STUDY PROTOCOL

Title: EMPOWER: Early signs Monitoring to Prevent relapse and prOmote Wellbeing, Engagement and Recovery

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2.0 Glossary of Terms

Abbreviation	Description (using lay language)
ACS	Adult Community Service
App	Mobile telephone application
CBT	Cognitive Behaviour Therapy
CI	Chief Investigator
CMHT	Community Mental Health Team
DMEC	Data Monitoring and Ethics Committee
EMPOWER	Early signs monitoring to Prevent relapse and pr0mote Wellbeing, Engagement, and Recovery
EWS	Early warning signs
IP	Intellectual property
JCPs	Joint Crisis Plans
MRC	Medical Research Council
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NIHR	National Institute for Health Research
NPT	Normalization Process Theory
PI	Principal Investigator
PSSUQ	Post-Study System Usability Questionnaire
RA	Research Assistant
RCT	Randomised controlled trial
SSC	Study Steering Committee
WP	Work Package

3.0 Summary in Plain English

BACKGROUND: Relapse in schizophrenia is a major cause of distress and disability amongst patients and their families. Relapse is predicted by changes in symptoms such as anxiety, depression and suspiciousness (early warning signs, EWS) and can be used as the basis for timely interventions to prevent relapse and rehospitalisation. Research shows that interventions focused on EWS can reduce these negative outcomes and enhance recovery. The quality of research evidence is poor so that it is not possible to estimate whether these can be applied in routine practice.

AIMS: To build an intervention (EMPOWER) that refines existing digital smartphone technology for the monitoring of EWS; that promotes help seeking and minimises the risk of false alarms. Therefore, we will seek to embed our digital technology into a Stepped-Care approach to enhance self- management and facilitate timely intervention from mental health services.

PARTICIPANTS: Eligible service users will be (i) adults (age 16+) (ii) in contact with a local community based services; (iii) who have been admitted to a psychiatric in-patient service at least once in the previous two years for a relapse of psychosis; (iv) a DSM-V diagnosis of Schizophrenia. Service users will also be invited to nominate a carer to participate.

SETTINGS: The study will take place in Glasgow (UK) and Melbourne (Australia).

DESIGN AND PROCEDURES: The study will last for 30-months. During months 1 to 7 we will explore the views of service users, carers and staff in integrate these into refinements to maximise acceptability of our digital technology. Months 8 to 9 we will undertake preliminary tests of this technology to further enhance acceptability. Months 10 to 26 we will undertake a pilot cluster randomised controlled trial where we will randomise Community Mental Health Teams (CMHTs) to EMPOWER or to Treatment as Usual. We aim to recruit 120 service user participants from 8 CMHTs and follow them up for 12-months. This pilot will enable us to investigate the feasibility of a larger scale (definitive) trial and the acceptability and safety of the EMPOWER intervention. Months 21 to 26 we will conduct a Health Economic study and we will also undertake wider engagement of service user, carer and NHS stakeholders to facilitate transition to the main study. Months 27 to 30 will involve analysis and write up of the study findings.

INTERVENTION: The EMPOWER intervention involves three levels of stepped care: (i) smartphone based early signs monitoring, (ii) individualised self-management support delivered through smartphone, and (iii) activation of a relapse prevention pathway into secondary care. Service user participants will have access to the EMPOWER App for the full 12-months of the study. EMPOWER will enable service users, their nominated carer and their care coordinator will agree and personalize (i) frequency settings (number of EWS alerts per day/week); (ii) thresholds for increasing the frequency of monitoring and delivery of motivational self-management messages and (iii) thresholds for

activating the relapse prevention pathway.

OUTCOMES: We will identify the feasibility of the main trial in terms of recruitment and retention to the study and the acceptability and safety of the EMPOWER intervention. We will assess relapse, symptom recovery, emotional recovery, empowerment and engagement. We will manualise the intervention and establish the methods to deliver the main (definitive) trial.

4.0 Background and Rationale

Schizophrenia is a severe mental illness (SMI) affecting 24 million people worldwide, costing the NHS in the UK £2bn and the Australian Health Sector Aus$1.34bn annually. Costs to the Australian Government are Aus$3.51bn annually and wider societal costs are estimated as Aus$4.9bn annually (Neil et al., 2014). Schizophrenia is a major public health burden and is associated with increased mortality with death occurring 10-15 years earlier than the population at large through both suicide and poor physical health and this differential mortality gap has widened over recent decades (Saha, Chant & McGrath, 2007).

Relapse influences the long-term course of psychosis with rates accumulating following a first episode to 20–35% after one year. In a recent, review the pooled prevalence of relapse of positive symptoms in first episode was 28% (range = 12-47%), 43% (35-54%), 54% (40-63%) at 1, 1.5-2, and 3. years follow-up, respectively (Alvarez-Jimenez et al., 2012). Relapse can occur in up to 80% at five years (Robinson et al., 1999). Relapse is associated with higher inpatient and outpatient costs (Fitzgerald et al., 2009; Ascher-Svanum et al., 2010). The cost of treating relapsing psychosis is four times that of stable psychosis. Despite the rise of community care, 70% of the UK costs of SMI are for unplanned inpatient care for relapse. The 2010 Second Australian National Survey of People Living with Psychotic Illness (Morgan et al 2011) reported that 61.5% of the treated population had a course of illness characterized by multiple episodes of psychotic symptoms with full or partial remission of symptoms between episodes. One-year incidence of hospital admission was 34% of the treated population, with 27.8% of those having one or more further admissions to hospital within the year. In Australia, almost half (46%) of health sector costs are generated by inpatient care, with psychiatric admissions accounting for 96% of these costs (Aus$609M). Relapsing or unstable psychosis has the greatest impact on these patterns of service utilisation. Raudino et al., (2014) found that psychiatric admissions (including use of emergency services) were associated with higher symptoms, suicidal ideation, poorer functioning and younger age.

4.1 Predictors of Relapse

One important predictor of relapse is lack of acceptance of treatment and unplanned discontinuation of antipsychotic medication (Alvarez-Jimenez et al., 2012). Poorer adherence often signals a lack of engagement with services and failure of services to build a collaborative working alliance (Subotnik et al.,

2011). Specifically, non-adherence to antipsychotic treatment is predicted by poorer insight, previous experience of involuntary treatment, poorer premorbid functioning, comorbid substance misuse, forensic history and a poor therapeutic relationship with the prescriber (Day et al., 2005; Lambert et al., 2010). Relapse itself is also an important marker of severity and complexity of illness. Relapse is predicted by previous suicide attempts (Novick et al., 2010), depression, hostility and embarrassment (Rummel-Kulge, Schuster, Peters & Kissling, 2008), poorer premorbid functioning, family criticism, substance misuse, social isolation (Alvarez-Jimenez et al., 2012), negative interpersonal style (probably linked to poorer utilisation of social support) (Gleeson et al., 2005) and greater fear of relapse itself (Gumley et al., 2014).

Birchwood et al (1989) pioneered the development of systematic early signs monitoring for relapse and its integration into routine care. It is now known that relapse is the culmination of a process of change starting days and sometimes weeks before psychosis symptoms re-emerge or are exacerbated. These early warning signs (EWS) include affective changes and incipient psychosis. A recent systematic review (Eisner, Drake & Barrowclough, 2013) to determine the validity of EWS as predictors of relapse in people with non-affective psychosis found that the sensitivity of early signs to relapse (proportion of relapses correctly predicted) ranged from 10% to 80% (median 61%) and specificity (proportion of non-relapses correctly identified) ranged from 38% to 100% (median 81%). Detection of relapse was improved by more frequent monitoring (at least fortnightly) and by the inclusion of both psychotic and affective symptoms.

4.2 Interventions to prevent relapse

Gumley et al., (2003) conducted the first study to evaluate the implementation of cognitive behaviour therapy (CBT) tailored towards the prevention of relapse. CBT delivered on the appearance of EWS lead to a significant reduction in relapse over 12-months. A significant barrier to relapse prevention was service users' fears of help-seeking arising from previous experiences of relapse. For example, service users may avoid calling their key worker in the context of an increase in EWS for fear of being admitted to hospital. In a randomised controlled trial (RCT) of relapse detection, Gumley et al., (2014) found that fear of relapse was as sensitive to the onset of relapse (Sensitivity = 72%, 95% CI = 52–86) as EWS (Sensitivity= 79%, 95% CI = 62–89).

A recent Cochrane Review focused on the effectiveness of interventions targeting recognition and management of EWS of relapse in schizophrenia (Morriss et al., 2013). Significant effects in favour of EWS interventions were found for the number of participants relapsing (15 RCTs, n = 1502, risk ratio (RR) 0.53 95% CI 0.36 to 0.79) and the number of participants being re-hospitalised (15 RCTs, n = 1457, RR 0.48, 95% CI 0.35 to 0.66); however, it was found that the quality of the trials conducted to date was poor in terms of randomisation, concealment and blindness. Therefore, future EWS interventions need to address methodological problems related to trials of EWS interventions that limit their generalizability to usual care. Specifically, these methodological problems (in terms of unclear

randomisation, blinding of outcome and incomplete outcome data) mean that EWS interventions cannot be recommended for routine implementation in health services (Morriss et al., 2013).

4.3 Barriers to relapse detection and prevention

There is also significant uncertainty surrounding the prognostic validity of EWS (Eisner et al., 2013), which results in the risk of unnecessary intervention that may sensitise service users and carers to heightened fear of relapse (a potential adverse event related to early signs monitoring; Gumley et al., 2014). Fear of illness and stigma are closely related to emotional dysfunction (Birchwood, 2003) and to poorer insight in schizophrenia (Day et al, 2005). Feelings of fear, depression and helplessness are common emotional experiences prior to full relapse (van Os & Kapur, 2009). Avoidant styles of coping are linked to increased risk of relapse. In an effort to minimise the stigma of illness and prevent relapse, service users can adopt avoidant coping styles (e.g. Birchwood, 2003). These coping styles are associated with greater insecurity in relationships, lower self-esteem, lower levels of adherence and reluctance to seek help in a crisis. Reluctance to seek help may result from greater fear of relapse arising from experiences of involuntary admission. In a recent systematic review, Gumley, Taylor, Schwannauer and Macbeth (2014) found that greater difficulties forming relationships was associated with poorer engagement with services, more problematic relationships with staff, and more frequent and longer hospital admissions. In sum, the detection of and action following these EWS may be constrained by avoidance, stigma, fear of relapse and reluctance to disclose.

In both UK and Australia, an important aspect of service provision for those service users at greatest risk of relapse is having access to an integrated mental health care system that enables clear shared planning for managing risk and relapse prevention. One example of this is the role of Joint Crisis Plans (JCPs) in the UK. The CRIMSON study (Thornicroft et al., 2013) was an individual level RCT that compared the effectiveness of JCPs with treatment as usual for people with schizophrenia. There was no significant impact on the primary outcome (reduced coercion into hospital). It was noted that when faced with crisis, in spite of the considerable effort in developing the JCP with service users, the teams reverted to 'custom and practice' and JCPs were not consulted by staff in planning the team response to a crisis. Furthermore, service users experienced an inability to influence clinicians behaviours and this was interpreted as signalling a lack of respect for their views and opinions. In consequence, they described their interactions as a "playing the game"; that is appearing comply with treatment decisions. Clinicians themselves experienced their interations with service users as ritualised especially in the context of responding to increase risk (Farrelly et al., 2015). Our work with service users (Gumley & Park, 2010) has highlighted that relapse prevention based on EWS monitoring relies on the service user initiating help-seeking in the context of feeling vulnerable and threatened. Many individuals find help-seeking a challenge and may have had difficult or traumatic experiences of psychosis. Delay in help-seeking narrows the window of opportunity for successful relapse prevention, which in

turn increases reliance on coercive measures confirming pre-existing negative expectations. It is therefore essential to develop and evaluate an intervention that can not only change the disclosure of relapsing individuals but one that can radically change the behaviour of mental health teams and the actions of their staff in a crisis.

4.4 Digital Technology

Digital technology offers such a step change that can influence the behaviour of both service users and mental health teams to enhance engagement with the early signs monitoring approach. Smartphones to support healthcare are promising for delivery of interventions that are unconstrained by the limitations of existing treatment settings. Mobile phones are widely available, affordable, and are continuously dropping in cost; there are now over 6 billion mobile phone subscriptions worldwide. Ben-Zeev et al. (2013) have shown that mobile phone usage is similar to the general population in people with serious mental illness including schizophrenia and that these individuals express an interest in engaging with mobile interventions. A recent systematic review concluded that Internet and mobile-based interventions for psychosis seem to be acceptable and feasible and have the potential to improve clinical and social outcomes. Specifically, 74-86% of patients used the web-based interventions efficiently, 75-92% perceived them as positive and useful, and 70-86% completed or were engaged with the interventions over the follow-up. In addition, online and mobile interventions showed promise in improving positive psychotic symptoms, hospital admissions, socialization, social connectedness, depression and medication adherence (Alvarez-Jimenez et al., 2014) In Schizophrenia, acceptability of using mobile phones to monitor symptoms appears to be high with rates of adherence to assessments of EWS estimated at over 80% over 3-months (Granholm et al. 2012) and 1-year (Spaniel et al., 2012). Self-ratings of symptoms using Smartphone demonstrate moderate to strong correspondence with clinician ratings derived from structured clinical interviews (Palmier-Claus et al., 2012). Service users with schizophrenia have also expressed potential benefits to the quality of care from Smartphone EWS monitoring in terms of assisting clinicians to have a better understanding of their service users' mental health, faster and more efficient data exchange, and aiding patient-clinician communication. They felt that mobile monitoring could be integrated easily into daily routines (Palmier-Claus et al., 2012). Mobile interventions enhancing self-management have been associated with rates of 85% adherence and high levels of satisfaction (Ben-Zeev et al., 2014). Members of our team have been at the forefront of this work in developing this approach to 'real time' monitoring and intervention (Palmier-Claus et al., 2011; Alvarez-Jimenez et al., 2013; Palmier-Claus et al., 2012; Ainsworth et al., 2013)

4.5 Digital Technology Development

We will refine existing technology (i.e., ClinTouch and CareLoop) to deliver EMPOWER. The Background intellectual property (IP) has already been well

established by researchers and software engineers based at the University of Manchester (Ainsworth, Lewis, Bucci). ClinTouch was developed through an MRC funded project (PI: Lewis) as a mobile phone based monitoring system to record real time data on current symptoms, establish the acceptability of mobile monitoring in this group and compare against conventional and gold standard measures of psychiatric symptoms. CareLoop, was also funded by the MRC (PI: Lewis), and builds on ClinTouch. CareLoop is a personalised mobile phone based system for mental health service users to record ambulant data on current systems, stressors and functioning to be uploaded in real time to a central server in a clinical team base and linked to prototypical management algorithms.

4.5 Alignment with Health Priorities

We will further develop and enhance our ClinTouch and CareLoop mobile applications and build a relapse prevention pathway that enables service users to become more aware of changes in their thinking, physiology, behaviour and feeling, and will seek to enable individuals to respond to these changes positively. The aim of self-management is to enhance acceptance, autonomy, empowerment and behavioural engagement rather than the patterns of fear, demoralisation, withdrawal, avoidance and defeat observed in the phenomenological studies of early signs. If using technology empowers service users to make informed choices in real time about their treatment and to act promptly under their own control, then we believe we have the potential to transform community care for people with SMI. Our proposal aligns with several emerging NHS and Australian health priorities: prevention; early intervention; personalised care; service user involvement/empowerment; social recovery and efficiency. To deliver innovative and effective community-based care, a major shift in the way care is delivered is needed which empowers service users to play an active role in illness management. The Australian Commission on Safety and Quality in Health Care have prioritised the development of effective partnerships between consumers and healthcare providers and organisations at levels of healthcare provision, planning and evaluation. The NHS Quality, Innovation, Productivity and Prevention (QIPP) Framework for long term conditions is to "empower service users to maximise self management including ensuring service users have appropriate information and knowledge about how to manage their condition". QIPP demands a focus on innovation to drive up the quality of care and increase the productivity of healthcare services.

5.0 Objectives:

The overall objective of this study is to evaluate the novel EMPOWER intervention in terms of relapse prevention in individuals with chronic schizophrenia. Our evaluation comprises two components: (i) evaluation of the system for a self-initiated and self-managed EWS using real time sampling methods; and (ii) to examine feasibility of EMPOWER through a 15-month pilot cluster randomised trial.

The specific aims of this pilot research are to:

(a) enhance and tailor our mobile phone software application (App) to deliver EWS monitoring, self management interventions and access to a relapse prevention pathway which is firmly embedded in *whole team* protocols and action
(b) assess the feasibility, acceptability and safety of the intervention and to determine preliminary signals of efficacy of the EMPOWER Relapse Prevention Intervention, and
(c) establish the data gathering frameworks required for a co-ordinated health economic evaluation of a full trial across the UK and Australia.

6.0 Trial Design

We will use a mixed methods approach including Phase 1 (mainly using qualitative methods) and Phase 2 (Mainly comprised of a Cluster Randomised Controlled Trial). Methods follow the Medical Research Council's (MRC) Framework for developing and evaluating complex interventions. At the heart of this study we will build upon existing technology (ClinTouch/CareLoop) developed and validated by members of our team at the University of Manchester by designing a study to evaluate real world implementation into routine service settings in the UK and Australia. For this reason we will draw on Normalisation Process Theory (http://www.normalizationprocess.org/ NPT; May 2013). This theory provides a conceptual framework for understanding and evaluating the implementation processes by which new health technologies and other complex interventions are routinely operationalized and embedded in everyday work, and sustained or integrated into routine practice. NPT offers a conceptual map for the process evaluation of complex interventions and for the organization of implementation processes. Here, NPT is concerned with identifying and understanding the ways that people make sense of the work of implementing and integrating a complex intervention (coherence); how they engage with it (cognitive participation); enact it (collective action); and appraise its effects (reflexive monitoring). Each Workpackage within the overall project has been designed to address these processes of coherence, cognitive participation, collective action and reflexive monitoring.

7.0 Research Management

The project comprises six Work Packages (WP); each package contains clear milestones and deliverables representing go/no-go points. The GANTT Chart provides an overview of the plan for delivery of the 6 WPs. These WPs will be undertaken across two centres: one UK centre (NHS Greater Glasgow & Clyde) and one Australian centre (North Western Mental Health Services, Melbourne, Victoria). This will enable a systematic and shared approach to identifying points of convergence and divergence across the research sites. The strength brought by the collaboration between Australia and UK means that we can systematically evaluate barriers to engagement and implementation in order to enhance the potential for international impact and generalisability of our findings.

Insert GANTT Chart about here

In line with recent MRC Guidance on process evaluation of Complex Interventions (Moore et al., 2015, Kellogg Foundation, 2004) we have produced a Logic Model for the EMPOWER intervention (Figure 1). Figure 1 provides a clear description of the intended intervention, how it will be implemented, and how it is expected to work. The Logic Model will provide the basis for organizing observations of processes and outcomes throughout the study and provide a basis to report and fully discuss intervention components for the main trial and implications for intervention theory and methods.

Insert Figure 1 about here

7.1 Project Management Committee (PMC)

Operational management and governance of transitions between Work Packages and implementation of the study with be through the EMPOWER Project Management Committee (PMC) comprising the following individuals:

- Professor Andrew Gumley (Chief Investigator)
- Trial Manager (To be appointed)
- Professor John Gleeson (Melbourne CI)
- Professor John Farhall (Melbourne CI)
- Professor John Norrie (Study Statistician)
- Professor Andy Briggs (Study Health Economist)
- Professor Alison Yung (University of Manchester)
- Matt Machin (Digital technology)
- Professor Max Birchwood (University of Warwick)
- Professor Matthias Schwannauer (University of Edinburgh)
- Simon Bradstreet (Scottish Recovery Network)

7.2 Project Advisory Group (PAC)

The PMC Group will report to the wider Principal Investigators Group on a regular basis. The PAC will convene on a three-monthly basis.

8.0 Phase 1 (Work Packages 1 to 3)

Phase 1 is comprised of three work packages: (WP 1) service user and carer engagement, software evaluation and improvement, (WP 2) professional staff engagement, modelling treatment as usual, mapping the relapse prevention pathway, identification of training needs, and (WP 3) software beta-testing. The aims of each work package that comprise Phase 1 of the research are outlined below.

- *Work package 1 (Months 2 – 7):* (i) To evaluate the acceptability and usability of mobile symptom recording using smartphones amongst service users and their carers; and (ii) the identification of incentives and barriers to use.
    - *Deliverables:* Software and protocol updates in response to feedback from service users and carers.

- *Work package 2 (Months 1 – 7):* (i) To evaluate the acceptability and usability of mobile symptom recording using smartphones amongst professional mental health care staff; (ii) to identify incentives and barriers to implementation by Northwestern Mental Health staff; and (iii) the identification of relapse prevention pathways and whole team responses.
    - *Deliverables:* (i) Software and team protocol updates in response to feedback from professional care staff. We will operationalize protocols for dealing with false positives and activation of relapse prevention pathways. (ii) The development of care pathways, identification of operational barriers and enablers. (iii) Identification of training needs of teams participating in our future pilot cluster randomized controlled trial.

- *Work package 3 (Months 8 – 9):* (i) To finalize the EMPOWER App for implementation in a pilot cluster randomized controlled trial that will compare EMPOWER to treatment as usual.
    - *Deliverables:* Agree on final modifications to EMPOWER App to enhance usability. Finalize measurement methods for assessment of self-report of acceptability and usability to be administered in our future pilot cluster randomized controlled trial.

8.1 Settings

Parallel arms of data collection for Phase 1 of the research project will take place in the UK and Australia. Data Collection for the UK arm will take place in NHS Greater Glasgow & Clyde. Data collection for the Australian arm of the study will take place across two NorthWestern Adult Community Mental Health Services.

8.2 Methods

8.2.1 *WP1: Task groups with service users and carers*

Task Groups (1 - 2 hours duration) are a type of focus group designed to generate qualitative data and the principles for action, which are grounded in the experience of group members. Task Groups will elicit views about experiences of relapse, incentives and barriers to help-seeking and optimal responses to relapse or the threat of relapse. Task groups will explore: (i) the utility of early signs monitoring, including service users' views about intermittent, low frequency and high intensity EWS monitoring; (ii) views about using self-management messages and what self-management messages would have greatest salience; (iii) the design parameters of the system that could best sustain their involvement; (iv) views about help seeking and activating a relapse prevention pathway; (v) the best way to involve carer stakeholders; (vi) the best way to contact mental health staff; and (vii) how would they like to use their data from EMPOWER. This will build on our initial PPI work and be informed by service users and carers recruited to the Study Steering Group. As part of the Task Groups, participants will have an opportunity to try out the EMPOWER App and system. These data will inform the final design and Beta Testing of EMPOWER to optimise the usability, salience, applicability and overall coherence of the intervention.

8.2.2 *WP 2: Task groups with professional mental health care staff*

The aim of the Task Groups with Mental Health Staff is to clarify the existing support pathways and procedures, systems, and policies in teams participating in usual care, and to clearly differentiate these from our experimental intervention. We will focus on the following questions: (i) What are the strengths and limitations of these existing pathways?; (ii) What are the relevant policies and procedures that guide treatment as usual?; (iii) What are the feasibility, risks and incentives to incorporate mobile phone technology into the monitoring and detection of risk of relapse?; (iv) What are the best methods to deal with false positives?; (v) How can we optimise pathways to relapse prevention?; In line with NPT we will distinguish EMPOWER from current practice; collectively agree about the purpose of the intervention; enable staff to understand what the intervention would require of them; and construct potential value of the intervention for their work.

8.2.3 *WP 3: Software beta-testing*

In each team, the software will be beta-tested with 10 service users, their carers, and mental health care staff (i.e., key workers and medical practitioners) over 7-days. Following the software beta-testing, we will follow up at a time and location mutually convenient to the researcher and participants. During this interview service user participants will be asked about the benefits and

problems of using the EMPOWER App, including investigating their views about the user interface, the number and frequency of questions, wording of items, omissions, fit with everyday life and other suggestions for improving usability. Consumer participants will also complete the Post-Study System Usability Questionnaire (PSSUQ) to test the usability of the application. The PSSUQ has been used previously in respected studies testing the usability of Apps in healthcare (e.g., Sheehan, Lee, Rodriguez, & Schnall, 2012).

Carer participants who partake in the follow up interview with consumers will be asked for their views of the usability and usefulness of the EMPOWER App. Professional mental health care staff will also be asked for their perspective on the usability and usefulness of the EMPOWER App in a separate follow up interview.

8.3 Study Population

8.3.1 Recruitment Procedure

8.3.1.1 WP 1

Potential service user participants will be identified and approached by key workers, who will ask them if they would be interested in meeting with the study RA to discuss the study. If the service user expresses an interest in participating their preferred contact details will be passed on to the study RA in order to make arrangements for providing the Participation Information Consent Form (PICF).

Following the provision of informed consent, service user participants will be invited to nominate a carer to participate. Once a carer has been identified the study RA will make arrangements via telephone to provide information about participation and seek informed consent. The latter will occur in a face-to-face setting. Should insufficient carers be recruited by this method, focus group participation will be opened to any carer associated with a participating site, and the opportunity made known though Carer Consultants employed within the service and flyers and/or posters at the service. Copies of any flyer, or poster, to be used will be lodged with the ethics committee prior to use.

NB. service user participants are still eligible for participation if they choose not to nominate a carer, if there is no individual that meets the inclusion criteria for a carer participant, or if their nominated carer does not wish to partake.

8.3.1.2 WP 2

Professional mental health staff will be identified through service managers and presentations at staff meetings by the study RA. Staff members will be invited to take part in a focus group and will be given a Participant Information Sheet/ Consent Form. They will be advised that participation is voluntary, and will sign the consent form before being interviewed. Should insufficient professional mental health staff be recruited by this method, focus group participation will be

opened to any clinician associated with a participating site, and the opportunity will be made known through email announcement from the relevant service manager. Copies of any flyer, or poster, to be used will be lodged with the ethics committee prior to use.

8.3.1.3 WP 3

In the first instance, service users who partake in WP 1 will be invited to partake in the software beta-testing. If an inadequate number of service users are recruited via this method, potential service user participants will be recruited in a manner akin to work package 1.

Service user participants will be asked of their preference regarding carer participation. Those who express interest will be asked to share their carer's contact details with the study RA. The study RA will then make arrangements to contact the nominated carer, so as to provide information about participation and obtain informed consent for participation.

The corresponding key workers and medical practitioner/ doctor for each service user participant will be invited to partake and provide information/ feedback regarding their experience of having a consumer utilize the program. If an inadequate number of professional mental health staff participants are recruited via this method, participants will be recruited in a manner akin to WP 2.

NB. Service user participants are still eligible for participation if they choose not to nominate a carer, if there is no individual that meets the inclusion criteria for a carer participant, or if their nominated carer does not wish to partake. Service user participants are also eligible for participation if their key clinician/ case manager chooses not to partake.

8.4 Eligibility Criteria

8.4.1 Service users and their Carers

Service users will be eligible for participation in work packages 1 and 3 if: (i) they are adults (18 + years of age), (ii) in contact with a local community based service, (iii) have been admitted to a psychiatric in-patient service at least once in the previous two years for a relapse of psychosis, (iv) have a diagnosis of a relevant DSM-5 schizophrenia related disorder (i.e., schizophrenia, schizoaffective disorder, or substance/ medication induced psychotic disorder), or depressive disorder with psychotic features (v) their current presentation Current presentation does not include severe acute symptoms, (vi) they are able to provide informed consent as adjudged by their care coordinator/ case manager, or if in doubt the responsible consultant, and (vii) they are able to manage the language requirement of participation.

Following the provision of service participant's informed consent, they will be asked to nominate a carer with whom they regular (i.e., weekly) contact. The frequency of contact is the only eligibility criterion for carer participation.

8.4.2 Professional mental health care staff

Professional mental health care staff will be eligible for participation if they have been working for the service for $\geq$ 2 months, so as to ensure that they have had an orientation to and are familiar with the service system.

8.4.3 Exclusion Criteria

Individuals will not be eligible for participation if they do not meet the inclusion criteria outlined above.

8.5 Consent

Written consent for participating in this research will be sought from all participants. Participants will have capacity to give informed consent for themselves. In order to provide informed consent, all participants will meet face-to-face with the study RA, who will present in written and verbal form the aims and procedures of the study, and the processes for withdrawal and for making enquiries or complaints.

8.6 Sample Size

The numbers projected for the WPs 1 and (i.e., 30 service users, 30 carers, and 20 – 30 professional mental health care staff) and WP 3 (i.e., 10 service users, carers, and professional mental health care staff) will provide sufficient data to create the framework of analysis. No formal sample size calculation (e.g., power analysis) was considered appropriate for these WPs, as they are not aimed at evaluating treatment effects. The number of participants recruited into each of the WPs will provide adequate information and insights to inform the design and size of a future definitive, pragmatic, multi-site, and multi-national pilot cluster randomized controlled trial.

8.7 Statistical Methods

Task groups (WPs 1 and 2) and follow-up interviews (WP 3) will be digitally recorded, transcribed and anonymized before being entered onto N-VIVO (a computer assister qualitative software package) to organize the data and enable progression to analysis. Analysis will draw upon Framework Analysis, which is a qualitative approach specializing in pragmatic, generalizable qualitative method

designed for real world implementation (Richie et al., 2013). The framework approach has been developed specifically for applied or policy relevant qualitative research in which the objectives of the investigation are typically set in advance and shaper by the information requirements of the funding body. The timescales of applied research tend to be short and there is often a need to link the analysis with quantitative findings. For these reasons, although the framework approach reflects the original accounts and observations of the people studied (that is, "grounded" and inductive), it starts deductively from present aims and objectives. The data collection is more structured than would be the norm for much other qualitative research and the analytical process tends to be more explicit and more strongly informed by an a priori approach (Pope, Ziebland, & Mays, 2000).

9.0 Phase 2 (Work Packages 4 to 6)

9.1 Objectives

To establish the feasibility of conducting a Cluster Randomised Controlled Trial comparing EMPOWER against Treatment As Usual (TAU). We will establish the parameters of the feasibility, acceptability and safety of an intervention as an adjunct to usual care that is easily deliverable in the NHS and Australian community mental health service settings and

(i) enhances the recognition of early warning signs by service users and their carers;
(ii) provides a stepped care pathway, that is either self-activated or in liaison with a carer and / or community healthcare professional, which then
(iii) triggers a relapse prevention strategy which can be stepped up to a whole team response to reduce the likelihood of a psychotic relapse.

Deliverables: In order to confirm the design and methods of the definitive trial we will demonstrate feasibility, acceptability, usability and safety of our proposed intervention. We will also explore possible unwanted effects such as increased fear of relapse. We will undertake quantitative analysis of (i) recruitment to the study; (ii) uptake and adherence of EMPOWER by service users, (iii) the engagement of carers and mental health staff in the relapse prevention pathway; and (iv) the assessment of primary and secondary outcomes and (v) a qualitative analysis of relapses to refine intervention in the main trial. We will deliver a plan for the next stage of development and delivery of EMPOWER.

9.2 Trial Design

We will evaluate EMPOWER using a multicentre, two arm, parallel groups cluster randomized controlled trial (C-RCT) involving eight purposively selected Community Mental Health Teams (CMHTs) (2 in Melbourne and 6 in Glasgow)

with 12-month follow-up. The CMHT will be the unit of randomization (the cluster), with the intervention delivered by the teams to individual patients and with outcomes assessed on these patients within these clusters. The study is planned and implemented in concordance with the Consolidated Standards of Reporting Trials (CONSORT) cluster trial extension (Campbell et al., 2004). We choose this design as the intervention enables individual service users to engage in real time EWS monitoring, which can activate a relapse prevention pathway involving a team based response that can enable us to deliver the intervention over 12 months and observe the primary outcome over the period of intervention. We will recruit over a 5-month period (Months 10-14). The intervention will last 12 months and at that time the primary outcome will be assessed. Therefore the last patient last visit will be at 26 months.

9.3 Study Settings

The study will take place in NHS Greater Glasgow & Clyde and Northwestern Mental Health Services, Melbourne. In Glasgow there are 21 CMHTs comprising 3246 active service users with a diagnosis of Schizophrenia. Of this group there were 906 hospital admissions between 1st August 2012 and 31st July 2014. Of this group, 558 (17.2%) have had one admission and 216 have had > 1 admission. In the Melbourne sites there are approximately 2150 service users with a diagnosis of Schizophrenia. Service utilization data here show that, one third (34.8%) of these individuals have had one or more psychiatric inpatient admissions in the previous year.

9.4 Eligibility Criteria

9.4.1 Community Mental Health Teams (CMHTs)

CMHTs will have a minimum of 5 care coordinators permanently employed and intending to remain so for a period of 12-months, each of which have a minimum of five eligible service users on their caseload will be eligible and willing to participate.

9.4.2 Service users

Service users of participating CMHTs are eligible for inclusion if

(i) they are adults (age 16+);
(ii) in contact with a local community based services;
(iii) who have been admitted to a psychiatric in-patient service at least once in the previous two years for a relapse of psychosis;
(iv) a diagnosis of Schizophrenia spectrum disorder (DSM-V) and
(v) able to provide informed consent as adjudged by the care co-ordinator or if in doubt the responsible consultant.

9.4.3 Carers

Carers who are nominated by eligible service users who provide informed consent will also be approached for their inclusion in the study. Service users can also nominate proxy-carers if they do not have a trusted other (e.g. Care Co-ordinator, Keyworker, Support Worker).

9.4.4 Exclusion Criteria

Individuals will not be eligible for participation if they do not meet the inclusion criteria outlined above. Ownership of a mobile phone will not be an inclusion criterion. We will provide participants with a Smartphone Handset with a monthly usage over the 12-months participation in the C-RCT.

9.5 Interventions

9.5.1 EMPOWER Relapse Prevention

The exact delivery of EMPOWER will be determined by service user, carer and professional care staff feedback in WP1 and WP2.

9.5.2 Service Users and Carers

Service user participants will have access to the EMPOWER App for the full 12-months of the intervention period. A Peer Support Worker will meet with service users, carers and their key-workers to introduce the service users (and their nominated carers) to the App and the handset use. EMPOWER will be developed as a flexible user-led EWS monitoring tool that incorporates (i) flexibility to tailor frequency of EWS monitoring; (ii) delivery of personalised self management messages directly to service users; (iii) flexibility to reduce numbers of items included in EWS; (iv) development of a user interface enabling service users to interact with and analyse their own data; and (v) ability for service users to send their data via email notification to their case coordinator and nominated carer. These IT characteristics mean that we can design a flexible stepped care model to relapse identification and prevention. This functionality permits a number of steps in a care pathway towards relapse detection and prevention. First, a baseline of EWS variance can be established over 4 weeks. Following a meeting with the service user, care coordinator and nominated carer familiarising the service user with the App they will be asked to monitor their EWS for a period of 4-weeks. The EMPOWER software will emit pseudo-random alerts 2-3 times per day, 6 days a week over 4-weeks. The Peer Support worker will also phone service users weekly to check in and remind them regarding mobile phone use and solve any practical problems. Following this baseline period a further visit will be made with the service user to review their EWS and to elicit preferences for electronic email notification, and personalised coping and self-management. A further visit with the service user, their nominated carer

and the care coordinator will agree and personalize (i) frequency settings (number of alerts per day/week); (ii) thresholds for increasing the frequency of monitoring and delivery of motivational self-management messages and (iii) thresholds for activating the relapse prevention pathway. Service users and the research team will be able to view patterns of EWS over time. Phone contact from the Research Team will support maintenance of monitoring, troubleshooting technical problems and discussions regarding activating the relapse prevention pathway.

9.5.3 Community Mental Health Teams

Following randomization we will provide training to mental health staff in teams randomized to EMPOWER in our model of relapse prevention which emphasizes (i) therapeutic alliance; (ii) barriers to help-seeking; (iii) developing an individualized formulation of risk of relapse and (iv) developing a collaborative relapse prevention plan. Following this we will meet with case coordinators of a fortnightly basis to provide supervision in the implementation of EMPOWER. This will also enable us to escalate stepped care procedures where EWS fail to resolve following self management or whether they escalate to such a level that necessitates immediate delivery of crisis care.

9.5.4 Treatment as Usual Control

We have chosen to use a treatment as usual (TAU) control condition in both the Glasgow and Melbourne Centres, as this provides a fair comparison with routine clinical practice. In Glasgow and Melbourne secondary care is delivered by adult Community Mental Health Teams, which largely involve regular, fortnightly, follow-up with a care coordinator and regular review by a psychiatrist. Through our Workpackages (see WP 2, 4 and 5) we will assess relevant policies governing delivery of routine care, service utilization, documentation of care plans and crisis intervention plans (including advance statements, early signs indicator forms and relapse prevention plans).

9.6 Outcomes

Outcomes will be measured by self-report, objective assessments and face-to-face interviews. All participants will be assessed at the following time points: baseline pre-randomisation (Months 10 to 14) and at 3, 6 and 12-month follow-up.

9.6.1 Feasibility Outcomes

9.6.1.1 Service user-centred

The proportion of eligible and willing service users who then consent; proportion continuing for 12-months to the end of the intervention; number

completing >33% EWS datasets; number of times data accessed and number of times data shared with mental health staff and carers. We will also assess self reported acceptability and usability using a purposely developed questionnaire (see WP 3) which will be derived from existing measures (e.g. System Usability Scale, Post Study System Usability Questionnaire, Technology Assessment Model Measurement Scales and Usefulness, satisfaction and Ease Questionnaire).

9.6.1.2 Mental Health Staff

The number of times data discussed with service-user; number of times service user has sought help; number of times service user has activated relapse prevention pathway; number of times EMPOWER triggered a change in management (e.g. appointment brought forward, medication change).

9.6.1.3 Safety Outcomes

Safety will be explored by exploring whether EMPOWER increases Fear of Relapse, serious adverse events (relapse, rehospitalisation, suicide and attempted suicide), and disengagement from EWS monitoring. We will also explore pathways to relapse and identify failures to respond to a threat of relapse in order to further refine our intervention.

9.6.2 Relapse Outcomes

We will measure relapse over the 12-months following introduction of the EMPOWER Relapse Prevention. There is a lack of agreement with respect to definitions of relapse and many studies fail to utilise standardized and validated observer-rated instruments (Gleeson et al., 2010). Bebbington et al., (2006) have developed reliable and valid criteria for relapse and remission that have strong clinical applicability. Independent and blind observer ratings are applied to detailed extracts taken from clinical notes. Ratings are based on changes in positive psychotic symptoms. Evidence is required of improvement in (for partial remission) or absence of (for full remission) positive psychotic symptoms continuing for at least 4 weeks. Relapse ratings are based on evidence of the re-emergence of, or significant deterioration in, positive psychotic symptoms of at least moderate degree persisting for at least 2 weeks. We will establish reliable and valid criteria for assessing severity of relapse. Following each relapse we will conduct an audit trail exploring help-seeking attempts and service responses to help-seeking. The identification of relapse "failures" will enable refinement of the intervention for the main trial. We will also measure symptoms, service engagement, coercion, empowerment, adverse events, emotional adjustment, and carer burden at baseline (pre-randomisation); 3, 6 and 12-month follow-up.

9.6.3 Mechanisms

Measures have been selected which map directly onto hypothesised mechanisms of change as well as known predictors of relapse. Mechanisms of patient benefit

are operationalised as improvements in recovery, empowerment, utilisation of social supports.

(i) *Recovery and Empowerment/Disempowerment:* The Empowerment Rating Scale (ERS), Questionnaire for Personal Recovery (QPR), Self Efficacy Scale (SCS), MacArthur Perceived Coercion Scale will be completed by service user participants.

(ii) *Social and Interpersonal Context:* The Sources of Support Scale, Psychosis Attachment Measure (SR) and Perceived Criticism Scale will be completed by service user participants. The participant's care-coordinator will complete the Psychosis Attachment Measure (Observer Version).

9.6.4 Secondary Outcomes

We will also assess changes in symptoms, substance use, emotional distress, carer burden, service enagement and adherence and health related quality of life.

(i) *Mental Health Status:* The Positive and Negative Syndrome Scale (PANSS) Global Assessment of Functioning (GAF) and the Calgary Depression Scale for Schizophrenia (CDSS) will be completed with service user participants.

(ii) *Substance use measures:* Time Line Follow Back for drugs and alcohol (TLFB); Alcohol Use Disorder Identification Test (AUDIT), the Drug Abuse Screening Test (DAST) and the Cannabis User Disorders Identification Test - Revised (CUDIT-R) will be completed with service user participants.

(iii) *Emotional distress:* Fear of Recurrence Scale (FoRSe), Hospital Anxiety and Depression Scale (HADS), Personal Beliefs about Illness Questionnaire-Revised (PBIQ-R) will be completed by service user participants.

(iv) *Carer experiences:* The Involvement Evaluation Questionnaire will be completed as a measure of carers' worrying, tension, urging and supervision.

(v) *Service Engagement:* The Service Engagement Scale will be completed by the participant's care coordinator. The Working Alliance Scale (Short Form: WAI-SF) will be completed by service user participants and care co-ordinators. The Service Attachment Scale (SAS) will be completed by the service user participant. The Medication Adherence Rating Scale will be completed by service user participants.

(vi) *Health Economics:* Euro-Qol Five Dimension (EQ-5D) and the Assessment of Quality of Life–Eight Dimension (AQoL-8D) and Client Service Receipt Inventory (CSRI).

9.7 Participant Timeline

	Baseline	Randomisation	3-months	6-months	12-months
Service Users	X	X	X	X	X
Carers	X	X	X	X	X
Mental Health Staff	X	X	X	X	X

9.8 Sample Size

No formal sample size calculation is appropriate for this pilot phase. The number of participants recruited to the various work packages will give adequate information and insights to inform the design and size of a future definitive, pragmatic, multicentre and multinational cluster randomised controlled trial.

The C-RCT will test the feasibility of the full scale C-RCT. The proposed sample size of 120 service users across 40 care coordinators in 8 CMHTs is sufficient for establishing the feasibility and obtaining parameters (including the relevant ICCs for the cluster design) to inform the main trial.

9.9 Recruitment and Randomisation

This is a cluster-randomized trial and the randomization will take place at the level of the CMHT (the cluster). Participating CMHTs will be randomized to the EMPOWER Relapse Prevention Intervention or to continue their usual approach to care. Recruitment and randomization will take place in Months 10 to 14 after completion of Workpackages 1 to 3. Final follow-ups will take place at Months 24 to 26.

Randomization procedures will be undertaken by the study statistician at the Centre for Healthcare Randomised Trials (CHaRT), University of Aberdeen. The order in which the set of eligible and willing care coordinators and then service users are approached will be in randomised order. Researchers will approach each eligible care coordinator in this order and seek their consent to participate in the trial, working down the list until the target sample size of five care coordinators per CMHT is achieved. Prior to randomisation, consenting care-coordinators will provide an anonymised list of their current service user caseload. This list will then be randomly ordered. Researchers will then approach these service users sequentially and seek informed consent to participate in the study. In situations where a service user does not wish to take part in the study, the researcher will continue to select the next service user from the list.

We aim to approach and consent 3 participants per care coordinator (giving a total of 120 potential participants). This means that we anticipate that 3 from 5 potential participants on each care coordinators caseload will consent to participate giving a rate of consent of 60% overall. After completing baseline assessments on all consenting service users in care coordinators' and CMHTs' caseload, the clinical trials unit will conduct randomisation of the CMHT. For Australia, with just two clusters, this will be by simple randomization. For Glasgow, with six clusters, we will create 3 pairs of teams based on similarity of the catchment area in terms of social deprivation (Carstairs) score. Then we will randomly allocate one member of the pair to the intervention, and the remaining member will be allocated to control.

We will explore in this pilot phase the best method of randomly allocating the clusters in the full trial, specifically to establish what matching factors (if any, and/or if matching at all is appropriate, methodologically) are suitable. Researchers and the statistician will remain blind to treatment allocation. Outcome assessments will only be conducted by researchers blind to the treatment arm.

Any violations of the study protocol will be recorded and reported to the Research Ethics Committee, SSC and the independent DMEC.

9.10 Methods (Data collection, management and analysis)

9.10.1 Data Collection Methods

All outcome measures will be administered at baseline and subsequently at 3, 6 and 12 months by RAs who will have been trained in the use of all the instruments and scales, to achieve a satisfactory level of inter-rater reliability. Regular training sessions including the use of video and role play will be conducted with all research assistants in order to maintain reliability and prevent rater drift. Participants will be offered choices regarding length of assessments, including the option of breaks and multiple occasions. Assessment measures will be clearly prioritised so that the most important will be collected first to avoid missing data. We will have a standard protocol for managing any distress that is associated with the completion of measures, which we have successfully utilised in several trials and has been developed in collaboration with service users; this includes telephone contact within 48 hours of assessments in order to check on participant well-being

9.10.2 Protection Against Bias

Single blind – assessors will be blind to treatment condition. Blindness will be maintained using a wide range of measures, such as separate offices for the Research Nurse and Peer Support Workers and RAs, protocols for answering telephones, message taking and secretarial support, separate diaries and pigeon holes and datafile security, using passwords and encryption of randomisation information. Maintaining rater blindness to treatment allocation is crucial, and the DMEC and SSC will regularly monitor unblindings by each centre, and implement corrective action if necessary. Following entry assessment and completion of baseline assessments, participants will be allocated to treatment groups through our web-based randomisation service and the Trial administrator will inform the participants of this decision. Any accidental unblindings will be recorded and outcome analyses will be repeated excluding these participants to determine the robustness of the findings.

9.10.2 Data Management

Each study participant will be assigned a unique trial identification number at the start of the assessment process. This number will be written on all clinical assessment forms/datasheets and databases used to record data on study participants. A hard copy of a record sheet linking patient identity, contact details and trial identification number for all participants will be kept at each site. It will be placed securely in a locked filling cabinet separate from datasheets. The local study co-ordinator will enter the data on to an electronic database, and all such data will be checked for errors before being transferred to the appropriate statistical package. All data will be kept secure at all times and maintained in accordance with the requirements of the Data Protection Act, and archived according to clinical trial GCP regulations.

9.10.3 Statistical Methods

The analysis will follow the guidelines of the CONSORT statement for clustered randomized trials and recommendations for the analysis of clustered randomized trials when presenting and analysing the data. Here, we have potentially repeated measures on individual patients nested within care coordinators who are nested within teams (the unit of randomization) who are nested within region (Australia and UK or possibly to be known as Scotland). The analysis will adjust for these factors using appropriate random (patient, if relevant; and care coordinator; and team) and fixed (region) effects. The trial statistician will remain blind until the main analyses are complete. Baseline characteristics of the study population will be summarised separately within each randomised group. Baseline characteristics will also be presented for dropouts and completers within each treatment group. The analysis will be performed on the basis of the intention-to-treat principle and will utilise all available follow-up data from all randomised participants.

9.11 Health Economics (Work Package 5: Months 21 to 26)

9.11.1 Objectives

We will focus on the development of economic measures as part of the trial including how to capture resource use and quality of life. We will work between different service systems in the UK and Australia to build comparability and utilise the pilot to refine the measurement and capture of economic data.

9.11.2 Deliverables

This will lead into the development of an analytic framework (model) for the health economic analysis in the definitive study as well as a protocol for the "within trial" evaluation. This pre-trial model will be used to help provide an economic rationale for the design of the definitive trial.

9.11.3 Methods

As part of the within trial economic evaluation we propose to test two health-related quality of life measures (which can be used to assess Quality-Adjusted Life Years, QALYs), the Euro-Qol Five Dimension (EQ-5D) and the Assessment of Quality of Life –Eight Dimension (AQoL-8D) in the feasibility trial. While the EQ-5D is very commonly used in the UK & Australian context its sensitivity and appropriateness in people with schizophrenia has been seriously questioned (Brazier et al., 2014). The AqoL-8D is a newer HRQoL measure and was developed to be sensitive to the domains of quality of life, which are important to people with mental health problems. A resource use questionnaire to capture costs incurred will also be tested. This questionnaire will need to be appropriate to both the UK and Australian context but may require some system specific modules for services, which differ between the two settings.

10.0 Research Governance

NHS Greater Glasgow & Clyde is the Sponsor of the Trial in the UK. In accordance with high standards of research governance we will ensure researchers receive training in the International Conference on Harmonisation (ICH) Guidelines - Good Clinical Practice. We will set up a Study Steering Committee (SSC) and an Independent Data Monitoring and Ethics Committee (DMEC) prior to the start of the study. The SSC will comprise study applicants, a representative of the HTA, and representatives of service users and providers, and have an independent chairman. An DMEC will also be established to monitor (1) recruitment of study participants, (2) ethical issues of consent, (3) quality of data (including missing data), (4) the incidence of adverse events, and (5) any other factors that might compromise the progress and satisfactory completion of the trial. This will also have an independent chairman, and include an independent statistician.

10.1 Study Steering Committee (SSC)

The role of the SSC is to provide overall supervision for a project on behalf of the Project Sponsor and Project Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. The SSC will be constituted following NIHR Guidance (Version date: May 2013). The membership of the SSC is described on Page 3 above.

10.2 Data Monitoring and Ethics Committee (DMEC)

The DMEC will have access to unblinded comparative data and monitor these data and make recommendations to the SSC on whether there are any ethical or safety issues on whether the study should continue. The DMEC will be constituted following NIHR Guidance (Version date: May 2013). The membership of the DMEC is described on Page 3 above.

10.3 Audit

NHS Greater Glasgow and Clyde will retain the right to audit implementation of the trial in the UK context.

1043 Measuring Adverse Events

Understanding and quantifying the risk of potential adverse effects of complex interventions is an important task. In this study we will measure the following:

10.4.1 Death caused by suicide

10.4.2 Suicide attempt

10.4.3 Suicidal crisis (explicit plan for serious suicidal activity without suicide attempt) as defined in Calgary Depression Rating Scale for Schizophrenia [CDSS], item 8, rating 2)

10.4.4 Increased Fear of Relapse as measured by the Fear of Recurrence Scale described above.

In addition to 1 to 4 above we will administer a measure of potential adverse effects from trial involvement at point of exit (used in the NIHR HTA FOCUS Trial). Many of the measures cannot be easily used to assess reasons for early discontinuation from the trial; However, our measure of adverse effects has been designed with this in mind and was designed to measure these broad categories: worsening difficulties; poor engagement (including low motivation); situational change; not getting benefit; stigma; increased conflict with others (care team, family etc.); felt better. One ethical consideration is that participant may feel

obliged to complete the measure. We make it explicit in the information at the start of the measure that they are under no obligation to complete the measure and if they decided not to do so that this will not affect any care they receive now or in the future. If people discontinue from the trial we will ask permission to administer this measure to assess their reasons for discontinuation. If we cannot contact the participant we will ask their care coordinator to attempt to administer the measure on our behalf.

11.0 Widening Stakeholder Engagement for the Main Trial (Work Package 6: Months 21 to 26)

11.1 Objectives

To engage with key services, and local service user user and carer organisations in the additional centres participating in the main trial (Scotland, Manchester and Birmingham).

11.2 Deliverables

We will develop a plan for transitioning from a pilot trial to the full scale main trial.

11.3 Methods

We will host three Knowledge Exchange (KE) Events in Edinburgh, Manchester and Birmingham and invite key representatives of NHS services, professional staff and local service user and carer organizations. In these events we will identify key learning outcomes from the EMPOWER project and work with stakeholders in developing plans for the main study phase. We will follow up these KE Events with active engagement with local NHS services, CMHTs and management, local R&D and Information Governance departments. We will identify potential changes to services that would threaten cluster randomization in a future trial. We will use the address the following aims:

(i) What is the latest evidence for relapse prevention in psychosis? What is the relapse rate for established psychosis in your service?

(ii) What is the process of relapse and the role of EWS? What experience do stakeholders have of EWS and importance in relapse?

(iii) Implementing our team based approach to early detection of relapse using mobile technology and showing (a) potential for relapse prevention of the approach, including the 12 month relapse rate in our control arm (to show that further interventions are needed), (b) experience of staff, service users and carers/supporters (c) developing the next stage evaluation.

(iv) Engaging teams for the next stage evaluation: what are the potential benefits, including the identification of the current rate of relapse in target areas for the next stage; what will be involved; how should we engage patients and staff from the teams? Can you help us to enlist teams from your area?

We will record the proceedings and disseminate our outcomes from these events to potential participant trusts/teams/user-groups.

12.0 Ethics and Dissemination

12.1 Research Ethics Approval

Before Phase 1 and Phase 2 of the study Research Ethics approval will be sought from West of Scotland Research Ethics Service (Glasgow) and NorthWestern Research Ethics (Melbourne).

12.2 Protocol Amendments

The views of the SSC and DMEC will be sought on any proposed amendments to the EMPOWER Protocol. Following this any proposed amendments will be submitted to the Study Sponsor and Research Ethics Committees for approval. Protocol amendments will be added to the EMPOWER Protocol and to the ISRCTN Registry.

12.3 Consent

Only those who agree to provide written informed consent will be included in the study. All potential participants, including Service Users, Carers and Mental Health Staff will be provided with a copy of a Participant Information Sheet and Consent Form that includes a contact number for the study team.

12.4 Confidentiality

The confidentiality of all study data will be ensured via the following security mechanisms.

12.4.1 Software systems, interface and compliance with UK security standards

Three general principles of information security (confidentiality, integrity and availability) will be followed in the design and implementation of EMPOWER. All data transmitted to and from EPOWER servers will be encrypted over https with strong ciphers as detailed in the Approved Cryptographic Algorithms Good Practice Guidelines (NHS, 2012 and Australian Equivalence). Cipher suites will be implemented in compliance with Section 6 ("Preferred uses of cryptographic algorithms in security protocols") of the Good Practice Guidelines. In cases

where participant data are downloaded from the EMPOWER sites, these data will be securely encrypted with a pass phrase of appropriate length and complexity. Data transfers are secured by using standards web security protocols. Uploading data to a central server in real time enables study data to be captured and so protects against data loss such as a phone, which can be lost or stolen. This removes the need for personal data storage on the device. The purpose of the server in this case is secure data storage.

12.4.2 Software systems, interface and compliance with Australian security standards

A range of measures are in place to help ensure the security of the EMPOWER App and the data generate by its users. The App is hosted on University of Manchester web server, and has standard measures in place to prevent unauthorized access. These measures are governed by the Australian Government standards contained in the Australian Government "Guide to securing personal information" (Office of the Australian Information Commissioner – Jan 2015) and the Australian National Privacy Principles (replaced National Privacy Principles March 2014), with regard to design principles for confidentially, integrity, availability and physical security. We will also incorporate ISO 25010 which provides for safety-in-use and measures satisfaction with security. These security measures correspond closely to the NHS standards with which ClinTouch currently complies.

12.4.3 Additional security measures:

There are a number of technical measures we will employ to protect personally identifiable data. Any data stored on the phone by the participant will be encrypted. We will also recommend that service users set a passcode to access their Smartphone. All Smartphones provided by the research team will require a passcode for access. All service users recruited to the study will give their informed consent, and this will include risks to data security. These measures should be sufficient to prevent unauthorized data access, should the phone be lost or stolen.

12.4.4 Other study data

Any hard copy/ paper copy information will be stored in a locked filling cabinets at local sites and will only be directly accessible by the CI and the study RA. Directly identifying participant information (e.g., consent forms) and de-identified data will be stored in separate locked filing cabinets. Data will be entered onto a secure web-based portal hosted by University of Aberdeen.

12.4.5 Type of information stored

The security arrangements and access for the code will be as follows. Each participant's dataset will have a unique code and will be stored in a password protected database. The unique code will be linked to the participant's name and contact details. The information linking the participant's unique code and contact details will be stored separately from the study database and will also be password protected.

12.5 Dissemination Plan

We will produce an EMPOWER Dissemination Policy. This document will outline a comprehensive list of possible papers with basic descriptions of objectives, contents, authorship, and journals to be targeted.

Dissemination will occur via a number of methods, which include publication of trial papers, conference presentations, book chapters, and the HTA final report (monograph and trials directory).

Participants will be informed of the results by being offered written and/ or face-to-face feedback.

We have an obligation to give the HTA notification of an output prior to any publication (whether in oral, written or other form) of data or the results of the project or of matters arising from such data or results. Therefore, the trial manager should be notified of any outputs (oral, written or other form). The trial manager will coordinate notification to the HTA. Research projects are contractually obliged to submit a draft final report for inclusion in the influential Health Technology Assessment journal series. The journal is indexed on MEDLINE, EMBASE and the ISI Science Citation Index, and assessed for inclusion in the Database of Abstracts of Reviews of Effectiveness. Before a draft final report is published it is peer-reviewed by at least four relevant experts to ensure scientific integrity and quality standards. An editor will review the external reviewers' comments and the draft version of the report, and feedback is given to the author. Ideally, this will take place within two months of receipt of the draft final report. The team is invited to resubmit their revised report within four weeks. There may be a further round of editorial review before the report is sent to the publisher. The NIHR Journals Library ensures that the results of pilot and feasibility studies which have been funded by the participating programmes are published, regardless of outcome or significance of findings in order to ensure that as much information as possible about each study is in the public domain. Authors are encouraged to report everything, be transparent in their reporting, be reflective and avoid overstating their findings.

12.6 Strategy for Knowledge Exchange and Impact

Our strategy for Knowledge Exchange and Impact means that we are ensuring service user and carer involvement from the outset of the study (for audit criteria see Ruppertsberg et al., 2014). This is reflected in a number of design features of the protocol.

(i) The Scottish Recovery Network (www.**scottishrecovery**.net/) are active collaborators on the project proposal and have actively been involved in the design of the EMPOWER Relapse Prevention Intervention (led by their Director Simon Bradstreet). A key impact of this early involvement has been to ensure that service users retain control of their data and can be empowered to make decisions to activate different stages of the relapse prevention pathway and share their data with carers and case coordinators.

(ii) In addition, the SRN will employ the Research Assistant evaluating the outcomes of the C-RCT and a Peer Support Worker who will engage with and support service user participants randomized to the EMPOWER Relapse Prevention Intervention. The main beneficiaries of the intervention are service users with a diagnosis of schizophrenia and their carers. At the outset of the study we will involve these stakeholders in evaluating the acceptability and usability of ambulant symptom recording using mobile phones and identifying key of incentives and barriers to use.

(iii) Our strategy for Knowledge Exchange and Impact also means that we are ensuring the involvement of professional care staff from the outset of the study. This is reflected in our work packages that explore the acceptability and usability of ambulant symptom recording using mobile phones amongst professional care staff, identify incentives and barriers to implementation by NHS Teams and identification existing relapse prevention pathways.

(iv) In addition, our use of a Cluster Randomised Controlled Trial design maximises our ability to learn how to implement the EMPOWER Relapse Prevention Intervention into routine care. Our inclusion of sites spanning the United Kingdom and Australia maximises the portability of this intervention across different health systems.

(v) We will work with and seek feedback from a Trial Steering Group following each WP phase. This will enable us to report transparently achievement of milestones and inform the next step of project development. The Trial Steering Group will comprise stakeholders including clinical academic, health service managers and clinicians, and service user and carers.

(vi) We will organize a number of events for carers, service users and professional staff in Glasgow, Edinburgh, Manchester and Birmingham to identify and share key learning experiences arising from the study

and to facilitate scoping and engagement of stakeholders participating in the main study.

14.0 Progression to Full Trial

We have identified 4 of the most important outcomes that will provide the basis for informing progression to the full trial. As advised these will form the basis of discussion rather than hard criteria.

14.1 Recruitment

Since submitting the full application in September 2014 we have initiated engagement with Community Mental Health Teams all of whom have expressed interest in participating in the study.

a) Each of these teams employ between 8 and 10 care coordinators. In order to recruit sufficient service user participants we anticipate having informed consent from 5 care coordinators in each team (a consent rate of between 50 and 62.5%).

b) In order to achieve a sample size of 120 participants we aim to approach and consent 3 participants per care coordinator (giving a total of 120 potential participants). This means that we anticipate that 3 from 5 potential participants on each care coordinators caseload will consent to participate giving a rate of consent of 60% overall.

14.2 Outcomes

It is well established that in mental health trials with challenging patient participant groups using Patient Reported Outcome Measures loss to follow-up is an important methodological concern. We will employ all evidence-based tactics to minimize loss to follow-up and by convention we would not expect loss to follow-up tat 12-months to exceed 20%. We will use established analytic techniques to adjust for missing data.

14.3 Process evaluation

In line with recent MRC Guidance on process evaluation of Complex Interventions (Kellogg, 2004; Moore et al., 2015) we have produced a Logic Model for the EMPOWER intervention (Figure 1). Figure 1 provides a clear description of the intended intervention, how it will be implemented, and how it is expected to work. The Logic Model will provide the basis for organizing observations of processes and outcomes throughout the study and provide a basis to report and fully discuss intervention components for the main trial and implications for intervention theory and methods.

14.4 Safety

We will monitor serious adverse events (relapse, rehospitalisation, suicide and

attempted suicide) carefully to detect if there are differences between randomized groups to ensure that it is safe to expose a greater number of participants to the EMPOWER intervention in the main trial.

15.0 References:

Ainsworth, J., Palmier-Claus, J., Machin, M., Barrowclough, C., Dunn, G., Rogers, A., Buchan, I., Barkus, E., Kapur, S., Wykes, T., Hopkins, R. & Lewis, S (2013). A Comparison of two delivery modalities of a mobile phone-based assessment for serious mental illness: native smartphone application vs text-messaging only implementations. *J Med Internet Res*, 15, e60.

Alvarez-Jiminez, M., Priede, A., Hetrick, S.E., Bendall, S., Killackey, E., Parker, A.G., McGorry, P., & Gleeson, J.F. (2012) Risk factors for relapse following treatment for first episode psychosis: A systematic review and meta-analysis of longitudinal studies. *Schiz Res*, 139, 116-128.

Alvarez-Jimenez, M., Alcazar-Corcoles, M.A., González-Blanch, C., Bendall, S., McGorry, P.D., & Gleeson, J.F. (2014). Online, social media and mobile technologies for psychosis treatment: A systematic review on novel user-led interventions. *Schiz Res, 156*, 96-106. doi: 10.1016/j.schres.2014.03.021

Alvarez-Jiminez, M., Bendall, S., Lederman, R., Wadley, G., Chinnery, G., Vargas, S., Larkin, M., Killackey, E., McGorry, P., & Gleeson, J. (2013) On the HORYZON: moderated online social therapy for long-term recovery in first episode psychosis. *Schiz Res*, 143, 143-149.

Ascher-Svanum, H., Zhu, B., Faries, D.E., Salkever, D., Slade, E.P., Peng, X., & Conley, R.R. (2010) The cost of relapse and the predictors of relapse in the treatment of schizophrenia. BMC Psychiatry 2010, 10:2 http://www.biomedcentral.com/1471-244X/10/2

Barlow, J., Bayer, S., & Curry, R. (2006) Implementing complex interventions in fluid multistakeholder environments: Experiences of 'telecare'. *Technovation*, 26, 396-406.

Ben-Zeev D, Davis KE, Kaiser S, Krzsos I, Drake RE. (2013) Mobile technologies among people with serious mental illness: opportunities for future services. *Adm Policy Ment Health*. 40:340–343.

Ben-Zeev, D., Brenner, C.J. Begale, M., Duffecy, J., Mohr, D.C., & Mueser, K.T. (2014) Feasibility, Acceptability and preliminary efficacy of a smartphone intervention for schizophrenia. *Schiz Bull*. doi:10.1093/schbul/sbu033

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. *Psychl Med*, 19, 649–656.

Birchwood, M. (2003). Pathways to emotional dysfunction in first-episode psychosis. *Br J of Psych*, 182, 373–375. doi:10.1192/bjp.182.5.373

Brazier, J., Connell, J., Papaioannou, D., Mukuria, C., et al. 2014. A systematic review, psychometric analysis and qualitative assessment of generic preference-based measures of health in mental health populations and the estimation of mapping functions from widely used specific measures. *Health Technology Assessment (Winchester, England),* 18**,** 1-188.

Campbell, M.K., Elbourne, D.R., & Altman, D.G. (CONSORT statement: extension to cluster randomised trials. *BMJ*, 328, 702-708.

Day, J.C., Bentall, R., Roberts, C., Randall, F., Rogers, A., Cattell, D., Healy, D., Rae, P., & Power, C. (2005) Attitudes towards antipsychotic medication: The impact of clinical variables and relationships with health professionals. *Arch Gen Psychiatry*. 62, 717-724.

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

Farrelly, S., Lester, H., Rose, D., Birchwood, M., Marshall, M., Waheed, W., Henderson, R.C., Szmukler, G. & Thornicroft, G. (2015) Improving therapeutic relationships: Joint Crisis Planning for individials with psychotic disorders. *Qualitative Health Research*. DOI: 10.1177/1049732314566320

Gleeson J.F., Rawlings, D., Jackson, H.J. & McGorry, P. (2005) Agreeableness and neuroticism as predictors of relapse after first episode psychosis: A prospective follow-up study. *Journal of Nervous and Mental Disease*, 193, 160-169. DOI: 10.1097/01.nmd.0000154841.99550.d3

Granholm E, Ben-Zeev D, Link PC, Bradshaw KR, Holden JL. (2012) Mobile Assessment and Treatment for Schizophrenia (MATS): a pilot trial of an interactive text-messaging intervention for medication adherence, socialization, and auditory hallucinations. *Schiz Bull*. 38, 414–425.

Gumley, A.I., O'Grady, M., McNay, L., Reilly, J., Power, K.G. & Norrie, J. (2003) Early intervention for relapse in Schizophrenia: Results of a 12-month randomised controlled trial of Cognitive Behavioural Therapy. *Psychl Med*, 33, 419-431.

Gumley A.I**.** & Park C. Relapse Prevention in Early Psychosis. In. P. French, M. Reed, J.Smith, M. Rayne, D. Shiers (Eds) Early Recovery in Psychosis: Promoting Recovery (2010)

Gumley A, Taylor H, Schwannauer M, Macbeth A. (2014) A systematic review of attachment and psychosis: Measurement, Construct Validity and Outcomes. *Acta Psychiatrica Scandinavica* 129, 257-274. doi:10.1111/acps.12172

Gumley, A.I., Macbeth, A., Reilly, JD., O'Grady, M., White, R.G., McLeod, H., Schwannauer, M., & Power, K. (2014) Fear of recurrence: Results of a randomized controlled trial of relapse detection in schizophrenia. *British Journal of Clinical Psychology*. DOI:10.1111/bjc.12060

Kellogg Foundation WK. Logic model development guide. W K Kellogg Foundation, 2004.

Lambert, M., Conus, P., Cotton, S., Robinson, J., McGorry, P.D., Schimmlemann, B.G. (2010). Prevalence predictors, and consequences of long-term refusal of antipsychotic treatment of first episode psychosis. *J Clin Psychopharmacology, 30,* 565-572

Lederman, R., Wadley, G., Gleeson, J., Alvarez-Jiminez, M. (2013) Using On-Line technologies to identify and track early warning signs of psychosis. *Proceedings of the 21st European Conference on Information Systems ECIS 2013 Research in Progress*. Paper 1. http://aisel.aisnet.org/ecis2013_rip/1

Morgan, V. A., Waterreus, A., Jablensky, A., Mackinnon, A., McGrath, J. J., Carr, V., ... & Saw, S. (2011). *People living with psychotic illness in 2010: Report on the second Australian national survey of psychosis.* Canberra: Commonwealth of Australia. ISBN: 978-1-74241-613-7 Online ISBN: 978-1-74241-614-4

May, C. (2013) Towards a general theory of implementation. *Implementation Science*, 8,18. http://www.implementationscience.com/content/8/1/18

Moore, G.F., Audrey, S., Barker, M., Bond, L., Bonell, C., Hardeman, W., Moore, L., O'Cathain, A., Tinati, T., Wight, D. & Baird, J. (2015) Process evaluation of complex interventions: Medical Research Council Guidance. British Medical Journal 350:h1258. doi:10.1136/bmj.h1258

Morgan, V. A., Waterreus, A., Jablensky, A., Mackinnon, A., McGrath, J. J., Carr, V., ... & Saw, S. (2012). People living with psychotic illness in 2010: The second Australian national survey of psychosis. *Australian and New Zealand Journal of Psychiatry*, *46*(8), 735-752.

Morriss R, Vinjamuri I, Faizal MA, Bolton CA, McCarthy JP. Training to recognise the early signs of recurrence in schizophrenia. *Cochrane Database of Systematic Reviews 2013*, Issue 2. Art. No.: CD005147. DOI: 10.1002/14651858.CD005147.pub2.

Mulhern, B., Mukuria, C., Barkham, M., Knapp, M., Byford, S., Soeteman D., & Brazier, J. (2014) Using generic preference-based measures in mental health: psychometric validity of the EQ-5D and SF-6D. *BJP* published online May 22, 2014

Neil, A., Carr, V.J., Mihalopoulos, C., Mackinnon, A., & Morgan, V.A. (2014) Costs of psychosis in 2010: Findings from the second Australian National Survey of Psychosis. *Aust N Z J Psychiatry*, 169–182 .DOI: 10.1177/0004867413500352

Novick, D., Haro, J.M., Suarez, D., Perez, V., Dittman, R.W., & Haddad, P.M. (2010) Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. *Psychiatry Research*. 176, 109-113.

Palmier-Claus J, Myin-Germeys I, Barkus E, Bentley L, Udachina A, Delespaul P, Lewis S, Dunn G. (2011). Experience sampling research in individuals with mental illnes: reflections and guidance. *Acta Psychiatrica Scandinavica*, 123(1), 12-20.

Palmier-Claus, J., Ainsworth, J., Machin, M., Barrowclough, C., Dunn, G., Barkus, E., Rogers, A., Wykes, T., Kapur, S., Buchan, I., Salter, E. & Lewis, S (2012). The feasibility and validity of ambulatory self-report of psychotic symptoms using a smartphone software application. *BMC Psychiatry*, 12, art172.

Pope, C., Ziebland, S., & Mays, N. (2000) Analysing qualitative data. *BMJ*, 320, 114- 116.

Raudino, A., Carr, V.J., Bush, R., Saw, S., Burgess, P., & Morgan, V.A. (2014) Patterns of service utilization in psychosis: Findings of the 2010 Australian National Survey of Psychosis. *Aust N Z J Psychiatry*, 48, 341–351. DOI: 10.1177/0004867413511996

Richardson J, Khan M, Iezzi A, Sinha K, Mihalopoulos C, Herrman H, Hawthorne G, Schweitzer I. (2009). *The AQoL-8D (PsyQoL) MAU Instrument: Overview September 2009*. Centre for Health Economics, Monash University, Melbourne.

Robinson, D., Woerner, M. G., Alvir, J., Bilder, R., Goldman, R., Geisler, S., . . . Lieberman, J. A. (1999) Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Archives of General Psychiatry*, 56, 241–246.

Rummel-Kluge C, Schuster T, Peters S, Kissling W. (2008) Partial compliance with antipsychotic medication is common in patients with schizophrenia. *Australian and New Zealand Journal of Psychiatry*. 42, 382-388.

Ruppertsberg, AI., Ward, V., Ridout, A., & Foy, R. (2014) The development and application of audit criteria for assessing knowledge exchange plans in health research applications. *Implementation Science*, 9:93.

Saha, S., Chant, D., & McGrath, J. (2007) A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Archives of General Psychiatry,* 64, 1123-1131.

Španiel F, Hrdlička J, Nov.k T, et al. (2012) Effectiveness of the information technology-aided program of relapse prevention in schizophrenia (ITAREPS): a randomized, controlled, double-blind study. *J Psychiatr Pract*. 18,269–280.

Subotnik, K. L., Nuechterlein, K. H., Ventura, J., Gitlin, M. J., Marder, S., Mintz, J., . . . Singh, I. R. (2011). Risperidone Nonadherence and Return of Positive Symptoms in the Early Course of Schizophrenia. *American Journal of Psychiatry, 168*(3), 286-292. doi: 10.1176/appi.ajp.2010.09010087

Thornicroft, G., Farrelly, S., Szmukler, G., Birchwood, M., Waheed, W., Flach, C., …. Marshall, M. (2013) Clinical outcomes of Joint Crisis Plans to reduce compulsory treatment for people with psychosis: a randomized controlled trial. *The Lancet*. 381, 1634-1641.