Protocol Title Page

LONG TITLE: A PSYCHOLOGICAL INTERVENTION FOR SUICIDE APPLIED TO PATIENTS WITH PSYCHOSIS: THE CARMS TRIAL (COGNITIVE APPROACHES TO COMBATTING SUICIDALITY).

SHORT STUDY ACRONYM: CARMS

Contents

Protocol Version, Number and Date

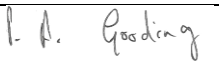
RESEARCH REFERENCE NUMBERS	NUMBER	DATE
IRAS	ID: 201644 17/NW/0089	31-03-17; TG
TRIAL REGISTRY NUMBER		
ISRCTN	ISRCTN17776666	
ClinicalTrials.gov	NCT03114917	
PROTOCOL VERSION NUMBER		
	5.0	27/04/2020
OTHER RESEARCH REFERENCE NUMBERS		
SPONSOR'S NUMBER		
University of Manchester	NHS001146	
FUNDER'S NUMBER		**DATE**
MRC/NIHR Efficacy and Mechanism Evaluation	13/161/25 Gooding	June 2016

Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator and Co-PI agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's Protocols, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Co-Principal Investigator 1: Name	Patricia Gooding
Co-Principal Investigator 1: Position	Senior Lecturer
Co-Principal Investigator 1: Signature	
Co-Principal Investigator 1: Date	27/04/2020
Co-Principal Investigator 2: Name	Gillian Haddock
Co-Principal Investigator 2: Position	Professor
Co-Principal Investigator 2: Signature	
Co-Principal Investigator 2: Date	27/04/2020

Key Trial contacts

Co-Principal Investigator 1

Patricia Gooding patricia.gooding@manchester.ac.uk 0161 275 1971

Co-Principal Investigator 2

Gillian Haddock gillian.haddock@manchester.ac.uk 0161 275 8485

Trial Statistician

Richard Emsley richard.emsley@kcl.ac.uk

CARMS Trial Manager/Project Co-ordinator

Charlotte Huggett charlotte.huggett@manchester.ac.uk 0161 271 0729

Greater Manchester Mental Health Trust (Host)

1. R&I research grants co-ordinator - Sue Dobson 0161 276 3310, susan.dobson@gmmh.nhs.uk
2. Research Support Coordinator – Rachel Rosenhead 0161 358 1689, Rachel.Rosenhead@gmmh.nhs.uk.
3. HR - Emma Murphy Emma.Murphy@gmmh.nhs.uk 0161 358 1952
4. GMMH communications (R&I contact) – Lisa Lee 0161 358 0649 Lisa.Lee@gmmh.nhs.uk; Communications@gmmh.nhs.uk

The University of Manchester (Sponsor)

1. Research Governance - Lynne Macrae 0161 275 FBMHethics@manchester.ac.uk; Lynne.Macrae@manchester.ac.uk
2. Contracts Manager - Helen Thornley 0161 306 3995 helen.thornley@manchester.ac.uk
3. Research Support Manager - Julie Saunders 0161 275 2436 julie.saunders@manchester.ac.uk
4. Personal Assistant to Gillian Haddock - Emma-Louise Cullen 0161 275 8485 Emma-louise.Cullen@manchester.ac.uk

The Manchester Clinical Trials Unit

Name	Role	Phone	Email
Matthew Smyth	Trial Manager	0161 306 3150	matthew.smyth@manchester.ac.uk

1.

The Independent Trial Steering Committee (TSC)

Role	Name	Email	Tel.
Chair	Prof. Thomas Craig	thomas.craig@kcl.ac.uk	0207 8840738/5062 07912379574
Service users	Caroline Hellewell		
	Joe Keaney		0161 969 7698
Charity CEO	Nicky Lidbetter (Self Help)	nicky.lidbetter@selfhelpservices.org.uk	0161 868 0547
Clinical Psychologist	Elizabeth Kuipers	elizabeth.kuipers@kcl.ac.uk	0207 848 0231
Clinical Psychologist	Prof. Bill Sellwood	b.sellwood@lancaster.ac.uk	01524 593998

The Independent Data Monitoring and Ethics Committee (DMEC)

Role	Name	Email	Tel.
Chair	Prof. David Kingdon (Psychiatrist)	D.Kingdon@soton.ac.uk	02380 718520/ 835577
Statistician	Michelle Collinson	M.Collinson@leeds.ac.uk	
Clinical Psychologist	Prof. Kate Davidson	kate.davidson@glasgow.ac.uk	0141 2113900

List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CARMS	Cognitive AppRoaches to coMbatting Suicidality
CI	Chief Investigator
CIn	Clinical Interview (by researchers)
Co-I	Co-Investigator
Co-PI	Co-Principal Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
EC	European Commission
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
IRAS	Integrated Research Ethics Application
DMEC	Independent Data Monitoring and Ethical Committee
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MAHSC	Manchester Academic Health Sciences Centre
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development

NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RA	Research Assistant
RF	Research Fellow
RCT	Randomised Control Trial
RDS	Research Design Service
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TM	Trial Manager
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File

Trial Management (funder, sponsor, host)

Who funded CARMS?

CARMS was funded by MRC/NIHR Efficacy and Mechanism Evaluation programme (https://www.nihr.ac.uk/explore-nihr/funding-programmes/efficacy-and-mechanism-evaluation.htm).

Who is the named host of CARMS?

The named host is Manchester Mental Health and Social Care Trust (now merged with Greater Manchester West NHS Trust as Greater Manchester Mental Health Trust [GMMHT]). This means that they are the organisation who is responsible for the administration of CARMS, and all the funding goes from the the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership funding stream to GMMHT. There is a sub-contract in place between GMMHT and the University of Manchester (UoM) to cover the FTE contribution of academic staff based at the Universities of Manchester and Lancaster, and to cover the cost of a 0.4 FTE Research Fellow and a 0.4 FTE Research Assistant to aid with statistical analyses, and a 0.2 FTE research assistant to help with the health economics data.

Who has responsibility over the budget?

The Chief Investigator and the Co-Principal Investigator have ultimate responsibility for the budget. However, budgetary responsibilities have been delegated to the CARMS Trial Manager/Project co-ordinator.

Who is the Research Governance sponsor?

The University of Manchester is the Research Governance Sponsor. The Research Governance Research Office at the University of Manchester is responsible for monitoring and audit of the proposed RCT. It will liaise with the CARMS Trial Manager/Project co-ordinator and MAHSC Clinical Trials Unit Trial Manager to ensure compliance with government regulations and good clinical practice (GCP).

The local level of management

At a local level, the CARMS co-investigators will meet once a month together with the CARMS Trial Manager and the CTU Trial Manager (*CARMS Project Meeting Chaired by theCo-PIs*). In addition, *an Operational Meeting* will occur either weekly or fortnightly, as needed, and may involve the CARMS Trial Manager, the therapists, and the research assistants working on the trial (*CARMS Research Operational Meeting Chaired by the Co-PIs*). This meeting will discuss all operational issues including training needs, recruitment, retention, adverse events (AEs), serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs). Fortnightly or monthly meetings (as required) will also occur between the five therapists and the clinical psychologists and psychiatrists to examine therapeutic fidelity and ways in which the CARMS therapy needs to be adapted for this client group (*CARMS Therapy Meeting Chaired by the Co-Principal Investigators*). The *CARMS SURG* (Service User Reference Group) will meet bi-monthly organised by the CARMS Trial Project Manager and the Research Fellow (Chair). Members of CARMS SURG, known as CARMers, will input into all aspects of the research process underpinning the CARMS Trial.

Each of the five NHS sites (now four since the merger of MMHSCT and GMW to GMMHT) will have an *NHS Site Principal Investigator* who will manage the running of the trial at that site, in collaboration with the two Trial Managers and the Co-Principal Investigators.

The external level of management

Trials funded by the MRC are required to be scrutinised by two independent committees. These are the Trial Steering Committee (TSC) and the Data Monitoring and Ethics Committee (DMEC). The MRC provides specific requirements regarding membership of these meetings and the frequency of meetings of each of these committees (please see https://www.mrc.ac.uk/documents/pdf/good-clinical-practice-in-clinical-trials/). The TSC and the DMEC will meet every six months in a co-ordinated fashion, such that the DMEC minutes can feed into the TSC.

A representative from the MRC/NIHR Efficacy and Mechanism Evaluation team will be invited to the TSC. The CTU Trial Manager will attend this committee as necessary.

Responsibilities for the study design, trial conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

Ultimate responsibility for these activities lie with Chief Investigator and Co-Principal Investigator, who are employed by the University of Manchester.

All co-investigators have made substantial contributions to the trial design, trial conduct and proposed analyses. It is expected that all co-investigators will contribute to manuscript writing and dissemination of results. There is a CARMS protocol which guides publication principles and authorship decisions.

Key words

1. Psychosis
2. Schizophrenia
3. Severe Mental Illnesses
4. Suicidal thoughts and/or acts
5. Psychological talking therapies focused on suicidal thoughts and acts
6. Qualitative and quantitative methods

1. Trial Summary Table

Trial Title	A PSYCHOLOGICAL INTERVENTION FOR SUICIDE APPLIED TO PEOPLE WITH PSYCHOSIS: THE CARMS TRIAL (COGNITIVE APPROACHES TO COMBATTING SUICIDALITY).
Short Title	CARMS
Trial Design	RCT, 2 arms – Treatment As Usual plus CARMS versus Treatment As Usual
Trial Participants	Adults (>18 years of age) living in the community with experience of psychosis and suicidal thoughts/acts in the past 3 months.
Planned sample size	Up to 333 which allowing for 25% attrition leaves 250 patient participants in total, with 125 in the Treatment condition and 125 in the control condition. Thirty health professionals will also be recruited for the qualitative work stream 1.
Treatment Duration	Up to 24 weeks of CARMS therapy estimated at 1 session per week with a duration of no more than 50 minutes.
Follow up duration	Questionnaire assessments will be collected at baseline, after 6 months upon therapy cessation, and at 12 months follow-up.
Primary outcome measure	Adult Suicidal Ideation Questionnaire (ASIQ)
Secondary suicide outcome measures	Beck scale for suicide ideation, Suicide Probability Scale, Frequency of suicidal thoughts and behaviours across 3 months..
Mechanistic variables	Difficulties in Emotional Regulation Scale; Social Problem-Solving Inventory; Social Support Appraisals Scale; Beck Hopelessness Scale; Defeat and Entrapment scales.
Clinical variables	Positive and Negative Syndrome Scale; Psychotic Symptoms Ratings Scale; Personal and Social Performance Scale; Calgary Depression Scale; Reasons for substance use; Time Line Follow-Back for substance use; DAST; AUDIT; Sleep Condition Indicator; Impact of Events Scale - Revised.
Visual Analogue mood scale	Used before and after every session to rate mood.
Qualitative work	There are three work streams: 1. Barriers and solutions to implementing suicide focused psychological therapies in NHS services; 2. Dealing with negative emotions and appraisals; 3. Therapeutic techniques which worked when therapy had ceased. In addition all participants will be asked about their experiences of taking part in suicide research, including

	the impact of COVID-19 on their mental health, suicidal thoughts and behaviour and taking part in suicide research.

2. Overview of the CARMS trial:

Estimates show that around 6% of people with experiences of psychosis die by suicide. Many more think about it and attempt suicide. A meta-analysis by our team illustrated that psychological therapies are effective in reducing suicidal thoughts and acts in people with psychosis as long as those therapies *target* suicidal thoughts, intentions and plans, and *not* the reduction of symptoms of mental illnesses. Based on this work, we have designed a psychological cognitive "talking" therapy (called CARMS) to reduce suicidal thoughts in people with experiences of psychosis which targets the psychological processes thought to underpin the pathways to suicidal thoughts and behaviours. An increasing body of work shows that many people with psychosis feel isolated, unable to cope with their emotions, or address personal problems. These appraisals can then induce and intensify perceptions of being hopeless, trapped and defeated, which in turn leads to suicidal thoughts and acts. CARMS aims to help people find practical ways to change these sorts of perceptions. Two of our pilot studies have demonstrated that CARMS is feasible and acceptable to people experiencing psychosis.

Hence, our next step is to test the *efficacy* of CARMS in the context of NHS mental health services and also to test whether the underlying psychological *mechanisms* on which CARMS is based are correct. We propose to test CARMS using a medium sized randomised controlled trial (RCT), with two arms of CARMS plus treatment as usual versus just treatment as usual. We will use both quantitative and qualitative methods and analyses to assess CARMS.

3. Background:

3.1 Prevalence of suicidal thoughts and behaviours in the general population: Suicidal thoughts, behaviours, and deaths are of substantial public, social, and societal concern (1, 2). Suicide death rates sampled from 2012 estimate that in the US there are 12.1 suicides per 100,000 people (3) and 6.2 suicides per 100,000 within the UK (4). These prevalence rates equate to 1 death by suicide every 40 seconds (4).

3.2 Prevalence of suicidal thoughts and behaviours in those with disorders on the schizophrenia spectrum: It is well established that risk of suicide is considerably elevated in those suffering from severe mental health problems, including disorders on the schizophrenia spectrum and non-affective psychoses (5-9). Suicidal thoughts and suicide attempts are common in this population, with up to 50% of such individuals experiencing suicidal ideation at any point in time or having a history of previous attempts (8, 10). A recent meta-analysis reported a 6 fold increase in death by suicide in those with schizophrenia spectrum disorders who had experienced suicidal ideation compared to 1.5 fold increase in death by suicide in those with affective disorders (11). A current large scale household survey in the US by DeVylder and colleagues (12) reported that people experiencing psychotic symptoms were five times more likely to report suicidal ideation, and 10 times more likely to have made a suicide attempt, compared to people who did not have psychotic symptoms, recorded during a 12 month period. Furthermore, this pattern was consistent across the lifespan, and was not restricted to younger individuals. This is consistent with a study recruiting psychotic participants who were older than 40, which reported that almost half of the sample (n=132) had attempted suicide at least once (13). In a cross-sectional study of 290 people with psychosis, suicidal ideation was found to be present in 41% of participants (14). The high rates of suicidal thoughts and behaviours in people with mental health problems on the schizophrenia spectrum can be compared with that of the general population where prevalence rates are 1% or less. It is clear that suicidal thoughts, behaviours, and deaths by suicide are a considerable problem in this population and one which should be urgently addressed. The Schizophrenia Commission Report advocated more psychological based research in this area (https://www.rethink.org/about-us/the-schizophrenia-commission).

3.3 The importance of examining suicidal thoughts: It has been argued that there is a progressive suicide continuum from ideation, to intent, to action and death (5). In the Devylder population

based house-hold study, the odds of a suicide attempt amongst individuals with psychosis reporting suicidal ideation versus no suicidal ideation was 3.5 (12), which is consistent with the purported suicide continuum. Thus, it is important clinically to target all points on this continuum, including suicidal thoughts which is the point where interventions can be the most preventative. It has also been pointed out that suicidal ideation is accompanied by considerable psychological distress and should be a mental health care priority (15).

3.4 Psychological models of suicidal thoughts and behaviours: Psychological interventions are most likely to be successful when they are clearly derived from a theoretical understanding of underlying psychological mechanisms (5, 16, 17). Advances in understanding the cognitive mechanisms underpinning suicidality have resulted in the development of empirically validated contemporary theoretical models of suicidality, such as, the Inter-Personal Theory (18), the Integrated Motivational-Volitional Model (IMV) (19) and the Schematic Appraisal Model of Suicide (SAMS) (16, 20) which was modified from the well-established Cry of Pain model (CoP) (21) developed with people experiencing depression. Common to the IMV, CoP and SAMS theories of suicidal thoughts and behaviours, is the centrality of perceptions of defeat, entrapment, and hopelessness. The role of defeat and entrapment in suicidal thoughts and behaviours is partially founded on evolutionary models of animal behaviour and represents a desire to escape which is continually blocked (22). Perceptions of entrapment, humiliation, and powerlessness are expressed in people with psychotic illnesses (23, 24). Furthermore, a recent review found extensive evidence for the role of defeat and entrapment in suicidal thoughts and acts (25). Perceptions of hopelessness have two components. First, that the future will be devoid of positive experiences and desired goals or values. Second, that only negative experiences and negative outcomes will occur in the future (26). There is a robust literature indicating that perceptions of hopelessness are a strong predictor of suicidal thoughts and behaviours (27, 28), and that high levels of hopelessness are observed in people with schizophrenia (6, 29). As suggested by the CoP model, it is important to determine whether defeat, leads to entrapment which then leads to hopelessness. The CoP model suggests that when entrapment becomes projected into the future, (e.g., "I am never going to be able to escape"), that hopelessness ensues (21).

It should be noted that the overlap between self-harm and suicidal thoughts and behaviours is complex. Some individual self-harm for reasons that are totally unrelated to suicidal thoughts and acts. For others self-harm is seen as “practice” for a suicide attempt. For other people, self-harm can be perceived as helping with emotional regulation and also as a precipitant of suicidal acts.

3.41 The Schematic Appraisal Model of Suicide (SAMS): The SAMS is unique in comparison to other contemporary models of suicidal thoughts and acts because it was developed from work with people experiencing psychosis (15, 16, 30). The SAMS has three core psychological components, namely, the presence of negative information processing biases, extensive ‘suicide schema’, and a negative and suicide focused appraisals system (16). To date, empirical evidence supports a multi-tiered negative appraisals system in the pathways to suicidality in people experiencing psychosis, and post-traumatic stress disorder (31-34), in which negative appraisals of emotional regulation (e.g., "I am unable to control my emotions", "I always feel threatened"), social support (e.g., "I have no-one to turn to", "I am a burden to everyone"), and personal problem solving (e.g., "I don't know what to do to make my situation better", "suicide is the only way to solve my problems") lead to perceptions of defeat, entrapment and hopelessness. These perceptions, in turn, lead to suicidal thoughts and behaviours (see figure 1). It is important to determine if one or more of these negative appraisals are differentially stronger predictors of suicidality, and furthermore, to determine whether therapy differentially modifies one or more of these appraisals. There is also some initial evidence that positive symptoms of psychosis exacerbate the relationship between negative appraisals, and perceptions of defeat, entrapment and hopelessness (33) which deserves further investigation.

It is negative appraisals of emotional regulation or emotional coping, social support, and interpersonal problem solving which are the foci of our CARMS intervention, and of the current grant proposal. It should be noted that focussing on these three appraisals fits with a broader body of work showing that i. fluctuations in negative emotions (35) is predictive of suicidal ideation; ii. social isolation worsens suicidality in people with severe mental health problems, including schizophrenia (36, 37), and

iii. poor problem solving in people with severe mental illnesses has been identified as a component in the pathways to suicidal thoughts and behaviours (38, 39).

3.5 Psychological interventions which target suicidal thoughts and behaviours: A meta-analysis of cognitive-behavioural interventions (CBT) to reduce suicide behaviour (40) conducted by members of our team demonstrated that CBT was effective in significantly reducing suicidal thoughts and behaviours in adults as long as the therapy was i. focused on suicide; ii. aimed at adults, and iii. used one-to-one therapy sessions, as opposed to group sessions. However, the interventions reviewed were not informed by psychological theory or by psychological mechanisms which underpin suicidal thoughts and behaviours. This means that psychological interventions for suicidality could be far more effective if they were guided by psychologically targeted mechanisms, and if they were focused on suicidal thoughts and acts (15, 17). Currently, psychological interventions are not targeted or focused in this way with respect to suicidal thoughts and behaviours in psychosis, nor are they widely available on the NHS in the UK.

3.6 The Cognitive AppRoaches to CoMbatting Suicidality (CARMS) psychological therapy: Our CARMS therapy was founded on the SAMS. Hence, as requested by the EME commissioning brief**,** our CARMS intervention is based on a scientifically grounded theoretical model of suicidal thoughts and behaviours (5). Thus, the specific psychological processes targeted by our therapy are appraisals of emotional dysregulation, social isolation, and poor interpersonal problem solving (15). As shown in figure 1, it is proposed that these three negative appraisals lead to perceptions of defeat, entrapment and hopelessness, which in turn lead to suicidal thoughts and behaviours. Although our suicide-focused therapy arose from work with psychosis and post-traumatic stress disorder it has the potential to be applied trans-diagnostically (15).

3.7 Differences between CARMS and traditional, generalised, Cognitive Behavioural Therapy (CBT): Traditional CBT for schizophrenia has been designed to target specific psychotic symptoms, such as, hallucinations and delusions, rather than suicidality specifically, and does not reduce suicidal behaviour (41). No psychological intervention for suicide in those with schizophrenia to date has been founded on a theory of suicide, nor have any interventions focused on particular psychological processes which drive suicide, making our intervention novel and unique in three ways. First, it has been developed from a psychological model of the mechanisms underlying suicidal thoughts and behaviours which has been generated and backed up with empirical evidence in this population (15). Second, the intervention directly targets three psychological appraisal processes which trigger and maintain suicidal thoughts and behaviours. Third, the intervention has the potential to address interactions between symptoms of mental health problems and these psychological processes. (See section 8 for concrete examples of techniques used in CARMS).

3.8 Pilot work using our CARMS intervention: Pilot data indicates that this intervention is acceptable and feasible in a community sample with psychosis (30) and in male prisoners with severe mental health problems (42). Qualitative interviews carried out by our group have highlighted the practical translation of the principles of our therapy to everyday functioning. For example, in prisoners aspects of the therapy were commented on, such as the stage-by-stage approach of our therapy, the value of one to one therapy and the nurturing of problem solving skills. Findings in two pilot randomized trials were promising in relation to recruitment, feasibility and acceptability of the approach in complex client groups and suggested that the approach may have the potential to be effective at reducing key suicide outcomes (15, 43) (see also section 4.3). In a community sample, the conclusions that CARMS is acceptable and feasible was backed up with qualitative work (44).

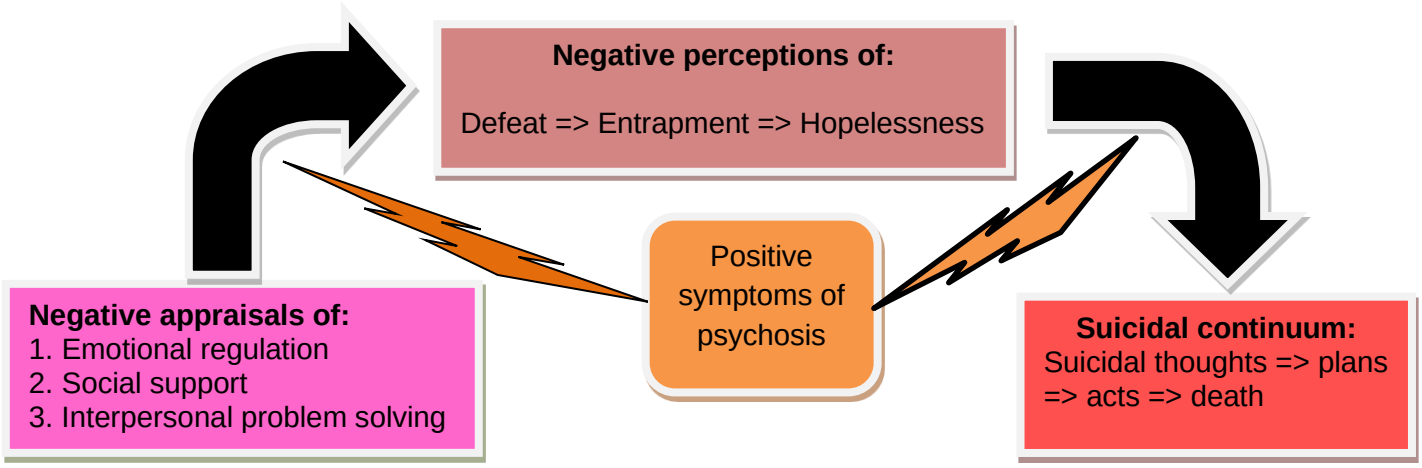
3.9 Implications for the proposed project: There is a strong rationale for the proposed project which is based on a psychological model of the mechanisms which underpin suicidal thoughts and behaviours, namely, the SAMS. Evidence supporting the SAMS has come from work with male prisoners (43, 45), people diagnosed with schizophrenia spectrum disorders (25, 30, 33), bipolar disorder (46) and PTSD (47). Furthermore, it was derived from an earlier psychological model of suicide, the Cry of Pain Model, meaning that the SAMS benefits from a large body of research by Williams and colleagues (21, 48, 49). Our CARMS therapy is specifically tailored to address suicidal thoughts and behaviours, and thus, is unique in the context of cognitive psychological therapies. Initial pilot work with respect to our

therapy is positive (30, 43). In conclusion, there is a sound rationale, backed-up by evidence, for our proposed RCT which will test both efficacy and mechanism. It should also be noted that NICE guidelines recommend that psychosocial therapies are targeted on self-harm and suicide (https://www.nice.org.uk/guidance/cg133/chapter/1-Guidance).

4. The proposed CARMS trial

4.1 Over-view of proposed work: We will use a two-armed Randomised Control Trial (RCT) of a cognitive psychological therapy (CARMS), to reduce suicidal thoughts and behaviours in people experiencing mental health problems on the schizophrenia spectrum and current suicidal thoughts and/or behaviours. In the treatment condition, participants will receive our CARMS therapy together with treatment as usual (TAU). In the control condition, participants will receive only TAU. Psychological assessments will be administered at baseline, upon therapy cessation (6 months), and at 12 months follow-up (FU). Up to 24, 50 minute sessions of therapy will be offered by therapists meeting the British Association for Behavioural and Cognitive Psychotherapies minimum training standards for practice of cognitive behavioural psychotherapies. They will receive specialist training and supervision in the CARMS approach from the applicants. A series of nested qualitative studies (see section 13) will explore potential barriers and solutions to implementing therapy within NHS services beyond the trial. This qualitative work will also provide pointers to ways in which proposed mechanisms of change to suicidal thoughts and behaviours can be meaningfully operationalised beyond therapy and will assist in the development of the implementation of the CARMS approach in NHS services.

FIGURE 1: SCHEMATIC REPRESENTATION OF THE PATHWAYS LEADING TO SUICIDAL THOUGHTS AND BEHAVIOURS WITH A FOCUS ON THE NEGATIVE APPRAISALS SYSTEM BASED ON THE SAMS. THE FIGURE ILLUSTRATES THAT POSITIVE SYMPTOMS OF PSYCHOSIS MAY AMPLIFY THE RELATIONSHIP BETWEEN NEGATIVE APPRAISALS AND DEFEAT, ENTRAPMENT AND HOPELESSNESS, AND NEGATIVE PERCEPTIONS AND SUICIDALITY.



4.2 Rationale for the current study:

As detailed in sections 3.1 and 3.2, suicidal thoughts and behaviours are a serious health concern. The risk of suicide increases with severe mental health problems, and includes a spectrum of suicidal ideation through to plans, attempts and death. Schizophrenia spectrum disorders are one such severe mental health problem. In 1999 costs of self-poisoning amounted to £47m each year (50) which at today's inflation rates is £70.5m. Using meta-analytic techniques we have established that psychological therapies which use cognitive techniques can attenuate suicidal thoughts and behaviours (40). A finding of our meta-analysis was that psychological therapies were most effective if targeted at suicide rather than, for example, reducing symptoms of mental health problems. We further advocated in our meta-analytic publication, that psychological therapies would be maximally effective if developed from psychological models or theories which aimed to understand the mechanisms that trigger, maintain

and worsen, suicidal thoughts and behaviours. We have developed such a psychological model, i.e., the SAMS. Furthermore, we have developed a psychological therapy, CARMS, which is designed to target the psychological processes which underpin suicidal thoughts and acts, based on the SAMS. Pilot work indicates that our therapy is acceptable and feasible in people experiencing psychosis in the community, and in prisoners. Furthermore, analyses of efficacy were encouraging (30, 42). The next step is to advance this work by conducting a fully powered trial to test the efficacy of our therapy and to test the purported psychological mechanisms which our model suggests underlies suicidal thoughts and behaviours. This is the goal of our proposed CARMS project.

5. Research objectives:

5.1 Objectives and purpose of the quantitative work

5.11 Efficacy objectives

1. To determine the efficacy of a specifically developed psychological cognitive therapy (CARMS) in combating suicidal thoughts and behaviours when delivered to people experiencing psychosis within NHS community mental health services.
2. To determine whether positive effects of therapy last over a 12 month follow-up (FU) period.

5.12 Efficacy hypothesis: We predict that

1. Thoughts of suicidality will be less frequent and less severe, and suicidal acts will be less frequent, in the treatment compared to the control condition, measured at therapy cessation (6 months) and after a 12 month FU period compared to baseline.

5.13 Mechanistic aims and objectives:

1. To investigate psychological suicide mechanisms focusing on negative appraisals of emotional regulation, social support, and inter-personal problem solving.
2. To determine the extent to which perceptions of psychotic symptoms interact with these negative appraisals and perceptions in the pathways to suicidality.
3. To investigate the extent to which our suicide-targeted psychological therapy changes these psychological processes involved in pathways to suicidal thoughts and behaviours.

5.131 Mechanistic exploratory aims and objectives:

1. To determine which appraisals of emotional regulation, social support, and inter-personal problem solving are i. the strongest predictors in the pathways to suicidal thoughts and behaviours, and ii. are most changed by our CARMS therapy.

5.14 Mechanistic hypotheses: We predict that:

1. Negative appraisals of social support, emotional regulation, and interpersonal problem solving will lead to stronger perceptions of being defeated, entrapped and hopeless, which will in turn lead to suicidal thoughts and behaviours.
2. Psychotic symptoms will amplify the relationships between negative appraisals of social support, emotional regulation, and interpersonal problem solving and perceptions of being defeated, entrapped and hopeless. These symptoms may also amplify the relationships between perceptions of defeat, entrapment and hopelessness and suicidal thoughts and behaviours.
3. Our psychological therapy will result in less severe negative appraisals, and reduced perceptions of defeat, entrapment and hopelessness. It will also reduce the amplification effects of positive psychotic symptoms.

5.2 Objectives and purpose of the qualitative work

5.21 Implementation objective: To determine potential barriers and solutions for implementation of our CARMS therapy in NHS community mental health services. We will undertake a nested qualitative study to identify potential barriers and solutions to future implementation from service users, therapists/supervisors involved in therapy delivery, and, mental health staff who would potentially deliver the therapy beyond the trial, and by NHS service providers and commissioners. This will provide vital information to maximise the likelihood that our intervention can be delivered efficiently and effectively after the trial has finished within the NHS.

5.22 Efficacy objective: To examine which aspects of our CARMS therapy have, and have not, been used by service users after therapy has finished, and which aspects of TAU have, and have not, been used by service users. This is important because it indicates which components of our therapy have been applied to real life contexts when individuals are no longer supported by therapists. It also indicates which aspects of TAU are utilised by service users which are important in further developing our psychological intervention and integrating it within existing services.

5.23 Mechanistic objective: To determine ways in which service users tackle the key psychological processes underlying suicidality (e.g., defeat, entrapment, hopelessness) in real life contexts. We will be able to use responses from participants in both arms of the trial meaning that we will be able to explore how our therapy techniques were translated into real life with respect to the SAMS model. This information provides further evidence about psychological suicide mechanisms and will provide potential convergent mechanistic evidence when coupled with the proposed quantitative work. Achieving this mechanistic objective has the potential to refine and adapt the theoretical model being tested within the trial.

6. Research design (see appendix 1 of this protocol for flow chart):

6.1 Research Design: The design of the proposed work has been developed with reference to CONSORT (http://www.equator-network.org/reporting-guidelines/consort/) and SPIRIT guidelines (http://www.spirit-statement.org/), and the TIDieR checklist and guide (http://www.bmj.com/content/348/bmj.g1687). The design is an RCT with two parallel arms, namely, a psychological intervention for suicide plus Treatment As Usual (TAU) [treatment condition] versus TAU only [control condition]. Outcome and mediational variables will be collected at baseline, after therapy cessation (6 months), and at 12 months follow-up (FU). Up to 24 individual therapy sessions, of 50 mins, will be offered. It is anticipated that sessions will be weekly. Participants will be randomised to one of two trial arms, with stratification (yes/no) based on anti-depressant medication and NHS site.

6.11 Establishing causal mechanisms:

The mechanism depicted in figure 1 will be tested using moderated mediation analysis (51) which is a form of path analysis. Negative appraisals are the predictor variables, perceptions of defeat, entrapment and hopelessness, are the mediator variables, psychotic symptoms is the moderator variable, and suicidal thoughts/acts is the outcome.

6.2 Methods to protect against sources of bias. Based on MRC Clinical Trial guidelines (http://www.mrc.ac.uk/documents/pdf/rcts-for-complex-interventions-to-improve-health/ and www.mrc.ac.uk/documents/pdf/good-clinical-practice-in-clinical-trials/) the following measures will be put in place:

1. The Manchester Clinical Trials Unit (CTU) will perform the randomisation of participants to the trial arms which protects against allocation bias.
2. Randomisation will take place only when potential participants have consented to participate.
3. Research assistants (RAs) performing the assessments will be blind as to the condition a participant has been allocated to, and housed in accommodation geographically separate from the therapists and the CARMS Trial Manager, thus countering ascertainment bias.
4. There will be procedures in place if an RA becomes un-blinded.

a. There will be a back-up independent assessor, for example a different RA on a different trial.
b. All instances of unintentional un-blinding will be recorded.

5. All variables have been defined prior to the RCT taking place.
6. The ManchesterCTU will oversee data handling.
7. The trial statistician (RE) will not know which condition is treatment and which is control.
8. Intention-to-treat analyses will be used
9. Participant throughput will be recorded, e.g., reasons potential participants opted not to participate.
10. Reasons why participants dropped out of the trial will be recorded.
11. The ManchesterCTU will have copies of all data.

12. The ManchesterCTU will develop and implement procedures for data checking and validation.

6.3 Findings of pilot work: We have published two papers (30, 42) describing the findings of pilot RCTs with community participants with psychosis and with prisoners. These two studies had a focus on acceptability and feasibility. Suicidal ideation was significantly reduced in the community sample of people with psychosis, and incidence of self-harm was reduced in the prisoner sample.

6.4 Discontinuation from the trial as decided by individual participants: As stated in the consent forms, deciding to no longer participate results in no detriment to participants. Reasons for discontinuing a trial, as decided by participants, are varied. For example, participants may find that they have family or work commitments which make it hard to keep attending therapy or research sessions. Participants may forget to attend appointments. This may occur despite our proposed use of automated reminding software.

6.5 Discontinuation criteria from the trial as defined by the CARMS protocol: There are no specific discontinuation criteria in this trial for individual participants. For example, if a participant moved geographical location to an area outside of Greater Manchester, the CARMS researchers/therapists would offer to travel to see them.

6.6 Criteria for electively stopping the trial or other research prematurely: Adverse Events (AEs) (pre-specified events only, see below), and Serious Adverse Events (SAEs) will be monitored throughout the trial from multiple sources and reviewed by the core research project team every two weeks, or weekly if required, to assess their research/therapy relatedness and review any actions which need to be taken. All SAEs will be reported to the host trust (GMMHT), the ManchesterCTU and the Chair of the Trial Steering Committee. Any which are considered to be research related, as judged by the core research project team, will be discussed immediately with the Chair of the TSC and appropriate authorities as required. If necessary, an emergency meeting of the TSC will be called. Causal relationships between SAEs and the CARMS therapy will be discussed with the Chair of the TSC collaboratively. If the SAEs are considered to be due to the CARMS therapy then appropriate action will be taken as defined by GCP guidelines, overseen by the Chair of the TSC. Prespecified expected adverse events are named below.

6.61 Definition of AEs and SAEs. Standard definitions of AEs and SAEs have been used as described by the University of Manchester Clinical Trials Policy (v.3 2015) [http://documents.manchester.ac.uk/display.aspx?DocID=29056]. See also section 17 of this protocol.

6.611 In the context of CARMS the following adverse events are likely to be expected during the trial: Self-harm, harm to others, and harm to property, which will be routinely recorded in the trial and it is expected that these will occur for some participants. Examples of these will include self-harm, such as, the use of a ligature to induce pain to relieve intense negative feelings, but with no injuries observed; in possession of non-prescription drugs; aggressive confrontation between a participant and an acquaintance; superficial cigarette burns; punching a wall through frustration; violent disagreement between married couples including throwing of furniture; threat to children; intoxication; minor scratches to arms or other body parts; and purging. It should be noted that these may become SAEs depending on the severity of injuries and outcomes of the behaviour.

All Adverse Events will be reviewed by the CARMS core research team, including the two Co-PIs, at regular meetings and data regarding the frequency and nature of AEs and SAEs will be reported to the TSC Chair after each meeting by the CARMS Trial Manager/Project Co-ordinator. Further follow up of these events is not necessary unless there is evidence that these are research related.

6.62 Adverse Reaction (ARs) that are considered critical to evaluating the safety of the trial:

Suicide attempts and suicidal behaviours (including self-harm) that result in hospital admissions or occur after admission to an in-patient psychiatric ward are considered critical to evaluating the safety of the CARMS trial if they are considered to result from the CARMS intervention. The core

research team, including the two Co-PIs, will make this decision in the first instance. However, these are expected serious adverse events (see 6.61 above) and will be monitored throughout to evaluate whether there is a disproportionate frequency occurring in the intervention (CARMS +TAU) group compared to the control group (TAU only). This information will be supplied to TSC and DMEC as appropriate.

6.7 Definition of 'End of Trial':

The trial will end when follow-up data at the 12 month time point has been completed and when all qualitative data has been collected.

7. Study population:

7.1 The inclusion criteria *are:*

i. ICD-10 diagnosis of psychosis (i.e. F20 – F29)
ii. Suicidal thoughts and/or acts in the past three months
iii. in contact with mental health services and under the care of a mental health services clinical team (i.e.., community or inpatient mental health care teams) with a care coordinator
iv. aged 18 or over
v. English-speaking (hence, not needing an interpreter)
vi. able to give informed consent as assessed by either a responsible clinician or by trial RAs following the British Psychological Society's guidelines on gaining informed consent (http://www.bps.org.uk/sites/default/files/documents/code_of_human_research_ethics.pdf).

7.2 The exclusion criteria *are:*

i. dementia, or an organic brain disorder
ii. unable to complete assessments due to language barriers.
iii. Currently taking part in a clinical trial

7.3 The withdrawal criteria *are:*

i. the participant decides to withdraw from the trial for any or no reason
iii lost to follow-up.

8. Planned interventions

8.1 The psychological treatment intervention

8.11 Experimental intervention [treatment condition-psychological intervention plus TAU]:

Our psychological therapy is a recovery-focused, structured, time-limited, socio-cognitive intervention. It is based upon our recently developed treatment manual (15) and pilot RCTs in the community (30) and in prison (52). The intervention modifies negative appraisals of emotional regulation, social support, and interpersonal problem solving. As a consequence, perceptions of defeat, entrapment, and hopelessness will be improved indirectly. In addition, perceptions of defeat, entrapment and hopelessness will be worked on directly during the therapy. As shown in Figure 1, such perceptions are antecedents of suicidal thoughts and behaviours.

The therapy protocol is formulation driven. It has the following six components which are individually tailored to the participant: Component 1 works on engagement which aims to raise the understanding of psychological therapy and motivate participants to attend appointments; components 2, 3 and 4 focus on changing negative appraisals of inter-personal problem solving, emotional regulation, and social support which give rise to perceptions of defeat, entrapment and hopelessness; component 5 builds on component 4, and cements ways of *not* feeling defeated, trapped and hopeless; and component 6 focuses on ending therapy and maintaining well-being (42, 52).

The techniques used throughout the therapy have concrete, practical, foci, which can be used in every-day settings. For example:

- ***Problem solving appraisals:*** defining problems simply; brainstorming and evaluating solutions; evaluating the pros and cons of each solution; selecting and implementing a solution; and evaluating

whether the solution "worked" provides a way of countering appraisals of poor problem solving ability. It, further, presents an alternative to seeing suicide as the only solution to problems, or the only way to escape from problems. Relatedly, this technique demonstrates that people do not need to feel defeated by their problems, because they can actively generate and "test" solutions.

- ***Emotion regulation appraisals:*** many negative emotions are threat related, and suicidal people can feel overwhelmed and not in control of such emotions. We have developed a simple multi-sensory technique called Broad Minded Affective Coping (BMAC)(53) which is based on the Broaden and Build theory of positive emotions (54) and uses positive memories to off-set negative emotions (55). Furthermore, the BMAC is short and can be done very easily in real-life settings. This illustrates that people do not have to feel "hijacked", trapped or defeated, by negative emotions. This technique has had the predicted positive effect when used with people with psychosis and PTSD (56, 57).
- ***Social support appraisals:*** people who are suicidal often feel that they are a burden to others, and that they do not "deserve" help from other people (18). We use social exchange theory (58) which posits that providing social resources is "money in the bank" with the consequence that social support can, then, legitimately be sought. Hence, individuals are encouraged to engage in helpful behaviour towards others, such as, friends, family and community groups.
- ***Perceptions of hopelessness:*** working with participants to set realistic and achievable goals which are related to cherished values can help to instil hope in people and off-set perceptions of hopelessness.

8.12 Control intervention [control condition, TAU only]:

TAU will include usual nursing, clinical and medical care.

8.2 Attrition rates at follow-up:

Based on an examination of 27 RCTs of psychological therapy with similar populations which identified a mean attrition rate of 23%, we are allowing for a more conservative attrition rate of 25% from baseline to final follow-up. Although our psychosis pilot trial had a slightly higher attrition rate than this at follow up (29%), the pilot allowed us to identify how we could improve on our follow up rates by i. ensuring sufficient RA support, i.e., we will have 5 RAs working on recruitment throughout the course of the RCT, ii offering participants the option for telephone support, iii. using an automated appointment reminder system, and iv. examining hospital records for suicide attempts or deaths. This means that we are confident that the retention rate will be at least 75%. A recent trial, in which members of our team were involved, recruited people with psychosis and substance use and retained 85% at 12 month follow-up (59). It should be noted that we developed a procedure indicating information which should be recorded regarding attrition (please see Appendix N of the supplementary material).

8.3 Therapist training and supervision:

Therapists will be experienced in cognitive therapy principles and techniques. Haddock and Pratt will conduct training in our suicide focussed CARMS therapy. Supervision will be with the clinical psychologists on the team (Haddock, Pratt, Lobban and Jones). In addition, peer supervision of therapists may be developed. With patient's consent, all therapy sessions will be recorded, allowing us to assess therapy fidelity during supervision sessions using an adapted therapy fidelity scale (60). We will utilise a detailed, operationalised protocol which has evolved from our pilot work with people experiencing psychosis and prisoners (30, 42), and our on-going pilot trial with in-patient psychiatric patients.

9. Proposed outcome measures: primary, secondary, mechanistic, clinical, therapy process, and health economics variables.

Suicide ideation is a predictor of suicide attempts and suicide death. Hence, the primary outcome acts as a surrogate measure of suicide attempts and death by suicide.

9.1 Primary outcome measure: This is the *Adult Suicidal Ideation Questionnaire* [ASIQ](61) which is a self-report measure.

9.2 Secondary outcome measures: Suicidal thoughts and behaviours are complex, meaning that different components should be collected, including plans and intent. We will use the following measures, the first three of which are self-report measures.

1. *The Suicide Probability Scale* (62) measures four components of suicide including negative self-evaluations and hostility.
2. The *Beck Scale for Suicidal ideation* (63) measures recent suicidal ideation, plans, intent, and previous attempt history.
3. The *Time Line Follow-Back* (TLFB) interview procedure (64) will be used to assess self-reported frequency of plans and attempts, over the past 6 months.
4. *Frequency of suicide attempts* will be collected from NHS records. Hence, this measure does not depend on participants completing questionnaires.

9.3 Measuring mechanisms: In order to test hypothesised mechanisms (see Figure 1), it is necessary to statistically model the pathways to suicidal thoughts and behaviours. To establish a causal pathway, there needs to be a temporal delay between baseline and follow-up measures (65) which means that they need to be collected at the three time-points. In addition, we need to determine whether our intervention affects the processes which are postulated to be central to triggering and maintaining suicidal thoughts and behaviours.

9.31 Mechanistic outcome variables, each of which assesses key components of our model using self-report questionnaires:

1. *Difficulties in Emotional Regulation Scale (66)* measures appraisals of emotional control.
2. *Social Problem-Solving Inventory (67)*, Short Form, tests appraisals of social problem solving and has 5 sub-scales (positive, negative, rational, impulsive, and avoidance).
3. *Social Support Appraisals Scale (68)* assesses social support.
4. *Beck Hopelessness Scale (69)* measures appraisals of a negative future. Hopelessness is a strong predictor of suicidal thoughts and behaviours.
5. *Defeat and Entrapment scales* (70) assess being defeated and trapped. Perceptions of defeat and entrapment are central to understanding suicide. Entrapment can be broken down into two sub-scales of internal and external entrapment.

9.4 Clinical variables: The following psychiatric symptoms will be measured in one clinical interview at the three time points of baseline, 6 and 12 month follow-up: *Positive and Negative Syndrome Scale (71),* the *Psychotic Symptoms Ratings Scale (PSYRATS) (72)*, the *Personal and Social Performance Scale (73) and the Calgary Depression Scale (74)*. In addition, The *Time Line Follow-Back* (TLFB) interview procedure (64) will be used to assess frequency and amount of alcohol use, prescription drug use, and non-prescription drug use. This procedure is the 'gold standard' for assessing a range of behaviours including substance use. This will be augmented with the DAST (75) and the AUDIT (76) which measure the severity of drug and alcohol use using 20 and 10 items respectively. In addition, the Reasons for Substance Use Scale (ReSUS) (77) will be used. As sleep problems contribute to mental ill health we propose to measure sleep issues with the Sleep Condition Indicator (SCI) (78). Information about current medication for mental health problem (e.g., ant-depressants) will be taken from clinical records.

9.5 Therapy process measures: **therapeutic alliance, *engagement, adherence and session ratings.***
For those in the therapy arm of the trial, the therapeutic alliance will be assessed twice (after approximately 4 sessions and towards the end of the therapy) over the course of the therapy sessions with the *Working Alliance Inventory – short form (79)*. Patients and therapists both fill-in this alliance inventory. The therapist completes the inventory based on their perceptions of the working alliance with the patient, and the patient completes the inventory based on their perceptions of the working alliance with the therapist.

Therapists will record the following information for each participant in the therapy arm of the trial using both qualitative clinical notes and quantitative data: i. number of sessions attended; ii. duration of each session providing a mean duration for each participant; iii. a rating and an assessment of engagement with the therapy broken down into the different therapy modules or components; a rating and assessment of what proportion of each therapy session focused on each mechanism.

Participants will be asked, prior to each therapy session, to provide ratings on 8 items which each correspond to a mechanism being assessed at baseline, 6 month follow up and 12 month follow up.

Participants will be asked to rate, on a likert scale (0 - 3), how they felt over the past week according to each mechanistic factor, where 0 is 'not at all' and 3 is 'completely'.

9.6 Health economics measures: It should be noted that the EME board (January 6th 2016) requested health economics measures to be included in our proposed work. This we have embraced by adding the EQ-5D [5L version] (http://www.nicedsu.org.uk/PDFs%20of%20reports/DSU%20EQ5D%20final%20report%20-%20submitted.pdf) and the Client Service Use Receipt Inventory (http://www.dirum.org/assets/downloads/634462388066137028-CSRI.pdf), amended for our proposed trial, to monitor service use. We intend to administer the two health economics measures at baseline and 12 months follow-up. We have also requested an RA 0.2 FTE for the final 12 months of the grant to analyse this data.

9.7 Visual analogue ratings of mood : a visual analogue scale (0-100) will be used to asses mood prior to all assessment and qualitative interview sessions, and after those sessions. This is to get a very quick rating of whether the assessment or interview sessions have negatively impacted mood.

Please see section 11 for the qualitative work.

9.8 Demographic information*:* We will collect demographic information at baseline and then check at follow-up whether factors such as relationship status, work status and education have changed at the two follow-up periods of 6 and 12 months. We will collect data concerning age, ethnicity, gender, type of work, length of time doing this work, and highest level of education. It should be noted that the health economics measures also collect demographic information, and this will be populated by the demographic information initially collected.

9.9 COVID-19 related measures: In light of the COVID-19 outbreak and government restrictions, we will collect information related to the impact of COVID-19 through several means.

1. During the clinical interview at baseline, 6 month follow up and 12 month follow up and therapy sessions, participants will be asked if they have any COVID-19 symptoms, if they have been self-isolating and the reason for self-isolating (e.g. on government advice as they are in the at risk group or due to others in the household presenting with COVID-19 symptoms.
2. The *Impact of Events Scale Revised (IES-R; 80)* assesses current personal distress related to a stressful life event. For the purposes of the CARMS trial, we will be using the IES-R to assess current personal distress related to COVID-19.
3. When the researchers are conducting the clinical interview measures (PANSS, PSYRATS, PSP, TLFB for suicide and TLFB for substance use) and administering the primary outcome measure (ASIQ), they will ask participants what they would be feeling if COVID-19 was not present. This will generate two sets of scores for each measure, namely, i. actual/current thoughts and feelings and i what people would be feeling if COVID-19 was not present.
4. Therapy process data: for those in the therapy arm of the trial, therapists will record the impact COVID-19 may be having on delivering the therapy, e.g. number of minutes talking about COVID-19 during a therapy session and if participants have declined therapy as it can only be conducted over the telephone.

Table 1 below provides a list of quantitative measures and the time points at which these measures will be taken. Table 2 below provides the clinical information which will be collected and the time point at which the information will be collected. (Please see Appendix K of the supplementary material for all measures.)

Table 1: Quantitative assessments, the time-points at which they will be used, and the mode of the assessment. For mode of assessment: PPT = self-report questionnaire/tool filled-in by participant (note that researchers can help participants to complete questionnaires). S = checklist asked of participant but filled in by researcher. CIn = clinical structured interview conducted by the researchers (RAs, RF). H = information collected from hospital records. T = information provided by therapists. FU= follow-up. 6 months FU is when 24 weeks of therapy ceases. 12 months FU is when there has been a 12 month lag from baseline data collection.

Questionnaire Assessments	*Identification/ Screening*	*Baseline*	*6 months FU*	*12 months FU*	*Post-12 months FU*	*Mode of assessment*
Inclusion/exclusion criteria						
ICD-10 psychosis diagnosis (yes/no)	√				√	S/H
Suicidality in past 3 months - checklist	√					S
ICD-10 Psychosis symptoms - checklist	√				√	S/H
Mood visual analogue scale (VAS)						
Pre-assessment, clinical interview, and qualitative interview		√	√	√		PPT
Post-assessment, clinical interview, and qualitative interview		√	√	√		PPT
Demographic questions		√				PPT/S
Changes in demographic information			√	√		PPT/S
Primary outcome suicide variable						
Adult suicide ideation questionnaire		√	√	√		PPT
Secondary outcome suicide variables						
Suicide Probability Scale		√	√	√		PPT
Beck Scale for Suicidal ideation		√	√	√		PPT
Time Line follow back of suicidal thoughts, plans and acts across six months		√	√	√		CIn
Frequency of suicide attempts (from hospital records)		√	√	√		H
Mechanistic outcome variables						
Difficulties in Emotional Regulation Scale		√	√	√		PPT
Social Problem-Solving Inventory		√	√	√		PPT
Social Support Appraisals Scale		√	√	√		PPT
Beck Hopelessness Scale		√	√	√		PPT
Defeat and Entrapment scales		√	√	√		PPT
Health Economics measures						
EQ-5D		√		√		PPT
Client Service Use Receipt Inventory		√		√		PPT
Debriefing Information sheet (given to patient participants after every session, including qualitative interviews).	√	√	√	√		NA
COVID-19 variables						
Impact of Events Scale Revised		√	√	√		PPT
Second score for ASIQ		√	√	√		PPT

Table 2: Clinical information which will be collected and the time point at which the information will be obtained and the mode of the assessment. For mode of assessment: PPT = self-report questionnaire/tool filled-in by participant (note that researchers can help participants to complete questionnaires). S = checklist asked of participant but filled in by researcher. CIn = clinical structured interview conducted by the researchers (RAs, RF). H = information collected from hospital records. T = information provided by therapists. FU= follow-up. 6 months FU is when 24 weeks of therapy ceases. 12 months FU is when there has been a 12 month lag from baseline data collection.
Information pertaining to the therapy process will be collected continuously by the therapist, and collated upon therapy cessation.

Information	Base-line	4th therapy session	Towards the end of therapy	Continuous	6 months FU	12 months FU	*Mode of assessment*
SAE/AE monitoring				√			Multiple sources
Current medication for mental health problems as prescribed at baseline assessment time point (from medical records)	√				√	√	H
Alcohol use (self-reported) AUDIT	√				√	√	PPT
Drug use (self-reported) DAST	√				√	√	PPT
Reasons for substance Use Scale	√				√	√	PPT
Working Alliance Inventory							
Therapist completes for therapist		√	√				T
Patient completes for patient		√	√				PPT
Therapy process							
Number of sessions attended				√			T
Duration of sessions				√			T
Engagement with therapy modules				√			T
CARMS session process ratings				√			T
CARMS session process ratings				√			PPT
Clinical interviews							
Depression	√				√	√	CIn
Positive and negative symptoms of psychosis	√				√	√	CIn
Psychotic symptoms rating scale	√				√	√	CIn
Personal and social performance scale	√				√	√	CIn
Substance Use Time Line Follow-Back over 3 months for alcohol, prescription drug use,	√				√	√	CIn

and non-prescription drug use							
Debriefing Information sheet (given to patient participants after every session, including qualitative interviews).	√			√ (as appropriate)	√	√	NA
COVID-19 interview							
Additional COVID 19 questions for CARMS appointments	√			√	√	√	Cln/T
Second score for the PANSS, PSYRATS, PSP, TLFB for suicide, TLFB for substance use.	√				√	√	CIn

10. Procedures for the assessment of efficacy/effectiveness:

Please note that Participant Information Sheets, Consent forms, and Measures can be found in Appendices E, F, and K of the supplementary material respectively. These procedures can be broken down into eight stages as follows:

10.1 Identification of patients (pre-screening): Potential participants will be identified by health professionals in the participant's mental health care team or researchers working on other projects using the inclusion and exclusion criteria provided to them. These staff members or researchers will then ascertain whether participants are willing to receive information about the study and to be contacted by a researcher. Please note that participants identified by researchers working on other projects will have already signed an item on the consent form for such project stating that they wish to be approached about taking part in other research studies.

10.11 Materials used to recruit patients

Recruitment materials will be used to enable patients to request that a member of their mental health care team (e.g., care co-ordinator) refer them into the research project. (The CARMS team will facilitate contacting a named care co-ordinator.) Permission will be sought to distribute posters in areas accessible to potential participants e.g., mental health wards, health service waiting rooms, community centres, libraries, employment centres, public transport areas, drop-in centres, employment centres, sheltered housing and at support groups. In addition, a smaller advert will be provided should a service, charities (e.g., Self Help, Mind, Samaritans) or organisations wish to include it within a newsletter or bulletin.

A dedicated CARMS website may be used to provide information about the CARMS trial to mental health care professionals working with individuals with psychosis, and to provide a contact email address for referrals to be made to the CARMS Trial Manager/Researcher. (Please see Appendix J of the supplementary material for adverts (i.e., flyers/posters).

10.12 Screening: If patients agree to receive information regarding the study and to being contacted by the researcher, the patient's name and contact details will be given to a member of the research team/Comprehensive Research Network Clinical Support Office (CSO) who will then approach the participant about the possibility of study participation. If the participant feels that they would like to take part, they will be asked to respond to two short *screening* checklists to determine whether or not the study is right for them. These two checklists are the suicidal thoughts and behaviours checklist and a psychosis checklist. Formal diagnostic information will be collected at the end of the trial via hospital records.

10.2 Identification of health care professionals for qualitative work stream 1: A range of channels will be used to recruit health care professionals into qualitative work stream 1. These include talks to community mental health care teams, posters, flyers, and NHS trust bulletins.

10.3 Providing information to potential participants and gaining consent

10.31 Providing information about the questionnaire assessments and the CARMS therapy: A researcher/CSO will approach potential participants who have been screened as eligible with information (PIS 1) about the CARMS trial. An appointment will be made to meet with the potential participant to go through the PIS in detail. Special attention will be paid to the nature of the psychological assessments, and what our CARMS therapy will involve. It is important that potential participants understand that they may not receive our CARMS therapy.

At least twenty-four hours will be left between providing the PIS and taking consent. The researcher/CSO will also be available for further discussion, clarifications, to answer questions and so forth prior to taking consent. This component of the trial involves baseline, 6 and 12 month assessments and therapy sessions for those randomised to that arm of the trial. The participant consent form will request access to clinical records by members of the research team for assessment purposes.

10.311 TAU versus TAU + CARMS – issues of communication:

We understand that participants may feel a sense of disappointment if they are assigned to the TAU arm of the trial. Based on our INSITE pilot trial, we have tried to off-set this disappointment by framing CARMS as “determining whether the addition of CARMS is better or worse than usual treatment”. We have used this stance in our PISs and in our leaflets. Research staff will also be trained in ways in which to deliver information about the trial sensitively.

10.312 Providing information to potential participants identified from other research projects:

Potential participants referred to the CARMS project via other research projects will have almost completed their involvement in such research project prior to consenting to the CARMS project. This means that they would be eligible for involvement in the CARMS project. The reason we have excluded the recruitment of participants currently participating in a clinical trial is, to ensure that CARMS participants are not actively receiving another experimental psychological intervention whilst taking part in CARMS, as this could skew the data for both trial arms.

To ensure that potential participants do not feel coerced into taking part in CARMS, a researcher from the research project they are taking part in will contact the participant prior to their final assessment as part of the other research project. The researcher will give them an overview of CARMS and ask if this is something they would be interested in. If they are interested, CARMS PIS 1, the appendix to CARMS PIS 1 and appendix 2 of the PIS for the other research project will be discussed over the phone with them, following the steps outlined in 10.31. Special attention will be paid to ensure that participants understand that if they provide informed consent for their data from other research projects to be used in the CARMS trial, then they would i) only complete the questionnaires in their initial appointment(s), ii) be asked to complete the clinical interviews and questionnaires at both 6 and 12 month follow up appointments. The researcher will then ask if the potential participant would like to be sent PIS 1 and the appendix to PIS 1 by post.

Please note that participants taking part in other research projects will have already signed an item on appendix 2 of the consent form to say that they agree for their data (which will be identifiable) to be used in other research projects overseen by a project team member. In order for CARMS to receive this data, the participant will need to also sign the corresponding item on appendix 1 of the consent form.

10.313 Providing information to current participants who would like to take part in other research projects:

If current participants are interested in taking part in other research projects and have signed the corresponding item on consent form 1, then the steps outlined in 10.312 would be followed. These steps will also be described in the other research projects' trial protocol. Prior to the participant's 12 month follow up appointment and as part of introducing another research project, the CARMS team will outline the information in appendix 2 of CARMS PIS 1, which describes that if participants are in agreement and interested in finding out more about other research projects, their data (which will be identifiable) will be shared with the corresponding research project. Appendix 2 of PIS 1 should be discussed alongside the PIS and appendix 1 of the PIS for other research projects.

10.314 Providing information to participants about the additional data collection and analysis of COVID-19 data:

All participants who are involved in the CARMS trial will be asked if they are interested in providing some information to us in relation to the perceived impact of COVID-19. Depending on which stage of the CARMS project participants are currently at, researchers should discuss Appendix 4 of PIS 1 following the steps outlined in 10.31 prior to the participant's baseline, 6 month or 12 month follow up appointment.

10.32 Providing information about the qualitative interviews: The PIS and consent procedures for the qualitative work streams 1 (implementing therapy in NHS services) and 2 (negative perceptions) will be initiated at the final baseline assessment session for patient participants. For the qualitative work stream 3 (assessment and use of CARMS post therapy cessation), participants will be contacted at a range of time points after the 6 month assessment session but before the 12 month assessments.

10.4 Gaining consent from potential participants: The researchers/CSOs will contact potential participants at least 24 hours after providing them with the PIS to see if they would like to take part. We would also like to record why participants agreed/ did not agree to take part, in their own words. Each potential participant who is eligible will be approached by researchers/CSOs for inclusion into the CARMS trial. There are separate PISs and consent forms for the CARMS trial (PIS 1), qualitative work streams 1 [barriers and solutions to rolling out a suicide focused talking therapy] and 2 (PIS 2), and the qualitative work stream 3 [longevity and use of therapy techniques and TAU coping strategies] (PIS 4). There is also a separate PIS and consent form for mental health professionals recruited into qualitative work stream 1 (PIS 3). The principles of obtaining consent remain the same for each of these stages. The PISs and consent forms can be found in Appendix E and F of the Supplementary Material). Participants who are eligible will be approached by the researcher/CSO, have the study explained verbally and be provided with relevant clear and written information (PIS) in a sensitive manner. The potential participant will be given the opportunity to ask questions about the research study and will be given at least 24 hours to consider the information sheet and decide if they want to take part. If they do decide to take part, consent will be given in writing.

Prior to taking consent, the researchers/CSOs will attempt to ensure that no sense of coercion is perceived by potential participants, that they fully understand what the study is about, what their participation consists of, who may have access to their data, how any data will be used and reported and how the final results of the study will be made available.

10.41 Assessing whether the potential participant is well enough to provide informed consent:

If the researcher /CSO suspects that any potential participant's ability to provide informed consent has been compromised by their mental ill health, a second opinion will be sought from the researcher's clinical supervisor, which may involve discussion with the potential participant's care-co-ordinator if suicide risk is an issue. If it is decided that the individual is too unwell to participate, consent would not be sought at that time and appropriate referrals to their health service contact (e.g., care co-

ordinator, key worker) will be made, in collaboration with the participant. In this event, the participant will be provided with the opportunity to participate at a later time.

The researchers/CSOs will have training in how to communicate information about CARMS and in how to take consent. They will also receive regular clinical supervision overseen by Prof. Haddock, a Professor of Clinical Psychology, and co-PI.

10.42 Taking informed consent from potential participants identified from other research projects:

Researchers will follow the steps outlined in 10.4 and 10.41 to take informed consent for the CARMS project. Researchers will then proceed to ask participants if they would like to consent to the optional items in appendix 1 of the consent form.

10.43 Taking informed consent from current participants who would like to take part in other research projects:

Researchers will follow the steps outlined in 10.4 and 10.41, however, note that at this stage, the participant will already be taking part in CARMS and will have been sent appendix 2 of PIS 1. Researchers will then proceed to ask participants if they would like to consent to the optional items in appendix 2 of the consent form.

10.44 Taking informed consent from participants about the additional data collection and analysis of COVID-19 data:

Researchers will follow the steps outlined in 10.4 and 10.41, however, note that at this stage, the participant may have already been taking part in CARMS. All participants will have discussed appendix 4 of PIS 1 with the participant and sent the document by post or email, where possible. Researchers will then proceed to ask participants if they would like to consent to the optional items in appendix 3 of the consent form.

10.45 Giving information to, and gaining consent for qualitative interviews with health care professionals (work stream 1):

The same principles as already described will be followed for providing information and gaining consent from health professionals (work stream 1).

10.46 Gaining informed consent from potential participants during the COVID-19 outbreak:

Recent guidance set out by both the government and Greater Manchester Mental Health NHS Foundation Trust in light of the COVID-19 outbreak, has advised that face to face contact with participants to be suspended. As such, researchers will seek to gain informed consent by either i. email, ii. postal service, iii. text message or iv. audio recording verbal consent. Researchers will ask which method of consent potential participants would be comfortable with, then seek to obtain informed consent via the chosen method:

i. Email: The potential participant would be emailed the consent form using NHS or university email addresses. The researchers will go through the consent form by phone and if the potential participant agrees to take part, they will fill the consent form in and send it back to the researcher by email.

ii. Postal service: The potential participant would be sent a physical consent form by post, along with a stamped and addressed envelope for them to return the consent form to an NHS building (and/or University when the buildings re-open). The researchers will go through the consent form by phone and if the potential participant agrees to take part, they will fill the consent form in and send it back to the researcher in the stamped and addressed envelope.

iii. Text message: The researchers will go through the consent form by phone and if the potential participant agrees to take part, they will send a text to the researcher with confirmation of which items of the consent form they agree to. The researcher will then take a screenshot of the text message to store on the NHS and/or University secure servers/drives.

iv. Audio recording verbal consent: The researchers will firstly seek verbal confirmation that the participant agrees to verbal informed consent being audio recorded. If the participant agrees to be audio recorded, then the researcher can press record on the audio recording device and go through the consent form over the phone with the potential participant. The research will ask the potential participant to state if they agree or disagree to each item of the consent form.

Note that files for all electronic methods of obtaining informed consent (email, text message and audio recording) will be stored on the NHS and/or University secure servers/drives separate to the anonymised research data.

For participants who chose to consent to take part in the CARMS study via email and text, we will collect hard copies of consent forms at their 6 or 12 month follow up appointment. If the study team are unable to obtain hard copies (e.g. due to withdrawal, lost to follow up or if the lockdown restrictions had not lifted by the point of the participant's 12 month follow up appointment), email addresses and/or mobile phone numbers will be retained for 15 to 20 years to show that the participant provided informed consent from their email address and/or mobile phone. Such retention period is in line with the current retention period for hard copies consent forms and audio recordings.

10.5 Questionnaire assessments and clinical interviews: Assessments will be completed in the participant's home, or on NHS premises. Demographic information will be collected first. These assessments will again be administered at 6 and 12 month time points (but health economics measures will only be collected at baseline and 12 months FU). Participants who have been recruited from another research project may choose to consent for their data collected as part of that project to be used in the CARMS trial. This would reduce participant burden in repeating assessment measures and would provide the opportunity for participants to take part in further research. In the last baseline assessment session, the researcher will determine if the participant is interested in taking part in qualitative work streams 1 and/or 2. Appropriate PISs will be left for those who are interested. We would like to assess whether taking part in suicide research affects participants' mood states. This means that we will use a very simple visual analogue scale to measure mood before and after every assessment session. (It should be noted that we will also use this visual analogue scale before and after every qualitative interview.)

10.6 Randomisation: Once the baseline assessments have been completed the randomisation process overseen by the Manchester Clinical Trials Unit (CTU) can be implemented. The ManchesterCTU have set up an external online randomisation system with Sealed envelope. The CARMS Trial Manager will input information needed for randomisation into an online randomisation form in Sealed Envelope, i.e., the participant's ID, the NHS Trust site, date of birth, date informed consent was provided and anti-depressant use of the participant (yes/no). The randomisation allocation will then be sent to the CARMS Trial Manager by email. The CARMS Trial Manager will then forward the randomisation allocation email to the CTU Trial Manager, who will remove the group allocation and distribute to the CTU data manager. Participants will be told which arm they have been randomised to and they will also be given a bespoke leaflet with additional information about the arm to which they have been randomised (see appendix G of the supplementary material).

10.7 Therapy sessions: For those assigned to the therapy arm of the CARMS trial, the goal is that the therapy sessions will begin no later than 4 weeks after the last baseline assessment session. The *working alliance inventory* will be completed by therapists and participants at approximately session 4 and towards the end of therapy (all participants assigned to this arm are offered up to 24 sessions of therapy). Therapists will also be asked to provide information about the number of sessions that each participant had, the duration of those session, and the modules/components completed by each participant. The definition of these modules/components are expected to change as the trial progresses. However, at this time point they can be predicted to be (see also section 8.1):

- Motivation for CARMS
- Engagement with CARMS
- Addressing negative attentional biases

- Addressing negative perceptions of emotional regulation, social problem solving and social support.
- Addressing appraisals of defeat, entrapment and hopelessness
- Scaffolding the end of therapy

10.8 Exploring experiences of patients: We would like to ask our participants to share their views on what it was like to take part in a research study about suicide after they finish baseline and follow up assessments, and after all qualitative interviews. We would like to follow this question up 1 month later, where possible, and where practical, via a short questionnaire. This data is qualitative.

10.81 Exploring experiences of patients – COVID-19: In addition to exploring experiences of suicide research, we would like to ask out participants to share their experiences of the COVID-19 outbreak, how they are feeling about taking part in CARMS during the COVID-19 outbreak and how they feel the COVID-19 outbreak has impacted on their mental health and suicidal thoughts/behaviour. This data is qualitative.

11. Proposed sample size

One hundred and twenty five participants in each arm (treatment and control), meaning 250 participants in total for the analysis set, across 4 NHS trust sites, (i.e., 100 participants from the merged MMHSCT and GMW sites and 50 from each of the remaining sites). To account for attrition, up to 333 participants will be recruited. This will be reviewed during the course of the trial based on ongoing retention rates. It is estimated that 50% of people will decline to take part. Therefore, approximately 666 participants will be identified as eligible, approached, and screened. (As noted above the screening checklists are very short and can be carried out by phone if more practical for potential participants.) In addition, up to 30 health professional participants will be recruited for the qualitative work with recruitment being spread across the 4 NHS sites.

11.1 Power calculations including assumptions:

We use an approach based on a simple t-test for the between group comparison in the primary outcome which is specifically designed to account for differential clustering or partial nesting between the two arms (80). It is implemented in –clsampsi- in Stata (81). This approach requires the following assumptions:

a. **Effect size:** A clinically meaningful difference on the primary outcome (ASIQ) is estimated as a 16 point reduction, which corresponds to an effect size of 0.42 (pooled standard deviation at baseline in the pilot trial was 38). In our pilot RCT, there were significant improvements in the primary outcome measure of suicidal ideation and intent (measured by the ASIQ, treatment effect=-12.3, SE=6.3, effect size 0.32). Thus, we will use a conservative effect size of 0.36, which corresponds to a 14 point change on the ASIQ.
b. **Attrition:** Based on a review of 27 RCTs with similar populations which identified a mean attrition rate of 23%, we are allowing for a more conservative attrition rate of 25% from baseline to final follow-up. Although our pilot trial had a slightly higher attrition rate than this at follow up (29%), the pilot allowed us to identify how we could improve on our follow up rates (see section 6.2) meaning that we are confident that the follow-up rate will be at least 75%, and we are aiming for 80% retention.
c. **Clustering:** we account for clustering of therapists in the CBT arm with an ICC=0.02. No prior estimate of the ICC is available, but we consider this a conservative estimate to what is typically found in psychotherapy trials. We will include pre-specified prognostic variables for the outcome in our analysis models to further reduce the ICC. This approach is robust to observed increases in ICC as the number of therapists (clusters) increases. For the calculation, we consider the control arm as clusters of size 1 with ICC=0.
d. **Therapist number:** From our planned staffing of 5 therapists at any one time, we have allowed for 6 therapists to be used during the course of the whole trial (to account for therapists leaving and being replaced). This also helps to improve the generalisability of the trial. We allow for a

variance in the number of participants seen per therapist (i.e., that this follows a Poisson distribution).

e. **Random allocation:** We assume 1:1 random allocation, 0.05 significance level, and 80% statistical power. In practice, some additional power would be gained by the use of multiple regression models in the analysis, but this cannot be incorporated into –clsampsi- at present because the software does not allow us to account for repeated measures and clustering in the same calculation. Given these assumptions, an analysis set of 250 (125 per group) has 80% power to detect an effect size of 0.36. Allowing for 25% attrition, this requires us to recruit 333 at baseline.

For our proposed mediational analyses, a sample size of over 250 has >80% power to detect a proportion mediated of 35%, and >70% power to detect a proportion mediated of 30% (calculated using PowerMediation in R). So, our sample size will have sufficient power for our proposed mediation analysis.

12. Statistical analysis

12.1 Analysis of the trial data to assess efficacy.

A detailed analysis plan will be prepared before any analysis is undertaken. In accordance with CONSORT principles, all participant flow in the trial will be reported (see Appendix 1). All analyses and summary statistics will be conducted on the Intention-To-Treat (ITT) population which is defined as all participants randomised regardless of non-compliance with the protocol or withdrawal from the study. All analyses will be carried out at the end of the last follow-up assessments; there will be no interim analyses. Data analysis will take place at King's College London. The Trial Statistician recently moved to King's College from Manchester. Consideration will be given to potential biases arising from loss to follow-up. Random effects regression models will be fitted to the repeated measures to estimate treatment effects for primary and secondary outcomes, including treatment centre, medication, and the corresponding baseline assessment for the outcome as fixed effects. If the number of therapists is different from the number of NHS sites, we will include therapist as a random effect. We will allow for the presence of missing data under the assumption that the data are Missing At Random with the possible addition of inverse probability weighting to adjust for the role of non-adherence to allocated treatment and other intermediate outcomes as predictors of future loss to follow-up.

To account for the possible prognostic effect of anti-depressant medication on outcomes, we will include anti-depressant use at baseline (yes/no) as a stratifying factor (and therefore include this in our analysis models). We acknowledge that use of anti-depressant medication after randomisation might account for a proportion of any observed treatment effect. We refer to this as a 'nuisance mediator', because it might lie on the causal pathway between randomisation and outcome but it is not targeted by the intervention itself. If there is a significant differential effect in the uptake of anti-depressant between the intervention and control groups, we will assess the role of anti-depressant medication as a mediator, in addition to our hypothesised target mediators.

12.2 Analysis of the trial data to assess mechanisms:

This will be carried out using methods similar to those of Baron and Kenny but advanced by newer approaches of structural equation models, instrumental variable analyses, and principal stratification to allow for hidden confounder variables (82-84). Moderator analyses will focus on examining the effects of psychotic symptoms as an amplifier (85). Stata will be used for all the analyses.

12.3 Qualitative analysis:

Thematic analysis will be used for the interview data (*see section 13*).

13. Qualitative Projects/ Work streams

13.1 The research questions:

There are three qualitative research questions which will be explored through a series of nested qualitative designs. These are 1. What are the potential barriers and solutions for implementation of psychological talking therapies with a focus on suicide (our CARMS therapy) in NHS community mental

health services as perceived by service users (estimated sample size =20), mental health staff potentially delivering the therapy, and by NHS service providers (estimated sample size =20) (work stream 1)? 2. How have service-users dealt with negative self-appraisals and perceptions of defeat, entrapment, and hopelessness (estimated sample size =20) (work stream 2)? 3. What aspects of therapy and what aspects of TAU have been utilised by service-users in "real life", post therapy cessation (estimated sample size =20) (work stream 3)? The first question investigates implementation issues from the perspectives of NHS staff and service users, and the second and third questions investigate the postulated underlying mechanisms thought to underpin suicide, as experienced by service users, and the extent of take-up of therapeutic techniques post therapy. We will also investigate experiences of service users in taking part in CARMS, including the questionnaire assessments and the qualitative interviews. As such experiences may change over time, where feasible, we will include a brief questionnaire which can be sent/emailed to participants 1 month after assessments/interviews have been completed, where feasible. The research question is what are the experiences of taking part in suicide related research? Furthermore, and in light of the COVID-19 outbreak, we will also investigate the experiences of services users in taking part in CARMS during/following the COVID-19 outbreak. This will include what their experience of the COVID-19 outbreak and how they feel it may have impacted on their mental health and suicidal thoughts/behaviours.

13.2 Sampling:

Purposive sampling will be used to address the first three research questions. This will ensure that the sample will include a range of views, time points, and maximum variance.

For the first question, a variety of mental health professionals who will potentially deliver the therapy will be interviewed (e.g., clinical psychologists, cognitive therapists, mental health nurses, supervisors, psychological services managers, psychological services directors) together with NHS service providers (e.g., commissioners). Data will also be gathered from service user participants. A sub-sample of service users offered (though not necessarily completing) therapy will be included, and therapists/supervisors involved in its delivery.

To address the second question, two groups of service users will be interviewed, one from the TAU arm and one from the Treatment arm. As this research question is mechanistic it will important to sample participants with a range of scores on baseline measures of suicidal thoughts and acts, defeat, entrapment hopelessness, and appraisals of emotional regulation, social problem solving, and social support. Finally, and if feasible, we will ask participants from the TAU arm about feelings of disappointment at not receiving our CARMS therapy.

To address the third research question, one group of participants will be recruited from the therapy arm. It is important to purposively sample participants with a range of scores on key variables to ensure maximum variance within the sample so that the final sample does not only include participants who have engaged with, and benefited most from, the intervention but also includes participants who have not gained from the intervention. This will be based on the suicide outcome measures, different levels of engagement with the therapy (assessed by attendance and therapist alliance), and scores on mechanistic variables of negative appraisals, defeat, entrapment, and hopelessness. If feasible, we will also purposively sample using the suicide outcome measures to explore *how* participants utilise aspects of therapy during times of distress and the extent to which they relied on techniques which were helpful when they received only TAU. Interviews will be conducted at varying times after therapy cessation (between 4 and 24 weeks) (or equivalent for the TAU sample). This allows participants to have experienced difficult life events.

Data which address the fourth research question about experiences of participating in suicide research will be collected from all participants, if feasible, because our experience thus far is that this data is relatively quick to gather. Further, data for the fifth research question about experiences related to taking part in suicide research during/following the COVID-19 outbreak will be collected alongside experiences of suicide research data from all participants.

The exact numbers of participants needed will depend on the quality of the data generated. Based on our previous work with similar patient and health professional groups, it is anticipated that sample sizes will comprise 20-25 mental health professionals and service providers, 20-25 service users

from the treatment arm of the trial. A further 25 service users from the TAU arm will be recruited (i.e., estimated maximum 75 participants). Sampling will occur in parallel with data analysis (see below) and cease when theoretical saturation has been reached, i.e., the point at which new data appears to no longer contribute to the findings due to repetition of themes and comments by participants (86).

13.3 Interviews:

One-to-one, semi-structured interviews will be conducted, each lasting approximately 50 minutes. All interviews will be digitally audio-recorded with prior participant consent. The interview topic guides will be designed with input and feedback from the service user reference group (SURG) in the first instance. Thereafter, the topic guide will be revised iteratively, after each interview has been conducted. Interviews will be transcribed verbatim (removing any identifying information, such as names and places) and audio-files destroyed. Topic guides evolve with each interview because they change and grow depending on the information provided by participants. However, initial Topic Guides can be found in Appendix I of the supplementary material).

13.4 Measuring mood:

The visual-analogue mood scale will be used before and after every interview to assess the extent to which the interview lowered mood. As with the quantitative assessments, up to 15 minutes will be used to ask about participants' experiences of participating in suicide research. Participants may be followed up one month later where feasible to further assess their reflections on taking part in our study via a brief questionnaire which can be sent/emailed to participants.

13.5 Analyses:

Data will be analysed using an inductive Thematic Analysis (TA) (87, 88) approach and taking an interpretative stance. TA is a method of qualitative enquiry which is widely used to organise rich qualitative data by coding developing data patterns and provides an accessible account of the data corpus. NVivo software will be used to organise and manage the data during the analysis. Coding will be undertaken inductively at the manifest level. Following familiarisation, a coding framework will be developed and codes assigned to themes. Data generation and analysis will occur in parallel using a constant comparative approach, cycling between the emerging analysis and incoming data (89). Disconfirming evidence will be sought and the analysis refined accordingly. Data generation will be determined when theoretical saturation is achieved. The analysis will be undertaken by a research assistant with a focus on the qualitative work and the research fellow, under the supervision of Peters who is an expert in qualitative methods. Regular discussion of emerging codes and themes will take place with the wider research team which includes service users, clinical and academic psychologists, and psychiatrists. This is a recognised method for maximising the trustworthiness of the final analysis (90).

14. Feasibility and recruitment risk analysis

14.1 The proportion of participants who meet the inclusion criteria:

Data from Manchester Mental Health and Social Care Trust (Central Manchester), now part of GMMH, indicates that 2465 patients have a diagnosis of schizophrenia aged over 18. Data from Lancashire Care Trust, which has a larger catchment area than central Manchester, shows that 5,500 adult patients have this diagnosis. It is estimated that a further 4500 adult patients have a diagnosis of schizophrenia from our remaining NHS trust sites of Greater Manchester West (now part of GMMH), Pennine Care, and Five Boroughs totalling 12,465. If 33-40% of these patients experience suicidal ideation (14) then 4,100 patients (33% x 12,465) will meet our inclusion criteria based on the current standing case-load. An ongoing pilot trial recruiting inpatient suicidal patients (RfPB INSiITE study), indicates that just under 50% of patients will agree to take part despite being acutely suicidal. If we take a conservative estimate that only one third of eligible patients would be willing to participate, then we will have ample numbers across the five trusts taking part. Our target is to recruit 333 patients at baseline (see power calculations in 9.1). This means that we need to capture 8-9%% of the available sample (333/4,114). Hence, this appears to be a feasible goal.

14.2 Evidence to support recruitment rates:

The team has considerable experience in recruiting patient samples that are difficult to engage. For example, we have run clinical trials with community patients with schizophrenia (30), with community patients with schizophrenia co-morbid with substance use (91), with community patients with bipolar disorders (92), with individuals who are imprisoned (42), with psychiatric inpatient or day patients (93), and currently we are running a pilot RCT (INSITE) with psychiatric inpatients all of whom have severe mental health problems, including schizophrenia. Our pilot RCT investigating suicide in prisoners recruited 65 participants at baseline across 18 months, which is a recruitment rate of 1.1 per week. For the psychiatric in-patients trial we have recruited 28 patients into the baseline stage across 7 months in one site. Again, this is a recruitment rate of 1 per week. To reach our recruitment targets for this proposed trial we need to recruit around patients a week from our NHS sites, which fits with our recent experiences of recruitment into RCTs. It is important to be "risk averse" and to retain a high proportion of the sample recruited at baseline. Based on our experience of running RCTs for psychological interventions, we have the skills to optimise the completion of our primary outcome measures in a large sample. For example, our primary outcome measure for suicidal thoughts and behaviours can be completed by phone where necessary.

15. Ethical arrangements:

The trial will be conducted in accordance with the principles of good clinical practice (GCP) and the Declaration of Helsinki. The Sponsor and ManchesterCTU will ensure that the study protocol, participant information sheet, participant consent form, GP/Mental Health professionals letters and submitted supporting documents have been approved by the research ethics committee(s) prior to any participant recruitment. Any agreed substantial amendments will also be approved by the sponsor and submitted for ethical approval prior to implementation.

The CI/Co-PIs, Manchester-CTU and Sponsor will ensure that the ethics committee is notified that the trial has finished (either as expected or prematurely) within required timeframes with summary reports to be provided as required. It is the Co-PIs' responsibility to update participants (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the participant's willingness to continue in the trial. The Co-PIs must ensure this is documented in the participant's medical notes and the participant is re-consented. It is the responsibility of the Co-PIs to ensure that the trial has local R&D approval and the sponsor and Manchester-CTU will verify this, plus the presence of all other essential documentation (and potentially an initiation meeting), before giving the "green light" to open the trial to recruitment. The Co-PIs are also responsible for ensuring that any subsequent amendments gain the necessary approvals.

15.1 Participant Information Sheets:

Ethical committee approved Participant Information Sheets (PISs), informed by service user involvement via the SURG will describe the rationale for the study and the possible benefits and risks of taking part. Participants will be asked to consent to participation at least 24 hours after reading the PIS. Participants will be asked to consent to i. a mental health professional (e.g., care co-ordinator) being contacted should researchers or therapists have concerns about their mental health, ii. qualitative interviews being audio-taped and analysed for research purposes, iii. therapy sessions being audio-taped to check therapy fidelity, iv. the use of audio recordings in supervision and training, v. the use of their quantitative and qualitative data (including therapy and clinical interview audio recordings) for research purposes, including secondary data analysis, and v. hospital/medical/clinical records being used to record suicide attempts in addition to other clinically relevant information. The participants will also be asked to consent that s/he understands that they may withdraw consent at any time without affecting their treatment.

15.2 Gaining informed consent:

At least 24 hours will be left between providing the PIS and taking consent. The researcher/CSO will also be available for further discussion, clarifications, to answer questions and so forth prior to taking consent. The participant consent form will request access to clinical records by members of the research team for assessment purposes (see also section 10.4).

15.3 Managing suicidal thoughts, feelings, plans, and acts:

The main ethical issue is that participants will be currently experiencing suicidality and that they also have a severe mental illness. A suicide risk protocol has been developed and will be utilised, in collaboration with the 5 NHS sites (now 4 sites after the merger between MMHSCT and GMW to form GMMHT) where recruitment will take place and the ManchesterCTU (see Appendix A, B and C of the supplementary material for the three relevant CARMS protocols – the first addresses the issue of reducing distress in participants, the second addresses steps to take should a participant become distressed, and the third addresses steps should be taken should a participant disclose suicidal intent). In addition we have developed a debriefing procedure (sign posting sheet to be gone through by researchers) to be used at the end of every assessment session and qualitative interview session (please see Appendix H of the supplementary material). Care co-ordinators of potential participants will be consulted about suicide risk prior to recruitment. Participants will be contacted approximately 24 hours after completing assessment sessions to check on their mental well-being, with a focus on suicidal thoughts and acts. If there are concerns about a participant's mental health, then care co-ordinators will be contacted, with the participant's consent. Letters will be sent to participants' Consultants or GPs and their mental health team, informing them of the participant's involvement (please see Appendix L of the supplementary material for letter templates). We will also write to these health care professionals if the participant fails to attend an assessment session.

We have developed a procedure in the event that research staff working with suicidal participants become distressed (please see Appendix D of the supplementary material).

15.4 Participant confidentiality:

Information provided by participants will be treated as confidential. However, any information disclosed to researchers or therapists indicating that a participant is a risk to themselves or another person necessitates confidentiality to be broken, and members of the participant's mental health care team to be informed of this risk. Where possible this information will be communicated to the health care team in collaboration with the participant. Participants will have consented on the consent form to confidentiality being broken in these instances.

Following data collection, all identifiable information will be removed and will not be entered onto the research databases. As our trial has follow up time points we need to store contact details for participants. However, these will not be stored with their data. Any identifiable information will be removed from the qualitative transcripts, and each participant will be assigned to a pseudonym to ensure confidentiality.

Representatives of the Manchester CTU and the regulatory authorities will be required to have access to participants' notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

Published results in, for example, academic journals, will not contain any personal data that could allow identification of individual participants.

15.5 Data storage:

All Investigators and trial site staff involved with the trial must comply with the requirements of the General Data Protection Regulation (GDPR) and Data Protection Act 2018 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The sponsor will be the data custodian/controller and trial investigators and site staff will be the data processors. Participant notes and trial files at NHS sites must be kept in a secure storage at the NHS site area with limited access, i.e., locked filing cabinets to which trial therapists/trial researchers only have access or locked desk drawers to which therapists/trial researchers only have access. Anonymised questionnaire assessments which are part of the CRF will be stored securely at the host NHS site. Copies of questionnaire assessments will be held by the Manchester CTU until data entry is complete. The Manchester CTU will perform data entry, and data checking for the trial database. All qualitative interview transcripts will be stored digitally with hard copies being stored securely in locked filing cabinets. Computers used to collate the data will have access restrictions via user names, passwords, and the use of encrypted digital files and storage media. Data will be held for 15 years to facilitate full

analyses of the data set and to promote secondary analyses (to which participants consent via the consent form).

16. Risks and benefits of CARMS

16.1 Risks:

The main risk to participants in the therapy arm of the trial is that the CARMS intervention will worsen suicidal thoughts and feelings. Our two published pilot RCTs using our therapy has not found this to be the case (30, 42). In addition, an on-going pilot trial of our therapy used in psychiatric in-patient settings which has carefully monitored serious adverse events, i.e., self-harm incidences, has found no evidence that therapeutic sessions have triggered acts of self-harm. A second risk to participants randomised to the control arm of the trial is that they may feel a sense of disappointment at not having the therapy. In our experience, this can be off-set by communicating that this may happen clearly and explicitly to participants face-to-face and in participant information sheets. A third risk, which is often encountered in trials, is that our target recruitment numbers may not be feasible. To address this possibility, we have added an additional NHS site, and performed a recruitment risk analysis.

16.2 Benefits:

The main benefit is that there is the potential to provide, via NHS services, a psychological therapy which addresses suicidal thoughts and behaviours in a high risk group. Suicidality is a significant cost to the NHS. Hence, reducing suicidal thoughts and behaviours has a long term health economics advantage. In addition, improving mental health and well-being in those with severe mental illnesses has the potential to improve functionality of individuals, and enhance their likelihood of remaining employed or gaining employment. Mental health problems affect people of working age.

16.3 How benefits justify risks:

The risks are low and manageable. The benefits of our proposed work for individuals, NHS services, and society are overwhelming.

17. Assessment of safety:

Adverse events (AE) are defined as harm, or deterioration in health, occurring to a participant during a trial (94). Serious adverse events (SAE) are defined as "reactions which, in their most severe forms, threaten life or function" (94, p782). For our proposed RCT, an SAE will involve life-threatening self-harm or a suicide attempt. AEs and SAEs (pre-defined, see section 6) will be monitored and recorded by the Research Fellow, CARMS Trial Manager/Project co-ordinator, Research Assistants, and trial psychological therapists. (It should be noted that prolonged hospitalisation on a psychiatric in-patient ward is not considered an AE or an SAE in itself. Such hospitalisations are common in this patient group and are expected.)

We will monitor adverse and serious adverse events routinely (i.e., fortnightly, or if the need arises weekly). All such events are discussed by members of the CARMS core project team who are un-blinded as to randomisation allocation to determine whether they are research/therapy related (e.g., the two co-PIs, the therapists, and the CARMS trial manager). All AEs and SAEs will be reported to the Manchester CTU trial manager, to the host NHS site, the Chairs of the Trial Steering Committee (TSC) and the Data Monitoring and Ethical Committee (DMEC) as appropriate. Incidents of SAEs will be communicated to these bodies via a written report which will provide details of the nature of the SAE, no later than two weeks after the occurrence of the SAE. Ethics will only be notified if an event appears to be related to the research and/or therapy, following instruction and advice from the TSC and DMEC. Our therapists and research staff will follow-up on all SAEs within 24 hours, checking on the mental health status of patients by personal conversations where possible, and by communications with care-co-ordinators or similar mental health professionals. Similarly, all researchers will contact participants approximately 24 hours after participating in any assessment or qualitative interview. We contact participant's Consultants/GPs and key team members of their mental health team by letter to inform them that they have taken part in our research (please see Appendix L of the supplementary material for letter templates to key health care professionals).

17.1 Emergency un-blinding of research staff (e.g., research assistants [RA]):

We foresee no reason to emergency un-blind Researchers in the face of an emergency related to self-harm or suicidal thoughts or acts. For example, and to take the worst case scenario, that a participant attempts suicide after an assessment session because their mood has plummeted. It will not help A&E staff to know whether or not this person has been receiving psychological therapy. Their priority is A&E care after a suicide attempt, and that immediate A&E care will not be changed because of engagement with psychological therapy.

18. Data Handling.

18.1 Data Handling at Manchester CTU

Completed CRFs, submitted to the Manchester CTU at regular intervals, will be reviewed by the designated data manager who will enter the data into the trial database. Data provided to the Manchester CTU will be checked for errors, inconsistencies and omissions. If missing or questionable data are identified, the Manchester CTU will request that the data be clarified where appropriate.

All aspects of data collection and handling throughout the life cycle of the trial will be described in trial specific documents provided by the Manchester CTU.

18.2 Handling qualitative data

The Manchester CTU will not be responsible for handling any qualitative data. Co-Investigator Dr Sarah Peters has responsibility for the handling and storage of all qualitative data. Any identifiable information will be removed from the qualitative transcripts, and each participant will be assigned to a pseudonym to ensure confidentiality. Published results will not contain any personal data that could allow identification of individual participants.

18.3 Storage of data during the trial

All data will be stored in accordance with ISO/IEC 27002 (Information Technology – Code of Practice for Information Security Management, 2005; 2007). Hard copies of data will be stored in locked filing cabinets in a secure office in GMMHT premises and MAHSC CTU as appropriate (the Manchester CTU will not need copies of qualitative transcripts).

Electronic data stored at King's College for analysis will conform to the same standards under the responsibility of the trial statistician who is currently employed at King's College.

19. Research Governance.

19.1 Trial management arrangements

The Manchester Mental Health and Social Care Trust (MMHSCT) is the host site which has now merged with Greater Manchester west to become Greater Manchester Mental Health Trust (GMMH). The University of Manchester is the Research Governance Sponsor. The Research Governance Research Office at the University of Manchester is responsible for monitoring and audit of the proposed RCT. It will liaise with the CARMS Trial Manager and Manchester Clinical Trials Unit to ensure compliance with government regulations and good clinical practice (GCP).

A Trial Steering Committee (TSC) will be chaired by an independent experienced clinical psychologist and trialist. The TSC will include membership from two service user representatives, a non-academic stakeholder, and a clinical psychologist. A representative from EME will be invited to TSC meetings, and will be copied in on all committee papers. The TSC will meet every 6 months. A separate independent Data Monitoring and Ethics Committee (DMEC) will also meet every six months. Project meetings, involving all co-applicants will take place monthly. Staff meetings in which discussions of the day-to-day running of the trial will take place fortnightly. [See also page 11 for trial management arrangements.]

19.2 Record retention and archiving

Consent forms will be retained as essential documents, but items such as contact details will be deleted as soon as they are no longer needed. In the event that participants wish to be contacted with information regarding future studies, then their personal contact details will be retained and used solely for this purpose. Furthermore, for participants who chose to consent to take part in the CARMS study via email and text message but who the study team were unable to obtain hard copies of consent forms

from, email addresses and/or mobile phone numbers will be retained for 15 to 20 years to show that the participant provided informed consent from their email address and/or mobile phone. Such retention period is in line with the current retention period for hard copies consent forms and audio recordings.

In accord with recommended good practice for research based on clinical samples or relating to public health we will retain the data for 15 to 20 years.
Audio-files will be destroyed when all information has been extracted and transcribed from them.
NHS trust sites will archive the site files (e.g., the consent forms). The sponsor is responsible for archiving the trial master file.
Data will be stored in a way that permits a complete retrospective audit if necessary. Research data will be archived in a durable form that is immune to subsequent tampering and falsification.

19.3 Trial Performance and monitoring

Before the trial can be initiated, the prerequisites for conducting the trial must be clarified and the organisational preparations made with the trial centre. The Manchester CTU must be informed immediately of any change in the personnel involved in the conduct of the trial.
On-site monitoring will be as necessary and based on a risk-based strategy and a thorough risk assessment completed by the Manchester CTU as part of the site set-up process to ascertain the frequency and intensity of monitoring visits required (although additional monitoring may be conducted if necessary). This risk assessment and associated delivery plan will be stored in the TMF. The Principal Investigator at each site will receive reasonable notification before each monitoring visit.

20. Insurance and/or Indemnity.

The NHS indemnity scheme will apply to the study once HRA approval is in place.

The University of Manchester will arrange insurance for research involving human subjects that provides (1) cover for legal liabilities arising from its actions or those of its staff or supervised students and (2) compensation for non-negligent harm to research subjects occasioned in circumstances that are under the control of the University of Manchester. Cover is subject to policy terms and conditions.

21. Peer review.

As part of gaining the funding, the full protocol and full application was reviewed by:

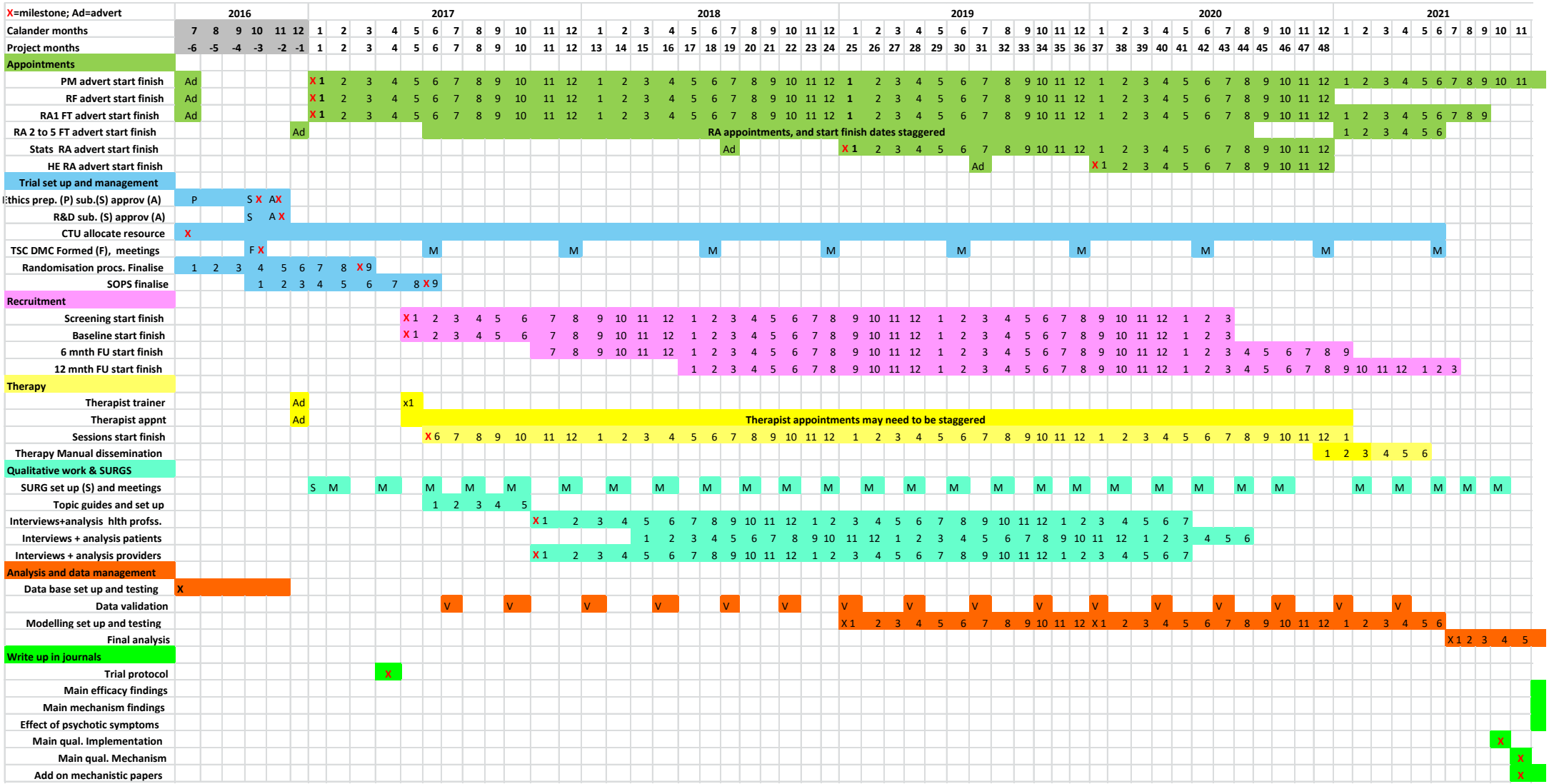
1. Two University of Manchester internal assessors (Prof. Bill Deakin and Dr Andrew Stewart).
2. Two NIHR NW Senior Resign Design Service advisors.
3. The funding Board members.
4. Five external reviewers appointed by the funders.

22. Detailed project timetable, milestones, and Gantt chart.

Duration of project: 48 months based on the need to recruit a total of 250 participants from 5 sites (now 4 sites since the merger of MMHSCT and GMW). Please note that in the Gantt chart provision has been made for researchers and trial therapists to begin work in a staggered fashion. For example, the last month that the 12 month assessment can finish is July 2021, with therapy having ceased end of Jan 2021, and therapy having started July 2020 and baseline assessments collected in July 2019.

Milestones (see red X on Gantt chart below)	
1.Appointments (PM; RF; RAs; stats RA; therapists)	9.Therapy sessions start
2.Ethics submission and approval; R&D approval	10.6 month FU begins

3.CTU allocate resources	11.12 month FU begins
4.Randomisation procedures finalised	12.Qualitative interviews begin
5. Database set up	13.Statistical procedures and model validation begins
6.Protocols finalised	14. Trial ends.
7.TSC and DMC formed; SURG formed	
8.Screening and baseline recruitment starts	


X=milestone; Ad=advert
2016
2017
2018
2019
2020
2021
Calander months
Project months
Appointments
PM advert start finish
RF advert start finish
RA1 FT advert start finish
RA 2 to 5 FT advert start finish
RA appointments, and start finish dates staggered
Stats RA advert start finish
HE RA advert start finish
Trial set up and management
Ethics prep. (P) sub.(S) approv (A)
R&D sub. (S) approv (A)
CTU allocate resource
TSC DMC Formed (F), meetings
Randomisation procs. Finalise
SOPS finalise
Recruitment
Screening start finish
Baseline start finish
6 mnth FU start finish
12 mnth FU start finish
Therapy
Therapist trainer
Therapist appnt
Therapist appointments may need to be staggered
Sessions start finish
Therapy Manual dissemination
Qualitative work & SURGS
SURG set up (S) and meetings
Topic guides and set up
Interviews+analysis hlth profss.
Interviews + analysis patients
Interviews + analysis providers
Analysis and data management
Data base set up and testing
Data validation
Modelling set up and testing
Final analysis
Write up in journals
Trial protocol
Main efficacy findings
Main mechanism findings
Effect of psychotic symptoms
Main qual. Implementation
Main qual. Mechanism
Add on mechanistic papers

References:

1. EU. Death due to suicide by gender. 2012.
2. CDC. Centers for Disease Control and Prevention: Morbidity and Mortality weekly report 2012 2012 [Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101a6.htm?s_cid=mm6101a6_w.
3. WHO. First WHO report on suicide prevention 2014 [
4. WHO. Mental Health: Data and Statistics 2014 [Available from: http://www.euro.who.int/en/health-topics/noncommunicable-diseases/mental-health/data-and-statistics.
5. Bolton C, Gooding P, Kapur N, Barrowclough C, Tarrier N. Developing psychological perspectives of suicidal behaviour and risk in people with a diagnosis of schizophrenia: We know they kill themselves but do we understand why? Clinical Psychology Review. 2007;27(4):511-36.
6. Caldwell CB, Gottesman, II. Schizophrenics Kill Themselves Too - a Review of Risk-Factors for Suicide. Schizophrenia Bulletin. 1990;16(4):571-89.
7. Cohen S, Lavelle J, Rich CL, Bromet E. Rates and Correlates of Suicide Attempts in First-Admission Psychotic-Patients. Acta Psychiatrica Scandinavica. 1994;90(3):167-71.
8. Hawton K, Sutton L, Haw C, Sinclair J, Deeks JJ. Schizophrenia and suicide: systematic review of risk factors. British Journal of Psychiatry. 2005;187:9-20.
9. Saha S, Chant D, McGrath J. A Systematic Review of Mortality in Schizophrenia. Is the Differential Mortality Gap Worsening Over Time? Arch Gen Psychiatry. 2007;64(10):1123-31.
10. Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia - A reexamination. Archives of General Psychiatry. 2005;62(3):247-53.
11. Chapman CL, Mullin K, Ryan CJ, Kuffel A, Nielssen O, Large MM. Meta-analysis of the association between suicidal ideation and later suicide among patients with either a schizophrenia spectrum psychosis or a mood disorder. Acta Psychiatrica Scandinavica. 2015;131(3):162-73.
12. DeVylder JE, Lukens EP, Link BG, Lieberman JA. Suicidal Ideation and Suicide Attempts Among Adults With Psychotic Experiences Data From the Collaborative Psychiatric Epidemiology Surveys. Jama Psychiatry. 2015;72(3):219-25.
13. Montross LP, Kasckow J, Golshan S, Solorzano E, Lehman D, Zisook S. Suicidal Ideation and Suicide Attempts Among Middle-Aged and Older Patients With Schizophrenia Spectrum Disorders and Concurrent Subsyndromal Depression. Journal of Nervous and Mental Disease. 2008;196(12):884-90.
14. Fialko L, Freeman D, Bebbington PE, Kuipers E, Garety PA, Dunn G, et al. Understanding suicidal ideation in psychosis: findings from the Psychological Prevention of Relapse in Psychosis (PRP) trial. Acta Psychiatrica Scandinavica. 2006;114(3):177-86.
15. Tarrier N, Gooding P, Pratt D, Kelly J, Awenat Y, Maxwell J. Cognitive behavioural prevention of suicide in psychosis: A treatment manual. London, UK: Routledge; 2013.
16. Johnson J, Gooding P, Tarrier N. Suicide risk in schizophrenia: Explanatory models and clinical implications, the schematic appraisal model of suicide (SAMS). Psychology and Psychotherapy-Theory Research and Practice. 2008;81:55-77.
17. O'Connor RC, Nock MK. The psychology of suicidal behaviour. Lancet Psychiatry. 2014;1(1):73-85.
18. Van Orden KA, Witte TK, Cukrowicz KC, Braithwaite SR, Selby EA, Joiner TE. The Interpersonal Theory of Suicide. Psychological Review. 2010;117(2):575-600.
19. O'Connor RC. The Integrated Motivational-Volitional model of suicidal behavior. Crisis-the Journal of Crisis Intervention and Suicide Prevention. 2011;32(6):295-8.
20. Johnson J, Tarrier N, Gooding P. An investigation of aspects of the cry of pain model of suicide risk: The role of defeat in impairing memory. Behaviour Research and Therapy. 2008;46(8):968-75.
21. Williams JMG. Cry of pain. Harmondsworth, UK Penguin; 1997.
22. Gilbert P. Evolutionary approaches to psychopathology: The role of natural defences. Australian and New Zealand Journal of Psychiatry. 2001;35(1):17-27.
23. Birchwood M, Mason R, MacMillan F, Healy J. Depression, demoralisation and control over psychotic illness: A comparison of depressed and non-depressed patients with a chronic psychosis. Psychol Med. 1993;23:387-95.

24. Rooke O, Birchwood M. Loss, humiliation and entrapment as appraisals of schizophrenic illness: A prospective study of depressed and non-depressed patients. British Journal of Clinical Psychology. 1998;37:259-68.
25. Taylor PJ, Gooding P, Wood AM, Tarrier N. The role of defeat and entrapment in depression, anxiety, and suicide. Psychological Bulletin. 2011;137(3):391-420.
26. O'Connor RC, Fraser L, Whyte MC, MacHale S, Masterton G. A comparison of specific positive future expectancies and global hopelessness as predictors of suicidal ideation in a prospective study of repeat self-harmers. Journal of Affective Disorders. 2008;110(3):207-14.
27. Beck AT. Hopelessness as a predictor of eventual suicide. Annals of the New York Academy of Sciences. 1986;487:90-6.
28. Beck AT, Brown GK, Steer RA, Dahlsgaard KK, Grisham JR. Suicide ideation at its worst point: A predictor of eventual suicide in psychiatric outpatients. Suicide and Life-Threatening Behavior. 1999;29(1):1-9.
29. Klonsky ED, Kotov R, Bakst S, Rabinowitz J, Bromet EJ. Hopelessness as a Predictor of Attempted Suicide among First Admission Patients with Psychosis: A 10-year Cohort Study. Suicide and Life-Threatening Behavior. 2012;42(1):1-10.
30. Tarrier N, Kelly J, Maqsood S, Snelson N, Maxwell J, Law H, et al. The cognitive behavioural prevention of suicide in psychosis: A clinical trial. Schizophrenia Research. 2014;156(2-3):204-10.
31. Panagioti M, Gooding PA, Tarrier N. Hopelessness, Defeat, and Entrapment in Posttraumatic Stress Disorder Their Association With Suicidal Behavior and Severity of Depression. Journal of Nervous and Mental Disease. 2012;200(8):676-83.
32. Pratt D, Gooding P, Johnson J, Taylor P, Tarrier N. Suicide schemas in non-affective psychosis: An empirical investigation. Behaviour Research and Therapy. 2010;48(12):1211-20.
33. Taylor PJ, Gooding PA, Wood AM, Johnson J, Pratt D, Tarrier N. Defeat and entrapment in schizophrenia: The relationship with suicidal ideation and positive psychotic symptoms. Psychiatry Research. 2010;178(2):244-8.
34. Taylor PJ, Wood AM, Gooding P, Tarrier N. Appraisals and suicidality: The mediating role of defeat and entrapment. Archives of Suicide Research. 2010;14(3):236-47.
35. Palmier-Claus JE, Taylor PJ, Gooding P, Dunn G, Lewis SW. Affective variability predicts suicidal ideation in individuals at ultra-high risk of developing psychosis: An experience sampling study. The British journal of clinical psychology / the British Psychological Society. 2012;51(1):72-83.
36. Hutton P, Bowe S, Parker S, Ford S. Prevalence of suicide risk factors in people at ultra-high risk of developing psychosis: a service audit. Early Intervention in Psychiatry. 2011;5(4):375-80.
37. Skodlar B, Tomori M, Parnas J. Subjective experience and suicidal ideation in schizophrenia. Comprehensive Psychiatry. 2008;49(5):482-8.
38. Pollock LR, Williams JMG. Problem-solving in suicide attempters. Psychological Medicine. 2004;34(1):163-7.
39. Grover KE, Green KL, Pettit JW, Monteith LL, Garza MJ, Venta A. Problem Solving Moderates the Effects of Life Event Stress and Chronic Stress on Suicidal Behaviors in Adolescence. Journal of Clinical Psychology. 2009;65(12):1281-90.
40. Tarrier N, Taylor K, Gooding P. Cognitive-Behavioral Interventions to Reduce Suicide Behavior A Systematic Review and Meta-Analysis. Behavior Modification. 2008;32(1):77-108.
41. Tarrier N, Haddock G, Lewis S, Drake R, Gregg L. Suicide behaviour over 18 months in recent onset schizophrenic patients: The effects of CBT. Schizophrenia Research. 2006;83(1):15-27.
42. Pratt D, Tarrier N, Dunn G, Awenat Y, Shaw J, Ulph F, et al. Cognitive Behavioural Suicide Prevention for Male Prisoners: An exploratory randomised controlled trial. Psychological Medicine. 2015.
43. Pratt D, Tarrier N, Dunn G, Awenat Y, Shaw J, Ulph F, et al. Cognitive-behavioural suicide prevention for male prisoners: a pilot randomized controlled trial. Psychological Medicine. 2015;45(16):3441-51.
44. Haddock G, Davies L, Evans E, Emsley R, Gooding P, Heaney L, et al. Investigating the feasibility and acceptability of a cognitive behavioural suicide prevention therapy for people in acute psychiatric wards (the 'INSITE' trial): study protocol for a randomised controlled trial. Trials. 2016;17.
45. Pratt D, Gooding P, Eccles S, Awenat Y, Tarrier N. Cognitive Behavioural Suicide Prevention for Male Prisoners: Case examples. Cognitive and Behavioral Practice. 2016;23(4):485-501.
46. Owen R, Dempsey R, Jones S, Gooding P. Defeat and Entrapment in Bipolar Disorder: Exploring the relationship with suicidal ideation from a psychological theoretical perspective. Suicide and Life-Threatening Behavior. 2016.

47. Panagioti M, Gooding P, Taylor PJ, Tarrier N. NEGATIVE SELF-APPRAISALS AND SUICIDAL BEHAVIOR AMONG TRAUMA VICTIMS EXPERIENCING PTSD SYMPTOMS: THE MEDIATING ROLE OF DEFEAT AND ENTRAPMENT. Depression and Anxiety. 2012;29(3):187-94.
48. Williams JMG, Crane C, Barnhofer T, Duggan DS. Psychology and suicidal behaviour: Elaborating the entrapment model. Hawton K, editor. Oxford: Oxford University Press; 2005. 71-89 p.
49. Williams JMG, Crane C, Barnhofer T, Van der Does AJW, Segal ZV. Recurrence of suicidal ideation across depressive episodes. Journal of Affective Disorders. 2006;91(2-3):189-94.
50. Kapur N, House A, May C, Creed F. Service provision and outcome for deliberate self-poisoning in adults - Results from a six centre descriptive study. Social Psychiatry and Psychiatric Epidemiology. 2003;38(7):390-5.
51. Emsley R, Dunn G, White IR. Mediation and moderation of treatment effects in randomised controlled trials of complex interventions. Statistical Methods in Medical Research. 2010;19(3):237-70.
52. Tarrier N, Kelly J, Maqsood S, Snelson N, Maxwell J, Law H, et al. The cognitive behavioural prevention of suicide in psychosis: A clinical trial. Schizophrenia Research. Accepted.
53. Tarrier N. Broad Minded Affective Coping (BMAC): A "Positive" CBT Approach to Facilitating Positive Emotions. International Journal of Cognitive Therapy. 2010;3(1):64-76.
54. Fredrickson BL, Branigan C. Positive emotions broaden the scope of attention and thought-action repertoires. Cognition & Emotion. 2005;19(3):313-32.
55. Fredrickson BL, Mancuso RA, Branigan C, Tugade MM. The undoing effect of positive emotions. Motivation and Emotion. 2000;24(4):237-58.
56. Johnson J, Gooding PA, Wood AM, Fair KL, Tarrier N. A Therapeutic Tool for Boosting Mood: The Broad-Minded Affective Coping Procedure (BMAC). Cognitive Therapy and Research. 2013;37(1):61-70.
57. Panagioti M, Gooding P, Tarrier N. An empirical investigation of the effectiveness of the Broad-Minded Affective Coping Procedure (BMAC) to boost mood among individuals with Posttraumatic Stress Disorder (PTSD). Behavior Research & Therapy. 2012;50(10):589-95.
58. Cropanzano R, Mitchell MS. Social exchange theory: An interdisciplinary review. Journal of Management. 2005;31(6):874-900.
59. Barrowclough C, Haddock G, Beardmore R, Conrod P, Craig T, Davies L, et al. Evaluating integrated MI and CBT for people with psychosis and substance misuse: Recruitment, retention and sample characteristics of the MIDAS trial. Addictive Behaviors. 2009;34(10):859-66.
60. Haddock G, Beardmore R, Earnshaw P, Fitzsimmons M, Nothard S, Butler R, et al. Assessing fidelity to integrated motivational interviewing and CBT therapy for psychosis and substance use: the MI-CBT fidelity scale (MI-CTS). Journal of Mental Health. 2012;21(1):38-48.
61. Reynolds WM. Adult Suicidal Ideation Questionnaire: Professional Manual. Odessa, FL: Psychological Assessment Resources; 1991.
62. Cull J, Gill W. Suicide Probability Scale (SPS) manual. Los Angeles, CA: Western Psychological Services.; 1988.
63. Beck AT, Steer RA. Manual for Beck scale for suicidal ideation. . New York: Psychological Corporation.; 1991.
64. Robinson SM, Sobell LC, Sobell MB, Leo GI. Reliability of the Timeline Followback for Cocaine, Cannabis, and Cigarette Use. Psychology of Addictive Behaviors. 2014;28:154-62.
65. Hayes A. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach. UK: Guildford Press; 2013.
66. Gratz KL, Roemer L. Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the difficulties in emotion regulation scale. Journal of Psychopathology and Behavioral Assessment. 2004;26(41-54).
67. D'Zurilla TJ, Nezu AM, Maydeu-Olivares. Social Problem-Solving Inventory-Revised: Technical Manual. New York: Multi-Health Systems; 2002.
68. Vaux A, Phillips J, Holly L, Thomson B, Williams D, Stewart D. The social support appraisals (SS-A) scale: Studies of reliability and validity. . American Journal of Community Psychology. 1986;14:195-219.

69. Beck AT, Weissman A, Lester D, Trexler L. The measurement of pessimism: The hopelessness scale. Journal of Consulting and Clinical Psychology. 1974;42:861-5.
70. Gilbert P, Allan S. The role of defeat and entrapment (arrested flight) in depression: An exploration of an evolutionary view. Psychol Med. 1998;28:585-98.
71. Kay SR, Fiszbein A, Opier LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Schizophrenia Bulletin. 1987;13(2):261-76.
72. Haddock G, McCarron J, Tarrier N, Faragher EB. Scale to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales (PSYRATS). Psychological Medicine. 1999;29:879-89.
73. Morosini PL, Magliano L, Brambilla L, al. e. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. . Acta Psychiatrica Scandinavica 2000;101:323-9.
74. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. . Schizophrenia Research. 1990;3:247-51.
75. Gavin DR, Ross HE, Skinner HA. DIAGNOSTIC VALIDITY OF THE DRUG-ABUSE SCREENING-TEST IN THE ASSESSMENT OF DSM-III DRUG DISORDERS. British Journal of Addiction. 1989;84(3):301-7.
76. Saunders JB, Aasland OG, Babor TF, Delafuente JR, Grant M. DEVELOPMENT OF THE ALCOHOL-USE DISORDERS IDENTIFICATION TEST (AUDIT) - WHO COLLABORATIVE PROJECT ON EARLY DETECTION OF PERSONS WITH HARMFUL ALCOHOL-CONSUMPTION .2. Addiction. 1993;88(6):791-804.
77. Gregg L, Barrowclough C, Haddock G. Development and validation of a scale for assessing reasons for substance use in schizophrenia: The ReSUS scale. Addictive Behaviors. 2009;34:830-7.
78. Espie CA, Kyle SD, Hames P, Gardani M, Fleming L, Cape J. The Sleep Condition Indicator: a clinical screening tool to evaluate insomnia disorder. BMJ Open 2014;4:e004183
79. Horvath AO, Greenberg LS. Development and validation of the Working Alliance Inventory. Journal of Counseling Psychology. 1989;36(2):223-33.
80. Walwyn R, Roberts C. Therapist variation within randomised trials of psychotherapy: implications for precision, internal and external validity Statistical Methods in Medical Research 2010;19:291-315.
81. Batistatou E, Roberts C, Roberts S. Stata Journal Volume 14 Number 1. 2014;14(1).
82. Dunn G, Fowler D, Rollinson R, Freeman D, Kuipers E, Smith B, et al. Effective elements of cognitive behaviour therapy for psychosis: results of a novel type of subgroup analysis based on principal stratification. Psychological Medicine. 2012;42(5):1057-68.
83. Dunn G. Pragmatic trials of complex interventions: methodological challenges. . Epidemiology and Psychiatric Sciences. 2013;22:105-9.
84. Emsley RA, Dunn G, White IR. Mediation and moderation of treatment effects in randomised controlled trials of complex interventions. . Statistical Methods in Medical Research. 2010;19(3):237-70.
85. Johnson J, Wood AM, Gooding P, Taylor PJ, Tarrier N. Resilience to suicidality: The buffering hypothesis. Clinical Psychology Review. 2011;31(4):563-91.
86. Morse J. Designing funded qualitative research. In: Denzin N, YS L, editors. Handbook of qualitative research. 2 ed. Thousand Oaks, CA: Sage; 1994. p. 220-35.
87. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006;3(2):77-101.
88. RE B. Transforming Qualitative Information. Cleveland: Sage; 1998.
89. Henwood K, Pidgeon N. Qualitative research and psychological theorizing. British Journal of Psychology. 1992;83(1):97-111.
90. Peters S. Qualitative research methods in mental health Evidence Based Mental Health. 2010;13:35-40.
91. Barrowclough C, Haddock G, Wykes T, Beardmore R, Conrod P, Craig T, et al. Integrated motivational interviewing and cognitive behavioural therapy for people with psychosis and comorbid substance misuse: randomised controlled trial. British Medical Journal. 2010;341.
92. Jones SH, Smith G, Mulligan LD, Lobban F, Law H, Dunn G, et al. Recovery-focused cognitive behavioural therapy for recent-onset bipolar disorder: randomised controlled pilot trial. British Journal of Psychiatry. 2015;206(1):58-66.

93. Lewis S, Tarrier N, Haddock G, Bentall R, Kinderman P, Kingdon D, et al. Randomised controlled trial of cognitive-behavioural therapy in early schizophrenia: acute-phase outcomes. British Journal of Psychiatry. 2002;181:S91-S7.
94. JP I, SJ E, PC G, RT ON, DG A, K S, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Annal of International Medicine. 2004;141:781-8.

Appendix 1: Consort Flow diagram