated one week later to confirm that the symptom increase has lasted at least a week. If a participant's report on the smartphone app exceeds the threshold two weeks in a row without any increase in symptoms being detected during the resultant phone call, the threshold will be recalibrated. The threshold recalibration will be based on an average of the previous four

smartphone app reports. The new threshold will be 1 point above than the average of the previous four app reports.

A subset of participants who report an increase in basic symptoms will receive an additional phone call from the researcher. The researcher will ask about their experience of basic symptoms and how it has changed in the past week. This is to get an idea of what people mean when they report a change on the basic symptoms scale on the phone app. As with all verbal contacts with the participant, the researcher will check the participant's mental state to assess risk. The general procedure for dealing with risk is detailed under the heading *Risk information and collateral contact*, below.

Case note checks

In cases where the symptom increase and duration criteria have been met (confirmed by telephone assessment), case notes will be checked for evidence of a management change. This includes a medication change, increased observation by the clinical team (including admission), or both. Case notes will also be routinely checked after 3 months and 6 months for evidence of a management change. This is to confirm that those who never reach symptom criteria for relapse using the phone app are not having symptom exacerbations that are being missed.

As a secondary measure, relapse will also be assessed using case notes at the end of the 6 month follow up period. Case note relapse will be defined as an exacerbation of psychotic symptoms that lasted longer than one week and required a change in patient management (medication change, increased observation by the clinical team (including admission), or both; Barrowclough et al, 2010). For each participant, the date of the start of a relapse will be recorded, as well as verbatim extractions from the notes describing changes in symptoms and management.

Debrief meeting

At the end of Phase 3 follow-up, all participants will take part in a face-to-face debrief in which they return the mobile phone handset (if applicable), are thanked for their participation and given the opportunity to ask any questions or raise any concerns about the study. They will be asked complete a face-to-face assessment of the five PANSS positive items (delusions, hallucinations, suspiciousness, grandiosity, conceptual disorganisation). This will be done within three days a verbal phone assessment of the same PANSS positive items to check the validity of assessing these via telephone (the verbal phone assessments will always be done prior to face-to-face assessments). In the face-to-face meeting they will also be interviewed with the SPI-A to assess whether or not they experienced any basic symptoms in the past 6 months. This will be used to validate the phone app basic symptoms assessment. The assessments conducted during the debrief meeting will be audio recorded. Finally, they will be asked if they are willing to take part in a brief qualitative interview (Phase 4) exploring their experiences using the phone app.

Prior to meeting with the participant, the researcher will obtain an up to date risk assessment from the care co-ordinator. For participants who stopped the phone app assessments because they relapsed during Phase 3, the researcher will check the clinical notes to find out when the individual is well enough to be debriefed. They will liaise with the care co-ordinator prior to arranging the debrief meeting to ensure that the participant is well enough to be contacted and to obtain an up to date risk assessment.

Phase 4: qualitative interviews

Sample

As many of the Phase 3 participants (n=18) as possible will be interviewed, including some who dropped out of the study. If possible, participants who were eligible to participate in Phase 3 but declined will also be included. Written informed consent will be obtained (Appendix K).

Interview procedure

We will conduct brief qualitative interviews exploring participants' experiences of using the phone application and evaluating the acceptability of this and other methodology used during Phases 2 and 3. Interviews will be conducted by a PhD researcher (EE) who has experience conducting and analysing qualitative interviews. They will last about 30-60 minutes and will be audio recorded.

A detailed topic guide is given in Appendix L. Throughout the interview, the approach will be flexible in terms of the order of questions and the vocabulary used, and probe questions will be used where applicable to prompt further elaboration by the interviewee. It is worth noting that the example questions and topic guide are necessarily preliminary. Topics may be further developed during the course of the interviews in Phase 4, as well as on the basis of feedback from Phase 1 participants and feedback during training with the phone app (Phase 3). The researcher will make brief notes after each interview on a pro-forma (Appendix M), including, for example, any important contextual details during the interview and whether any alterations to the topic guide are needed for the next interview. Audio recorded interviews will be transcribed verbatim.

Analysis

Qualitative interview data will be analysed using framework analysis (Ritchie & Spencer, 1994) with an a priori focus on the following key issues:

- What were participants' experiences of using the app?
- Are there barriers to using the app in routine clinical practice?
- What were participants' experiences of participating in the study?
- Were there any barriers to participation?

The majority of the analysis will be conducted by a PhD researcher (EE) under the supervision of a clinical psychologist with experience of qualitative research (FL) and with support from the wider research team (RD, SB, CB). The following steps will guide the analysis process.

1. **Familiarisation**. As soon as the first five interviews have been transcribed, the PhD researcher will begin examining the interview data and the accompanying field notes. She will read each interview several times in order to become immersed in the content and will list potential themes and other key ideas at this stage.

2. **Identifying a thematic framework**. Based on the PhD researcher's notes during the familiarisation phase, the research team will set up a thematic framework. In doing so they will take into account a priori issues and relevant emergent themes. The initial thematic framework will be applied to the first five interviews and further refined on this basis.

3. **Indexing**. The thematic framework will then be systematically applied to all transcripts by the PhD student (EE) with the aid of the NVivo software package. Meaningful units of text within the interview transcripts will be assigned an index corresponding to a theme. A segment of text may be assigned more than one index and conversely some segments may not be assigned an index at all if they are not relevant to the research objectives. All indexed transcripts will be read by another member of the research team and any discrepancies will be discussed in the wider research team.

4. **Charting**. At this stage the data will be will be tabulated so that the researchers can get an overview of the distribution of the themes across the sample. Data will be lifted from their original context, summarised and rearranged in a table in which each row represents a participant and each column represents a theme. Separate charts will be constructed to explore key areas of interest, including (but not limited to) the a priori questions listed above.

5. **Mapping and interpretation**. Guided by the original research questions, the researchers will review the charts and research notes in order to examine the data at a more abstract level. They will compare and contrast the views of participants with different demographic or clinical characteristics, search for patterns within participants' experiences and examine the relationships between themes to give a thorough synthesis of the data.

Internal and external validation

As has been mentioned, the PhD researcher (EE) will make brief notes after each interview (on the pro-forma provided in Appendix M) and will keep ongoing memos of new ideas and insights relating to analysis. She will also keep detailed notes on all decisions made during data collection and analysis. Together these will provide an audit trail that gives a transparent account of the data collection and analysis process (Meyrick, 2006).

For external validation, all indexed transcripts will be read by and discussed with at least one other member of the research team. The thematic framework will be discussed and refined within the wider team to ensure transparency and rigour.

General procedural issues (Phases 1-4)

Risk information and collateral contact

All participants will be informed about the limits of confidentiality during the consent process and at each subsequent verbal or face-to-face contact with the researcher. This includes that information may be passed on to the clinical team if the researcher is concerned that there is a risk to the service user themself or to another person. All relevant information will be taken into account when making this decision. All cases in which the researcher believes there may be cause for concern will be discussed with a consultant psychiatrist on the research team (RD) and information will be passed on to the service user's clinical team as appropriate.

If information gathered during a verbal PANSS assessment (phone call or face-to-face) suggests that the participant may be relapsing, the researcher will ask for the participant's permission to pass this information on to their clinical team. If they decline, information will only be passed on to the clinical team if we believe there is a risk of harm to the participant or to another person.

As this is not an interventional study, we will not automatically inform participants' care co-ordinators if they report the hypothesised relapse indicators via the phone app. Since we do not yet know a) whether these hypothesised indicators accurately predict relapse or b) whether the phone app accurately measures these, it would not be appropriate to present these assessments to care co-ordinators as definite indicators of imminent relapse in the current study. However, if we believe there is a risk of harm to the participant or to another person we will disclose this, as outlined above.

Participants will be given the option of the research team routinely passing phone app assessments on to their clinical team during Phase 3 (opt in consent will be sought; participation is not contingent on this). They will also be asked if we can contact their care co-ordinator if they don't respond to the phone app prompts and we are unable to contact them for several weeks (opt out consent will be sought; again participation is not contingent on consent to this). For those in close contact with a family member or significant other, permission will be sought to contact this individual in the event that the participant cannot be contacted (opt in consent; participation is not contingent on this). In cases where participants agree to information being passed on to others, written permission will be sought at the beginning of Phase 3 (see Appendix H for consent form).

Safe working

The PhD student (EE) will follow the School of Psychological Sciences (University of Manchester) policy and Trust-specific lone worker policies for home visits. Participants' care co-ordinators, or another professional involved in their care, will be contacted prior to all visits and a risk assessment will be undertaken regarding safety for lone home visits. If there are any concerns, the student will arrange a joint visit or will request the possibility of booking a room at the community mental health team to meet the participant. The student will receive training in lone working safety and breakaway techniques.

During a visit the PhD student will leave contact details and a proposed time for the end of the appointment with a member of the research team. An arrangement will be made for the PhD student to phone the research team on leaving the participant's home, or the person undertaking the safety check will phone at the proposed end time if they have not heard from the student. If attempts to contact the student are unsuccessful, a pre-arranged escalation procedure will be acted upon.

Alternatively, an automated lone worker safety system will be used. For example under the system used by Manchester Mental Health and Social Care Trust the researcher phones a central number to initiate an 'amber alert' prior to a visit, providing the monitoring station with the location and duration of the visit. If the researcher has concerns about their personal safety at any point during the visit, they will phone a 'red alert' number which will enable the monitoring station to listen in to the conversation and act upon a pre-arrange escalation procedure, including requesting assistance from the emergency services if necessary.

Data protection and confidentiality

All participants will be allocated a unique study number. From then on, all participant data will be identified by this number only. Participant data will be stored securely and will only be accessible by the research team. Interview recordings will be transferred to a password protected computer disk which will be stored in a locked filling cabinet. Other anonymous data will be kept on a password protected University computer or in a locked filing cabinet (depending on the format).

Participants' responses to the questions on the phone app will be wirelessly uploaded to a secure server at the University of Manchester using the same system as the CareLoop study (REC reference 14/WM/0045). The informatics team who developed the system (and who will design the app) have a long experience of safeguarding the secure transfer and storage of this type of data and have previously explored the pertinent ethical issues in detail. The three general principles of information security (confidentiality, integrity and availability) are followed in the design and implementation of the system (NHS, 2009). All data transmitted to and from the server(s) will be encrypted over https with strong ciphers as detailed in the Approved Cryptographic Algorithms Good Practice Guidelines (NHS, 2012). Cipher Suites will be implemented in compliance with Section 6 ("Preferred uses of cryptographic algorithms in security protocols") of the Good Practice Guidelines. Members of the research team will be given their own individual logins for the web interface (via which participant data can be accessed) with their own username and password. Management of login accounts and passwords will be in accordance with the User Account Management Standard Operating Procedure. To ensure the safety of the data communicated, the pass phrase will be communicated to the recipient independently of the encrypted data, as recommended in the NHS Information Governance Guidelines (Department of Health, 2008). In cases where participant data is downloaded via the web interface or emailed to members of the research team for further analysis, this data will be anonymised and securely encrypted with a pass phrase of appropriate length and complexity.

Personal information will be kept in a separate locked cabinet to any participant data. In line with University of Manchester policy, data will be safely stored for 5 years after the last publication of the study or for 10 years, whichever is greater, and then destroyed. Consent forms will be kept as essential documents but other personally identifiable information such as contact details will be deleted as soon as they are no longer required. Confidentiality of information provided during the research will only be broken if a service user is assessed to be at risk to themselves or others; participants will be informed of this procedure prior to giving consent.

Financial reimbursement

To show our appreciation, we will give participants £10 in shopping vouchers for each Phase of the study that they complete (i.e. up to £30). We will provide £10 phone credit per month for those participating in Phase 3 of the study (i.e. up to £60) and £5 shopping vouchers for every phone interview participants complete. We will also reimburse reasonable travel expenses.

References

Almond, S., Knapp, M., Francois, C., Toumi, M., & Traolach, B. (2004). Relapse in schizophrenia: costs, clinical outcomes and quality of life. *Br J* Psychiatry, 184, 346-51.

Andreasen, N., Carpenter, W., Kane, J., Lasser, R., Marder, S., Weinberger, D. (2005). Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry, 162*(3), 441-9.

Appleby, L. (1992). Suicide in psychiatric patients: risk and prevention. *Br J Psychiatry, 161*, 749-758.

Barrowclough C., Haddock, G., Wykes, T., Beardmore, R., Conrod, P., Craig, T., Davies, L., Dunn, G., Eisner, E., Lewis, S., Moring, J., Steel, C., Tarrier, N. (2010). Integrated motivational interviewing and cognitive behavioural therapy for people with psychosis and comorbid substance misuse: randomised controlled trial. *British Medical Journal, 341*, c6325.

Bechdolf, A., Schultze-Lutter, F., & Klosterkötter, J. (2002). Self-experienced vulnerability, prodromal symptoms and coping strategies preceding schizophrenic and depressive relapses. *Eur Psychiatry*, *17*, 384-93.

Ben-Zeev, D., Kaiser, S, Brenner, C., Begale, M., Duffecy, J., & Mohr, D. (2013). Development and Usability Testing of FOCUS: A Smartphone System for Self-Management of Schizophrenia. *Psychiatric Rehabilitation Journal, 36*(4), 289-96.

Birchwood, M., Smith, J., Cochrane, R., Wetton, S., Copestake, S. (1990). The Social Functioning Scale. The development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. *British Journal of Psychiatry, 157*, 853-859

Birchwood, M., Smith, J., Macmillan, F., Hogg, B., Prasad, R., Harvey, C., & Bering, S. (1989). Predicting relapse in schizophrenia: the development and implementation of an early signs monitoring system using patients and families as observers, a preliminary investigation. *Psychol Med, 19,* 649-56.

Birchwood, M., Spencer, E., & McGovern, D. (2000). Schizophrenia: early warning signs. *Advances in Psychiatric Treatment, 6,* 93-101.

Craig, P., Dieppe, P., Macintyre, S., Mitchie, S., Nazareth, I., Petticrew, M. (2008). Developing and evaluating complex interventions: the new Medical research council guidance. *British Medical Journal, 337,* a1655.

Department of Health (2008). NHS Information Governance Guidelines on use of encryption to protect person identifiable and sensitive information. Available online at:
http://systems.hscic.gov.uk/infogov/security/encryptionguide.pdf

Drayton, M., Birchwood, M., Trower, P. (1998). Early attachment experience and recovery from psychosis. *British Journal of Clinical Psychology, 37*(3), 269–284.

Eisner, E., Drake, R., Barrowclough, C. (2013). Assessing early signs of relapse in psychosis: Review and future directions. *Clinical Psychology Review*, *33,* 637-653.

Eisner, E., Drake, R., Lobban, F., Barrowclough, C. Early indicators of psychosis relapse: conventional early signs, basic symptoms and their status in current practice. In preparation.

Eisner, E., Barrowclough, C., Lobban, F., Drake, R. (2014). Qualitative investigation of targets for and barriers to interventions to prevent psychosis relapse. *BMC Psychiatry, 14, 201.* DOI: 10.1186/1471-244X-14-201.

First MB, Spitzer RL, Gibbon M, Williams JBW. (1997). *Structured clinical interview for DSM-IV axis 1 disorders—clinician version (SCID-CV).* American Psychiatric Press.

Fusar-Poli, P., Bonoldi, I., Yung, A. R., Borgwardt, S., Kempton, M. J., Valmaggia, L., Barale, F., Caverzasi, E., & McGuire, P. (2012). Predicting Psychosis: Meta-analysis of Transition Outcomes in Individuals at High Clinical Risk. *Arch Gen Psychiatry, 69,* 220-9.

Gumley, A., O'Grady, M., McNay, L., Reilly, J., Power, K., & Norrie, J. (2003). Early intervention for relapse in schizophrenia: results of a 12-month randomized controlled trial of cognitive behavioural therapy. *Psychol Med, 33,* 419-31.

Gumley, A., MacBeth, A., Reilly, J., O'Grady, M., White, R., McLeod, H., Schwannauer, M., & Power, K. (2014). Fear of recurrence: Results of a randomized trial of relapse detection in schizophrenia. *British Journal of Clinical Psychology,* 54, 49-62.

Herz, M. I., Lamberti, J. S., Mintz, J., Scott, R., O'Dell, S. P., McCartan, L., & Nix, G. (2000). A program for relapse prevention in schizophrenia: a controlled study. *Arch Gen Psychiatry, 57,* 277-83.

Hogan TP, Awad AG, Eastwood R. A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. *Psychol Med, 13,* 177-83

Holmes, T. & Rahe, R. (1967). The social readjustment rating scale. *Journal of Psychosomatic Research, 11* (2), 213-218

Hooley, J., Parker, H. (2006). Measuring expressed emotion: An evaluation of the shortcuts. *Journal of Family Psychology, 20*(3), 386-396

Kay S, Fiszbein A, Opler L. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull,13,* 261-76.

Kemp, R., Hayward, P., Applewhaite, G., Everitt, B., David, A. (1996). Compliance therapy in psychotic patients: randomised controlled trial. *BMJ, 312,* 345.

Lee, S. H., Choi, T. K., Suh, S., Kim, Y. W., Kim, B., Lee, E., & Yook, K. H. (2010). Effectiveness of a psychosocial intervention for relapse prevention in patients with schizophrenia receiving risperidone via long-acting injection. *Psychiatry Res, 175,* 195-9.

Maclean, C. (2008). *An interpretative phenomenological analysis of service users' perspectives and experiences of relapse in psychosis.* University of Glasgow.

Mangalore, R., & Knapp, M. (2007). Cost of schizophrenia in England. *J Ment Health Policy Econ, 10,* 23-41.

Meyrick, J. (2006). What is good qualitative research? A first step towards a comprehensive approach to judging rigour/quality. *J Health Psychol, 11*(5), 799-808.

MHRA. (2014). *Guidance on medical device stand-alone software (including apps).* Retrieved from http://www.mhra.gov.uk/Howweregulate/Devices/Software/index.htm.

Musonda, P., Farrington, C., Whitaker, H. (2005). Sample sizes for self-controlled case series studies. *Statistics in Medicine, 25*(15), 2618-2631

NHS (2009). General Principles for Securing Information Systems, Good Practice. Guideline, Crown Copyright. Available online at: http://systems.hscic.gov.uk/infogov/security/infrasec/gpg/gensec.pdf on 23.12.13.

NHS (2012). Approved Cryptographic Algorithms Good Practice Guideline, Crown Copyright. Available online at: http://systems.hscic.gov.uk/infogov/security/infrasec/gpg/acs.pdf

Palmier-Claus, J., Ainsworth, J., Machin, M., Barrowclough, C., Dunn, G., Barkus, E., Rogers, A., Wykes, T., Kapur, S., Buchan, I., Salter, A., Lewis, S. (2012). The feasibility and validity of ambulatory self-report of psychotic symptoms using a smartphone software application. *BMC Psychiatry, 12*, 172

Ritchie, J. & Spencer, L. (1994). Qualitative Data Analysis for Applied Policy Research. In A. Bryman, & R. G. Burgess (Eds.), *Analysing Qualitative Data.* (pp. 173-194). Abingdon, UK: Routledge

Robinson, D., Woerner, M. G., Alvir, J. M., Bilder, R., Goldman, R., Geisler, S., Koreen, A., Sheitman, B., Chakos, M., Mayerhoff, D., & Lieberman, J. A. (1999). Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry, 56,* 241-7.

Robson, P. (1989). Development of a new self-report questionnaire to measure self esteem. *Psychological Medicine, 19* (2), 513-518

Schizophrenia Commission (2012). The abandoned illness: A report from the Schizophrenia Commission. London: Rethink Mental Illness.

Schultze-Lutter, F., Addington, J., Ruhrmann, S., & Klosterkötter, J. (2007). *Schizophrenia Proneness Instrement: Adult Version (SPI-A).* Rome, Italy: Giovanni Fioriti Editore.

Sheehan, D., Lecrubier, Y., Sheehan, K., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G. (1998). The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59* (suppl 20), 22-33.

Tait, A., McNay, L., Gumley, A., & O'Grady, M. (2002). The development and implementation of an individualised early signs monitoring system in the prediction of relapse in schizophrenia. *Journal of Mental Health, 11,* 141-53.

Tarrier, N., Haddock, G., Lewis, S., Drake, R., & Gregg, L. (2006). Suicide behaviour over 18 months in recent onset schizophrenic patients: The effects of CBT. *Schizophrenia Research, 83*(1), 15-27.

Waller et al (1996). Types of dissociation and dissociative types: A taxometric analysis of dissociative experiences. *Psychological Methods*, 1(3), 300-321.

Waller & Ross (1997). The prevalence and biometric structure of pathological dissociation in the general population: Taxometric and behavior genetic findings. *Journal of Abnormal Psychology*, 106(4), 499-510.Wiersma, D., Nienhuis, F., Slooff, C., & Giel, R. (1998). Natural course of schizophrenic disorders: a 15-year followup of a Dutch incidence cohort. *Schizophrenia Bulletin, 24,* 75-85.

Zigmond, AS; Snaith, RP (1983). "The hospital anxiety and depression scale". *Acta Psychiatrica Scandinavica, 67*(6), 361–370

List of Appendices

Appendix A - detailed aims of feasibility study

Appendix B - phone app items

Appendix C - participant feedback form

Appendix D - participant information sheet (Phase 1)

Appendix E - consent form (Phase 1)

Appendix F - clinician leaflet (Phases 2-4)

Appendix G - service user leaflet (Phases 2-4)

Appendix H - participant information sheet (Phases 2-4)

Appendix I - consent form (Phase 2)

Appendix J - consent form (Phase 3)

Appendix K - consent form (Phase 4)

Appendix L - topic guide (Phase 4)

Appendix M - post-interview report form (Phase 4)

Appendix N - care co-ordinator information letter

Appendix O - no contact letter

Appendix P - PIS cover letter and appointment reminder

Appendix Q - researcher CV – Emily Eisner

Appendix R - research supervisor CV – Christine Barrowclough

Appendix S - research supervisor CV – Richard Drake

Appendix T - research supervisor CV – Sandra Bucci

Appendix U - research supervisor CV – Fiona Lobban

Appendix V - research supervisor CV – Richard Emsley

Appendix W - study design

Appendix X - overview of Phase 3 assessments

Appendix Y - procedure for defining relapse