PRODIGY: Prevention and treatment of long term social disability amongst young people with emerging severe mental illness: A definitive randomised controlled trial

Version	3.0
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Sponsor	Sussex Partnership NHS Foundation Trust
Trial registration	ISRCTN47998710
CTA #	[N/A]
NRES #	185153

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1 Administrative information

This document was constructed using the Norwich Clinical Trials Unit (NCTU) Protocol template Version 4. It describes the PRODIGY trial, sponsored by Sussex Partnership NHS Foundation Trust and co-ordinated by NCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at NCTU.

NCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on an adaptation of the University College London CTU protocol template (2012) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials (Chan et al., 2013a). The SPIRIT Statement Explanation and Elaboration document (Chan et al., 2013b) can be referred to, or a member of NCTU Protocol Review Committee can be contacted for further detail about specific items.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). International sites will comply with the principles of GCP as laid down by ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC, the European Directive 2001/20/EC (where applicable) and other national and local applicable regulations. Agreements that include detailed roles and responsibilities will be in place between participating sites and NCTU.

Participating sites will inform NCTU as soon as they are aware of a possible serious breach of compliance, so that NCTU can fulfil its requirement to report the breach if necessary within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the participants in the trial, or
- The scientific value of the trial.

1.2 Sponsor

Sussex Partnership NHS Foundation Trust is the trial sponsor and has delegated activities for aspects of the overall management of the PRODIGY trial to the Chief Investigator and the NCTU, as indicated in the Sponsor Delegation of Activities log. Queries relating to sponsorship of this trial should be addressed to the sponsor, trial team or the Director, NCTU.

1.3 Structured trial summary

Delete this box on final protocol: This summary is adapted from a World Health Organisation (WHO) recommended minimum standard list of items to be included in a trial registry for a trial to be considered fully registered (http://www.who.int/ictrp/network/trds/en/index.html). The structured summary's inclusion in the protocol can signal an update required to the registry when associated protocol sections are amended.

Primary Registry and Trial Identifying Number	ISRCTN: 47998710
Date of Registration in Primary Registry	Assigned 29/11/12
Secondary Identifying Numbers	NIHR HTA reference: PRODIGY: 10/104/501 Sponsor ID:
Source of Monetary or Material Support	NIHR Health Technology Assessment Programme
Sponsor	Sussex Partnership NHS Foundation Trust
Contact for Public Queries	research@sussexpartnership.nhs.uk
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Public Title	PRODIGY: Prevention of long-term social disability amongst young people with emerging psychological difficulties
Scientific Title	PRODIGY: Prevention and treatment of long term social disability amongst young people with emerging severe mental illness: A definitive randomised controlled trial
Countries of Recruitment	England
Health Condition(s) or Problem(s) Studied	Young people who present with social withdrawal and severe and complex non-psychotic mental health problems and who are at risk of long term social disability and mental illness.
Intervention(s)	**Intervention** Social Recovery Cognitive Behavioural Therapy (SRCBT) with Enhanced Standard Care (as defined below). The SRCBT intervention used will be as described in the PRODIGY therapy manual. The intervention is delivered in a median of 15 sessions over 9 months by Trial Therapists. It is designed for use in secondary early detection and intervention mental health services and differs substantially from currently available short term CBT available in adult mental health,

	Improving Access to Psychological Therapies (IAPT) and CAMHS services. Trial Therapists offer a combination of clinic based appointments but also outreach work and offer home visits to maximise engagement and the application of learning to real life settings. The intervention involves promoting a sense of agency, hope and motivation by encouraging activity while managing symptoms of severe and complex mental health difficulties and associated problems such as emotional dysfunction and cognitive neuropsychological deficits. The focus is pragmatic and combines multisystemic working with use of specific CBT techniques. Trial Therapists adopt assertive outreach youth work principles and also draw from successful social and vocational interventions such as supported education and employment interventions. **Control** Enhanced standard care alone. This existing NHS standard outpatient treatment for young people with non-psychotic severe and complex problems and social disability can involve a range of services. To standardise and enhance current practice, all referrers receive a best practice manual for standard treatment which summarises good practice including referral to primary care, mental health services, IAPT services and medication management where appropriate.
Key Inclusion and Exclusion Criteria	**Inclusion criteria** 1. Young people aged 16 to 25 years with severe and complex mental health problems and showing early signs of persistent social disability. 2. Presence of impairment in social and occupational function indicated by patterns of structured and constructive economic activity of less than 30 hours per week and a history of social impairment problems lasting for a period of longer than 6 months. 3. Presence of severe and complex mental health problems defined operationally as a) having attenuated psychotic symptoms which meet criteria for an At risk Mental State, or b) having severe and complex mental health problems which score 50 or below on the Global Assessment of Function Scale (which indicates the presence of severe symptoms of at least two of depression, anxiety, substance misuse, behavioural or thinking problems, or subthreshold psychosis to the degree to impair function) with at least moderate symptoms persisting for longer than 6 months.

	Exclusion criteria 1. Age below 16 or above 25 years 2. Active positive psychotic symptoms or history of first episode psychosis. 3. Severe learning disability problems (though mild to moderate learning difficulties will not be excluded). 4. Disease or physical problems likely to interfere with capacity to take part in interventions and assessments. 5. Non-English speaking to the degree that the participant is unable to fully understand and answer assessment questions or give informed consent.
Study Type	The study will be a single blind, randomised controlled trial comparing Enhanced Standard Care (ESC) plus Social Recovery Cognitive Behavioural Therapy (SRCBT) with ESC alone. Randomisation will be stratified by: • age (16-19, 20-25); • severity of social disability (withdrawn = 16 to 30 hours of structured activity per week; and extremely withdrawn = 0-15 hours of structured activity per week); • meeting symptomatic criteria for an At Risk Mental State or not; and • site (Sussex, East Anglia, Manchester).
Date of First Enrolment	1 September 2015
Target Sample Size	270 patients (100 already recruited in internal pilot)
Primary Outcome(s)	Primary Outcome: Hours per week engaged in structured activity (Time Use). Metric/Method of measurement: This assessment of social functioning is derived from the Office of National Statistics Time Use Survey interview. Timepoint: 15 months post randomisation.
Key Secondary Outcomes	The following outcomes will be evaluated at 9 and 24 months post randomisation. Outcome: Hours per week engaged in structured activity Metric/Method of measurement: This assessment of social functioning is derived from the Office of National Statistics Time Use Survey interview. The following outcomes will be evaluated at 9, 15 and 24 months post randomisation. Outcome: Level of attenuated psychotic symptoms and associated psychopathology

	Metric/Method of measurement: Comprehensive Assessment of At Risk Mental States (CAARMS) interview Outcome: Mental Health difficulties / symptoms experienced by participants in the study Metric/Method of measurement: Structured Clinical Interview for DSM-IV Outcome: Self-reported Emotional disturbance Metric/Method of measurement: Social Interaction Anxiety Scale and the Beck Depression Inventory-II Health economic outcomes Outcome: Resource use Metric/Method of measurement: Health Services Resource Use Questionnaire and the Time Use Survey will be used to evaluate resource use from the perspective of the NHS and personal social services. Outcome: change in quality of life from baseline Metric/Method of measurement: EQ-5D measures pre and post intervention. Moderation and mediation outcomes will also be evaluated using: • Beck Hopelessness Scale • Meaning in Life Questionnaire • Trait Hope Scale • Schizotypal Symptoms Inventory • Brief Core Schema Scales • Experiential Avoidance • Logical Memory I subtest of the Wechsler Memory Scale (Third Edition) (measured at baseline and 15 months only) • Controlled Oral Word Association Test (measured at baseline and 15 months only) • Alcohol Use Disorders Identification Test • Drug Use Disorders Identification Test • Scale for the Assessment of Negative Symptoms • **Premorbid Adjustment Scale** • **National Pupil Database**

1.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

1.4.1 Protocol contributors

Name	Affiliation	Role
Professor David Fowler	University of Sussex	Chief Investigator – contributed to protocol development, drafting and review
Professor Paul French	Greater Manchester West Mental Health NHS Foundation Trust	Co-Chief Investigator– contributed to protocol development, drafting and review
Dr Garry Barton	University of East Anglia	Co-Investigator and lead Health Economist – contributed to protocol development, drafting and review
Dr Jo Hodgekins	University of East Anglia	Co-Investigator – contributed to protocol development, drafting and review
Dr Caitlin Notley	University of East Anglia	Co-Investigator, Qualitative Researcher – contributed to protocol development, drafting and review.
Professor Lee Shepstone	University of East Anglia	Co-Investigator, Lead Statistician – contributed to protocol development, drafting and review
Dr Rory Byrne	The University of Manchester	Co-Investigator, Service User Researcher – contributed to protocol development, drafting and review
Professor Robin Banerjee	University of Sussex	Co-Investigator – contributed to protocol development, drafting and review
Professor Alison Yung	The University of Manchester	Co-Investigator – contributed to protocol development, drafting and review
Dr Jonathan Wilson	Norfolk and Suffolk NHS Foundation Trust	Co-Investigator – contributed to protocol development, drafting and review
Dr Sophie Parker	Greater Manchester West Mental Health NHS Foundation Trust	Co-Investigator – contributed to protocol development, drafting and review
Dr Kathryn Greenwood	Sussex Partnership NHS Foundation Trust	Co-Investigator– contributed to protocol development, drafting and review
Dr Rick Fraser	Sussex Partnership NHS Foundation Trust	Co-Investigator and Principle Investigator – contributed to protocol development, drafting and review
Dr Tim Clarke	Norfolk and Suffolk NHS Foundation	Trial Manager (outgoing) and Principle Investigator - contributed to protocol development, drafting and review

	Trust	
Dr Clio Berry	University of Sussex	Trial Manager (incoming) – contributed to protocol development, drafting and review

1.4.2 Role of trial sponsor and funders

Name	Affiliation	Role
Dr Mark Hayward	Sussex Partnership NHS Foundation Trust	Sponsor; Research Director.
Ms Philippa Case	Sussex Partnership NHS Foundation Trust	Research Manager, Administrative Authority and Finance Office; NHS Costs Nominated Signatory.

1.4.3 Trial Management Team

Name	Affiliation	Role and responsibilities
Professor David Fowler	University of Sussex	Chief Investigator
Professor Paul French	Greater Manchester West Mental Health NHS Foundation Trust	Co-Chief Investigator
Dr Clio Berry	University of Sussex	Trial Manager (incoming)
Dr Jo Hodgekins	University of East Anglia	Clinical Psychologist and Co- Investigator at Norfolk and Suffolk NHS Foundation Trust
Dr Caitlin Notley	University of East Anglia	Senior Qualitative Researcher
Dr Rory Byrne	The University of Manchester	Service User Researcher
Professor Robin Banerjee	University of Sussex	Co-investigator
Professor Alison Ruth Yung	The University of Manchester	Co-investigator
Dr Jonathan Mark Wilson	Norfolk and Suffolk NHS Foundation Trust	Co-investigator
Dr Kathryn Greenwood	Sussex Partnership NHS Foundation Trust	Co-investigator
Dr Rick Fraser	Sussex Partnership NHS Foundation Trust	Co-investigator and Principle Investigator

Brioney Gee	Norfolk and Suffolk NHS Foundation Trust	Lead Research Assistant
Dr Sophie Parker	Greater Manchester West Mental Health NHS Foundation Trust	Co-Investigator and Trial Therapist
Dr Tim Clarke	Norfolk and Suffolk NHS Foundation Trust	Norfolk Site Co-ordinator, Trial Manager (outgoing), Principle Investigator and Research Trial Therapist

1.4.4 Norwich Clinic Trials Unit Team

Dr Garry Barton	University of East Anglia	Lead Health Economist
Professor Lee Shepstone	University of East Anglia	Lead Statistician and NCTU Associate Director
Dr Erika Sims	University of East Anglia	Senior Clinical Trial Operations Manager. Operational oversight and quality assurance
Tony Dyer	University of East Anglia	NCTU Head of IT and Data Management Systems; design, development and implementation of study database according to study requirements
Professor Ann Marie Swart	University of East Anglia	Director of Norwich CTU
Mrs Leodie Alibert	University of East Anglia	Norwich CTU Quality Assurance Lead
Antony Colles	University of East Anglia	NCTU Database Programmer; programme study database according to study requirements as set out in database specification developed by Head of IT and Data Management Systems

1.4.5 Trial Management Group

Name	Affiliation	Role and responsibilities
Professor David Fowler	University of Sussex	Chief Investigator
Professor Paul French	Greater Manchester West Mental Health NHS Foundation Trust	Co-Chief Investigator and Principle Investigator
Dr Jo Hodgekins	University of	Clinical Psychologist and Co- Investigator at Norfolk

	East Anglia	and Suffolk NHS Foundation Trust
Dr Caitlin Notley	University of East Anglia	Senior Qualitative Researcher
Dr Rory Byrne	The University of Manchester	Service User/Researcher
Professor Robin Banerjee	University of Sussex	Co-Investigator
Dr Jonathan Wilson	Norfolk and Suffolk NHS Foundation Trust	Principle Investigator
Brioney Gee	Norfolk and Suffolk NHS Foundation Trust	Lead Research Assistant
Dr Tim Clarke	Norfolk and Suffolk NHS Foundation Trust	Norfolk Site Co-ordinator, Trial Manager (outgoing), Principle Investigator and Research Trial Therapist
Dr Clio Berry	University of Sussex	Trial Manager (incoming)

1.4.6 Trial Steering Committee

Name	Affiliation	Role and responsibilities
Professor Max Birchwood	University of Birmingham	Member; Independent
Professor Daniel Freeman	Department of Psychiatry, Warneford Hospital, Oxford	Chair; Intendent
Dr David Shiers	Not affiliated	Member; Independent
Dr Lucia Valmaggia	Institute of Psychiatry, Psychology and Neuroscience	Member, Independent
Dr Rick Fraser	Sussex Partnership NHS Foundation Trust	Member; Independent
Mrs Suzanne Syrett	University of Glasgow	Member; Independent (Service User Researcher)
Professor David Fowler	University of Sussex	Member; Not Independent
Dr Paul French	Greater Manchester West Mental Health Foundation Trust	Member; Not Independent
Professor Swaran Singh	University of	Member; Independent

	Warwick	
Dr Jo Smith	Worcestershire Health and Care NHS Trust	Member, Independent
Dr Kathryn Greenwood	University of Sussex	Member; Not Independent
Dr Timothy Clarke	Norfolk and Suffolk NHS Foundation Trust	Member; Not Independent

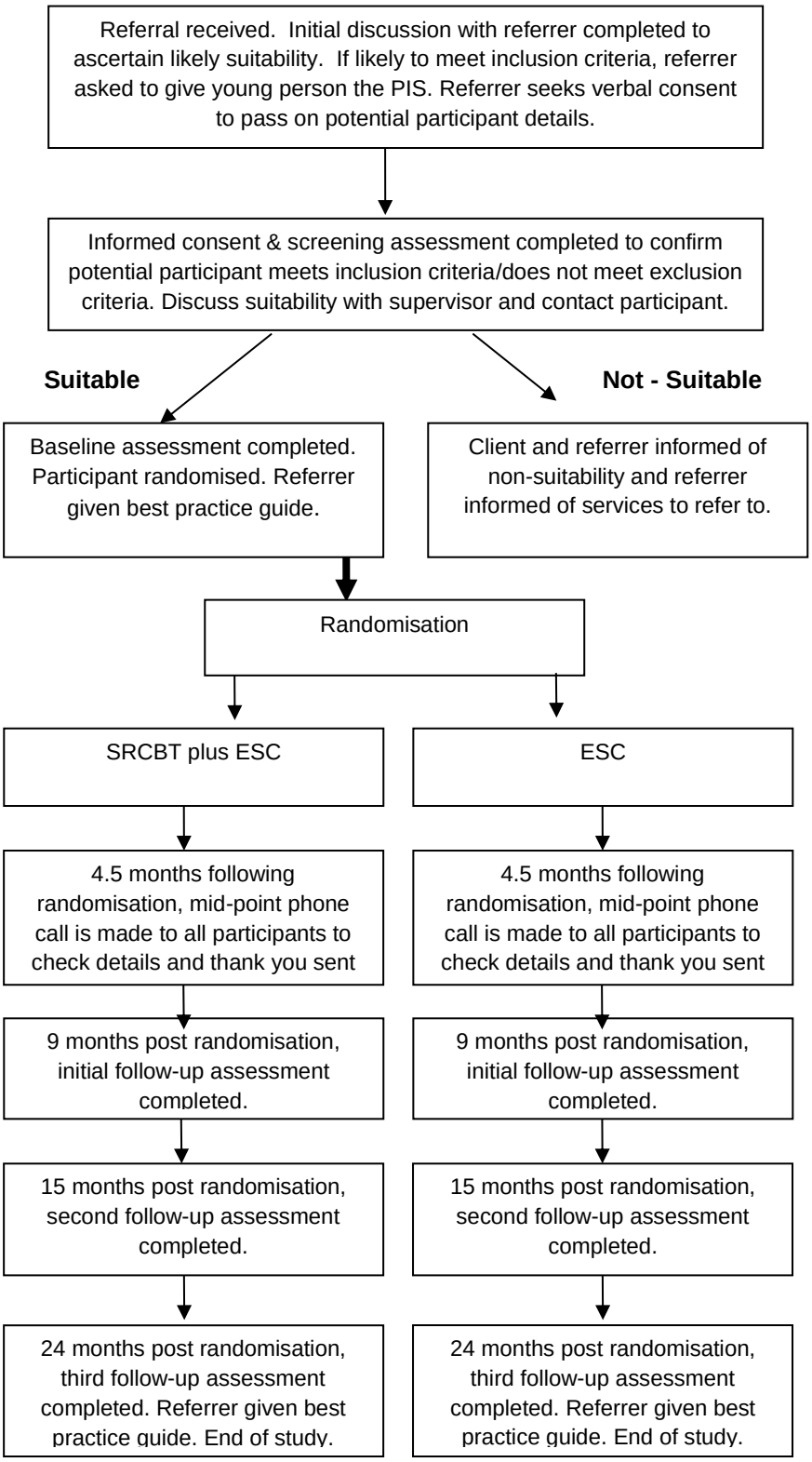
1.4.7 Data Monitoring Committee

Name	Affiliation	Role and responsibilities
Professor John Norrie	Centre for Healthcare Randomised Trials (CHaRT) Health Services Research Unit University of Aberdeen	Member; Independent
Professor Andrew Gumley	Institute of Health and Wellbeing, College of Medical, Veterinary and Life Sciences, University of Glasgow	Chair; Independent
Professor Richard Bentall	Institute of Psychology, Health and Society, University of Liverpool	Member; Independent

1.4.8 Other Trial Oversight Groups

Name	Affiliation	Role and responsibilities
PRODIGY Advisory Team	None	A service user researcher group chaired by Dr Rory Byrne. The Advisory Group reviews trial materials providing a service user perspective.

2 Trial Diagram



3 Abbreviations

AE	Adverse Event
AR	Adverse Reaction
CAARMS	Comprehensive Assessment of At Risk Mental States
CAMHS	Child and Adolescent Mental Health Services
CI	Chief Investigator
CRF	Case Report Form
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
ESC	Enhanced Standard Care
EU	European Union
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
IAPT	Improving Access to Psychological Therapies
ICH	International Conference on Harmonisation
ITT	Intention to Treat
NCTU	Norwich Clinical Trials Unit
NEET	Not in Education, Employment or Training

PI	Principal Investigator
PIS	Participant Information Sheet
PSS	Personal Social Services
QA	Quality Assurance
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
RA	Research Assistant
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SRCBT	Social Recovery Cognitive Behavioural Therapy
SSA	Site Specific Approval
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TSC	Trial Steering Committee

4 Glossary

Acceptance and Avoidance Questionnaire II (AAQ-II)
A brief self-report measure of the presence of absence of experiential avoidance/psychological inflexibility; unwillingness to experience one's own negative thoughts or emotions.

Alcohol Use Disorders Identification Test (AUDIT)
A brief self-report measure capturing the presence or absence of levels of harmful alcohol use.

Assertive Outreach
A model of care for people with complex needs which emphasises flexible engagement and visiting people in community settings.

At Risk Mental States (ARMS)
A state or phase in which a person is considered to have an elevated risk of developing psychosis. ARMS includes attenuated symptoms of psychosis, and may include changes in mood, cognition, thought content, and behaviours.

Attenuated symptoms of psychosis
Experiences such as mild confusion in thinking, suspiciousness, odd beliefs and perceptual distortions which are not quite of psychotic intensity or duration.

Beck Depression Inventory-II (BDI)
A brief self-report measure capturing the presence or absence of symptoms associated with depression.

Beck Hopelessness Scale (BHS)
A brief self-report measure capturing the presence or absence of hopelessness.

Brief Core Schema Scale (BCSS)
A brief self-report measure capturing the presence of absence of positive and negative evaluations of oneself and other people.

Child and Adolescent Mental Health Services (CAMHS) / Children and Young People's Services (CHYPS)
These are the names for NHS-provided services for children, generally until school-leaving age, in the mental health arena in the UK.

Cognitive Therapy Rating Scale Revised (CTRS-R)
A brief measure focusing on competent use of Cognitive Behavioural Therapy (CBT).

Comprehensive Assessment of At Risk Mental States (CAARMS)
A structured mental state interview conducted by a trained assessor which is used to assess attenuated psychotic symptoms and associated psychopathology, drug use and risk to self and others.

Constructive Economic Activity
Scored from the Time Use Survey; a measure of hours spent in paid or voluntary work, education, child or other caring activities and household chores.

Controlled Oral Word Association Test (COWAT)
A brief neuropsychological assessment conducted by a trained assessor in which people verbally generate words beginning with a given letter in 60 second trials.

Drug Use Disorders Identification Test (DUDIT)
A brief self-report measure capturing the presence or absence of levels of harmful drug use.

Early Intervention in Psychosis
A model of care provision for young people (typically 14 to 35 years although variable nationally) for young people during, and for two or three years after, the first episode of psychosis. The model of care involves care co-ordination and medical, psychological, and psychosocial intervention.

EuroQol-5D (EQ-5D)
A brief generic self-report measure of quality of life.

Global Assessment of Functioning (GAF)
A 0-100 scale rated by a trained assessor which captures the presence or absence of severe symptoms of at least two of depression, anxiety, substance misuse, behavioural or thinking problems, or subthreshold psychosis to the degree that they impair function.

Health Service Resource Use Questionnaire (HSRUQ)
A brief self-report measure capturing utilisation of physical health and mental health support services modified from the Client Service Receipt Inventory.

Logical Memory I
A brief neuropsychological assessment conducted by a trained assessor in which people verbally recall a short story immediately after its auditory presentation by the assessor.

Meaning in Life Questionnaire (MLQ)
Brief self-report measure assessing the perception of searching for and of experiencing meaning and purpose within one's life.

Multisystemic
A model of care which focuses on working with the systems around a young person including family, peer, school and community.

National Pupil Database (NPD)
Contains detailed information about pupils in schools and colleges in England.

Premorbid Adjustment Scale (PAS)
A retrospective rating scale administered by a trained assessor evaluating premorbid social and school functioning.

Scale for Assessment of Negative Symptoms (SANS)
A scale scored by a trained assessor evaluating the presence or absence of symptom domains including affective blunting, apathy, impoverished thinking, asociality, and disturbance of attention.

Schizotypal Symptoms Inventory (SSI)
A brief self-report measure capturing the presence or absence of unusual and anomalous experiences, including paranoia.

Social Interaction Anxiety Scale (SIAS)
A brief self-report measure capturing the presence or absence of social anxiety.

Structured Activity
Scored from the Time Use Survey; a measure of hours spent in constructive economic activity plus structured leisure and sports activities.

Structured Clinical Interview (SCID)
A structured clinical interview conducted by a trained assessor designed to categorise symptoms and experiences according to the major diagnoses from the Diagnostic and Statistical Manual of Mental Disorders (DSM).

Time Use Survey (TUS)
Derived from the Office of National Statistics Time Use Survey, this is an established measure with good psychometric properties which assesses hours per week engaged in constructive economic and structured activity. Data are captured within a semi-structured interview conducted by a trained assessor and scored in the metric of hours of activity.

Trait Hope Scale
A brief self-report measure capturing the presence or absence of general trait hopefulness. This measure is presented as 'The Future Scale' to participants.

5 Introduction

5.1 Background and Rationale

It is now widely recognised that most socially disabling chronic and severe mental health problems begin in adolescence with 75% of all severe and chronic mental illnesses emerging between 15 and 25 years (Kessler, et al., 2005; Kim-Cohen, et al., 2003). A series of retrospective studies have consistently shown that severe mental illness is often preceded by social decline, that this often becomes stable, and that such pre-morbid social disability is predictive of the long term course of the disorder (see Fowler, et al., 2010 for review). Between 3% and 5% of adolescents present with complex mental health problems associated with social disability (Kim-Cohen, et al., 2003). The young people at highest risk of long term social disability present with emerging signs of social decline, in association with low level psychotic symptoms, emotional and behavioural disorder often accompanied by substance misuse problems and risk to self and others (Kim-Cohen et al., 2003; Kessler et al., 2005). Despite poor outcomes and cost of disorders leading to social decline, young people with complex needs frequently do not access treatment and fewer than 25% of young people and their families who have needs get access to specialist mental health services (DoH, 2008; Singh et al., 2010). More complex cases are found in areas of social disadvantage, and amongst those who are not in employment, or education. The economic costs of not addressing this disability are very large (Mangalore & Knapp, 2007). Persistent mental health problems associated with social disability in young people do not resolve naturally and may persist across the life course resulting in severe distress and social disability and high costs to health and a range of social and other services (Kim-Cohen et al., 2003; Kessler et al., 2005). Health economic modelling of lifelong costs in this area are emerging, however, one recent estimates suggest that mental health problems in childhood and adolescence can result in a 28 per cent reduction in economic activity at age 50 with consequences across domains of marital satisfaction self-esteem and quality of life leading to a £388,000 lifetime loss per person (Knapp et al., 2011). Young people who have a combination of severe and persistent mental health needs and who are socially disabled present with problems which have the highest lifelong burden.

Several recent reports have highlighted that there is a major gap in identifying and managing the mental health problems of young people with severe and complex mental health problems and particularly those at risk of social disability (DoH, 2008; NICE, 2013a; Singh et al., 2010). New approaches to detection and intervention are required to meet the needs of these young people. There is a gap in the evidence base for these types of cases. Several NICE guidelines have highlighted this issue including those for social anxiety (NICE, 2013b), depression (NICE, 2005), and detection of cases at risk of psychosis and the research recommendation deriving from the NICE guideline on psychosis and schizophrenia in children and young people (NICE, 2013a). Young people who have severe but non-psychotic mental health problems and who are socially disabled are complex and thus tend not to be suitable or respond to short term evidence based therapies for more discrete mental health problems, such as CBT for anxiety, depression and conduct disorder which are available via the Improving Access to Psychological Therapies (IAPT) initiative. Also while this group show clear evidence of social disability, they do not meet criteria for First Episode Psychosis and so they are not suitable for first episode psychosis services for which there is now considerable evidence of benefits on social functioning (Addington & Gleeson, 2005; Bertelsen et al., 2008; Fowler et al., 2009a). Our aim in the present project is to identify and target the group of young people who

are socially disabled and have severe non-psychotic mental health problems and are at risk of long term severe mental illness to offer a new psychological intervention specifically tailored to their needs.

5.1.1 Explanation for choice of comparators

Current evidence for effective interventions to address social disability amongst young people in the early course of severe mental illness is very limited (Fowler et al., 2010). A series of studies have been undertaken which have aimed to identify cases at Ultra High Risk (UHR) of poor long term outcome associated with severe mental illness, focusing predominantly on risk of psychosis (Addington et al., 2007; Klosterkotter et al., 2005; McGorry et al., 2002; Morrison et al., 2004; Yung et al., 2004; Yung et al., 2006). The success of the UHR studies is that it has been shown that it is possible to set up services to identify and treat cohorts of young people who can be identified as having At Risk Mental States (ARMS) using defined operational criteria and structured assessment tools (Yung et al., 2002). Furthermore, these studies have consistently identified that those who are at the highest risk are young people who present with social decline as well as sub-threshold psychotic symptoms (Lin et al., 2011; Yung et al., 2010). However, the focus of these studies has been on prevention of episodes, or symptoms of psychosis, not social disability. Recent studies have shown that cohorts identified using these criteria may have more transient problems than previously thought and only a subset go on to have long term social disabling mental health problems (Lin et al., 2011; Yung et al., 2010). Several prominent UHR researchers are now highlighting an alternative strategy which is to examine functional outcome in the UHR group. This study is consistent with this strategy.

Systematic reviews of CBT for psychosis including NICE guidelines have consistently shown moderate effect size on improvements in social disability where this has been assessed as a secondary outcome (Wykes et al., 2008). This has been confirmed in the recent review for the NICE guidelines for schizophrenia (NICE, 2014). However, these studies have predominantly been carried out amongst chronic participants, not young people. The feasibility of using CBT with young people who are at UHR of long term poor outcome has been shown the recently completed EDIE 2 multicentre study (Morrison et al., 2012) which has shown reductions in severity of psychotic symptoms. However, the focus of the therapy in EDIE 2 was symptom reduction (French & Morrison, 2004) and this approach neither targeted nor had a significant benefit on social disability. EDIE 2 clearly demonstrated the ability of collaborating sites to recruit young people at high risk and successfully retain them in research and therapy. However, as described above, the group recruited in EDIE 2 were heterogeneous in terms of social disability. The present trial moves on from EDIE 2 by focussing on a group which have a more homogeneous set of social disability problems defined by low activity levels and targeting this group with a multisystemic intervention which specifically aims to address social disability.

Better outcomes on social disability and hopelessness can be obtained from a more targeted intervention specifically focussed on improving social disability amongst those who have low functioning. A multisystemic form of CBT has been developed which targets social disability and has been published (Fowler et al., 2013). A successful MRC trial was carried out with a group of young people who had established chronic and severe social disability problems up to 8 years after a first episode of psychosis. This trial demonstrated gains in structured activity and hope as well as

reductions in symptoms (Fowler et al., 2009b). Clear indications of health economic benefits were also demonstrated (Barton et al., 2009). However, the trial was small and there was a large level of uncertainty associated with these estimates.

The intervention used in this study has been refined from experience in previous studies to apply it to socially withdrawn young people with non-psychotic severe and complex mental health problems (Fowler et al., 2013). The feasibility phase of the substantive study described in this protocol has been completed. This will become the internal pilot. One hundred participants were recruited on time and to target. A qualitative study (Notley et al., 2015) has confirmed the acceptability and satisfaction of participants with both trial procedures and the therapy. The procedures for training and supervising Trial Therapists and the monitoring of adherence and competence were tested in the internal pilot phase. This protocol therefore reflects the processes and procedures for continuation of recruitment and for undertaking a definitive trial of the effectiveness and cost-effectiveness of this intervention. This trial will be the first to specifically address both social disability and mental health problems amongst a high risk population of young people presenting with social disability and severe mental non-psychotic health problems.

5.2 Objectives

To undertake a definitive randomised trial to determine the clinical and cost-effectiveness of Social Recovery Cognitive Behaviour Therapy (SRCBT) compared to Enhanced Standard Care (ESC) in young people who present with social withdrawal and severe and complex non-psychotic mental health problems, and who are at risk of long term social disability and mental illness.

The primary hypothesis is:

1) In young people who are socially disabled and have severe and complex non-psychotic mental health problems, SRCBT will be superior to ESC in improving social recovery (as measured by hours in constructive activity assessed on the Time Use Survey), over a 15-month follow-up period.

Secondary hypotheses are:

2) SRCBT will be superior to ESC in terms of cost-effectiveness.

3) SRCBT will be superior to ESC in effects on mental health symptoms (attenuated psychotic symptoms and emotional disturbance).

5.3 Trial Design

This is a pragmatic, multi-centre, single blind, controlled superiority RCT with ascertainment of clinical and cost-effectiveness of Social Recovery Cognitive Behavioural Therapy (SRCBT) delivered over a 9 month period plus Enhanced Standard Care (ESC) compared to ESC alone on young people (aged 16 to 25 years) with severe and complex mental health problems and showing early signs of persistent social disability. Primary and secondary outcomes will be evaluated at 15 months post

randomisation (i.e. 6 months after the end of intervention or control) and limited assessment of longer term outcomes will also be evaluated at 24 months post randomisation. The study will include the results from a 24 month, 100 participant pilot study.

6 Methods

6.1 Site Selection

The trial sponsor has overall responsibility for site and investigator selection. Some activities have been delegated to the Chief Investigator and NCTU as indicated in the Sponsor's Delegation of Activities Log.

6.1.1 Study Setting

Participants will be drawn from Secondary Mental Health care settings including outpatient Youth Mental Health, Early Detection, and Early intervention services in Mental Health Trusts in East Anglia (Norfolk and Suffolk), Sussex and Manchester. Participants may also be identified via youth services in these areas and outreach into Primary Care Mental Health settings, home visits and accompanied activities.

6.1.2 Site/Investigator Eligibility Criteria

Three research sites will be participating in this study; East Anglia (Norfolk and Suffolk), Sussex and Manchester. Two of the three sites, East Anglia (Norfolk and Suffolk) and Manchester participated in the internal pilot study that preceded this study. A new site, Sussex will be established following the move of the Chief Investigator from the University of East Anglia to the University of Sussex. Staff working on the preceding pilot (PIs, Trial Therapists, and several Research Assistants) will continue to participate in this study. The three trial sites will be issued with the PRODIGY Site File (TMF) documentation to use when applying for Site-Specific Approval (SSA) or local institutional approval as applicable, or this approval will be sought centrally by the Trial Manager based at the sponsoring organisation.

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing to to comply with the trial protocol (agreement with and confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, familiarity with the appropriate use of any investigational products, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related activities.

6.1.2.2 Resourcing at site

All participating sites have demonstrated the potential for recruiting the required number of suitable subjects within the agreed recruitment period (i.e. the investigator(s) regularly treat(s) the target population). All participating sites have received funding for an adequate number of qualified staff for the foreseen duration of the trial to enable them to conduct the trial properly and safely. Funding for staff at the participating sites was awarded based on the review of the pilot study. Two full-time Research Assistants have been funded at each site (two are required as assessments are frequently carried out in home visits requiring travel and time, and with risky participants buddy systems and doubling up is needed to ensure safety). Trial Therapists (equivalent to 1.6 FTE) will be trained at each site. A Site Coordinator, who is also a Trial Therapist, will be appointed at each site. The investigator(s) will be responsible for the appointment of study staff. Sites have sufficient data management resources to allow prompt data return to NCTU. Sites will be expected to complete a delegation of responsibilities log and provide staff contact details.

6.2 Site approval and activation

On receipt of confirmed agreement to comply with the protocol , approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The Trial Manager or delegate will notify the PI in writing of the plans for site initiation. The Trial Manager or delegate will be responsible for confirming a green light to recruit.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and which was given favourable opinion by the Research Ethics Committee (REC). The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the team at NCTU. A list of activated sites may be obtained from the Trial Manager.

6.3 Participants

6.3.1 Eligibility Criteria

Young people aged between 16-25 years presenting with persisting signs of social disability operationally defined as engaged in less than 30 hours structured activity per week and who are presenting to youth services in East Anglia (Norfolk and Suffolk), Sussex, and Manchester. They will also be presenting with either a) attenuated symptoms of psychosis which meet criteria for an at risk mental state, or b) less severe attenuated psychotic symptoms and the presence of severe and complex mental health problems operationally defined by a score of 50 or less on the Global Assessment of Functioning (GAF) score. All potential referrals are screened first with GAF score, then activity levels will be checked by the Time Use Survey and symptoms assessed by the Comprehensive Assessment of At Risk Mental States (CAARMS).

6.3.1.1 Participant selection

There will be **NO EXCEPTIONS** (waivers) to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed PRIOR to attempting to randomise the participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only clinically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar presentations. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

6.3.1.2 Participant Inclusion Criteria

1. Young people aged 16 to 25 years with severe and complex mental health problems and showing early signs of persistent social disability.

2. Presence of impairment in social and occupational function indicated by patterns of structured and constructive economic activity of less than 30 hours per week and a history of social impairment problems lasting for a period of longer than 6 months.
3. Presence of severe and complex mental health problems defined operationally as
    a. having attenuated psychotic symptoms which meet criteria for an At Risk Mental State, or
    b. having severe and complex mental health problems which score 50 or below on the Global Assessment of Function Scale (which indicates the presence of severe symptoms of at least two of depression, anxiety, substance misuse of behavioural or thinking problems or subthreshold psychosis to the degree to impair function) with at least moderate symptoms persisting for longer than 6 months.

6.3.1.3 Participant Exclusion Criteria

1. Age below 16 or above 25 years
2. Active positive psychotic symptoms or history of first episode psychosis.
3. Severe learning disability problems (mild to moderate learning difficulties will not be excluded).
4. Disease or physical problems likely to interfere with ability to take part in interventions and assessments.
5. Non-English speaking to the degree that the participant is unable to fully understand and answer assessment questions or give informed consent.

6.3.1.4 Eligibility Criteria for Individuals Performing the Interventions

The intervention is delivered by Trial Therapists who have had training in CBT skills either as part of a post-qualification training course in CBT or as part of a post graduate Clinical Psychology training programme, or both. All Trial Therapists recruited to work on the trial have experience in working with this type of case and will be trained in SRCBT. There has been a series of pre-trial workshops and ongoing training and supervision from expert therapists (David Fowler and Paul French). Trial Therapists from Sussex have joined those from Manchester and Norfolk in the most recent workshops in preparation for the trial and are currently undertaking training cases.

To minimise drift, Trial Therapists are asked to record sessions with clients and to rate the use of specific treatment techniques in notes and recording sheets. Any therapy recordings are rated using the Cognitive Therapy Rating Scale Revised (CTS-R; Blackburn et al., 2001) and a specific adherence tool suitable for the manual. Regular supervision for each Trial Therapist occurs weekly and at least fortnightly with the local CI/PI to ensure continued adherence to the model and minimise Trial Therapist drift. David Fowler and Paul French are active in supervision in order to maximise adherence to the SRCBT model. Trial Therapists rate themselves on each session using an SRCBT adherence scale and enter this on to the electronic database. Trial Therapists continue to record sessions wherever possible and a sub-sample are peer rated (across centres) to assess for adherence to the SRCBT model and competence in line with the CTS-R. CI/PI will rate samples of tapes to cross check competence and adherence. Therapy supervisors will review all therapy session notes and/ rate adherence to the SRCBT model. The data from the pilot shows good adherence to the model.

6.3.1.5 Co-enrolment Guidance

Those who participated in the PRODIGY Pilot study will not be eligible to participate in this study. Participants will not be permitted to enrol in this trial if they have been enrolled in any other clinical trials of mental health interventions in the previous 6 months. This will be assessed by questioning

the patient during the screening assessment. PRODIGY screening failures will be permitted to re-screen.

6.3.1.6 Screening Procedures and Pre-randomisation Investigations

Written informed consent to enter and be randomised into the trial must be obtained from participants, or parents/guardians/person with legal responsibility (including legal authorities) for children, after explanation of the aims, methods, benefits and potential disadvantages of the trial and **BEFORE** any trial-specific procedures are performed for the trial. Participant Information Sheets are provided before undertaking the informed consent process. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed with all patients in the same situation as a usual standard of care.

Following written informed consent being obtained, all patients will be asked to complete a screening assessment. The screening assessment includes:

The screening assessment comprises of:

- Global Assessment of Functioning (GAF; APA, 2000) score,
- activity levels, as measured by the Time Use Survey (Short, 2006), and
- symptoms assessed by the Comprehensive Assessment of At Risk Mental States (CAARMS; Yung et al., 2002).

Following completion of the screening assessment, results are discussed within the trial team at the site to obtain agreement on eligibility. Eligible participants will be advised of their eligibility to participate and invited to attend a baseline visit at which they will be asked to complete the remaining study measures. The baseline visit may be completed in one or 2 visits dependent upon the participant's time availability and/or time required to complete the measures. Following completion of the baseline visit, participants will be randomised into the study. Those participants not meeting the eligibility criteria will be advised of their ineligibility to participate and will be provided with a summary letter of the findings of the screening assessment in line with normal clinical care. The participant's referrer will be advised of the outcome of the screening assessment.

6.4 Interventions

6.4.1 Arm A (Intervention)

6.4.1.1 Social Recovery Cognitive Behavioural Therapy plus Enhanced Standard Care (ESC)

The intervention is Social Recovery Cognitive Behavioural Therapy (SRCBT) plus Enhanced Standard Care (ESC). SRCBT will be as described in the PRODIGY therapy manual (Fowler et al., 2013). The therapy is based on a Cognitive Behavioural model which suggests that social disability evolves as a result of lifestyle patterns of low activity, which are adopted as functional behavioural patterns of avoidance and maintained by lack of hope, a reduced sense of agency, and low motivation. The intervention involves promoting a sense of agency, hope and motivation and encouraging activity while managing psychotic symptoms and associated problems, such as emotional dysfunction and cognitive neuropsychological deficits. The focus is pragmatic and combines multisystemic working with use of specific CBT techniques. Trial Therapists adopt assertive outreach youth work principles and also draw from successful social and vocational interventions, such as supported education and

employment interventions. The intervention specifically focuses on engaging young people with severe and complex mental health problems into treatment and addresses the presence of multiple co-morbidities and potential cognitive difficulties.

The intervention involves three stages:

- Stage 1 involves assessment and developing a formulation of the person in social recovery. This often involves validation and acceptance of real barriers, threats and difficulties, while focusing on promoting hope for social recovery.

- Stage 2 involves identifying and working towards medium to long term goals guided by a systemic formulation of barriers to recovery. A particularly important aspect of this is identifying specific pathways to meaningful new activities. Where relevant this includes referral to relevant vocational agencies, or alternatively direct liaison with employers or education providers. Cognitive work at this stage involves promoting a sense of agency, consolidating a positive identity and addressing feelings of stigma and negative beliefs about self and others.

- Stage 3 involves the active promotion of social activity, work, education and leisure linked to meaningful goals, while managing symptoms. This involves specific cognitive behavioural work managing symptoms using behavioural experiments.

Intervention visits

Intervention visits are face to face meetings between the participant and the Trial Therapist. It is anticipated that each participant will have approximately 15 meetings with their Trial Therapist, although this may vary between participants according to individual needs. Following each meeting, the Trial Therapist will collect the following information:

- Meeting notes
  Including a detailed review of the meeting, progress to date and agreed future objectives
- Adherence to therapy
  The Trial Therapist's assessment of adherence to the intervention model
- Trial Therapist time
  Time spent with the participant
- Trial Therapist resource use
  Expenses incurred during the face to face visits. This may include, but not be limited to, travel fares and refreshment expenses incurred while accompanying the participant

SRCBT will be delivered in addition to Enhanced Standard Care (ESC) is as described in ARM B.

6.4.1.2 Treatment Schedule

SRCBT plus ESC is delivered over a median of approximately 15 sessions over a 9 month therapy window. Referrers receive the Best Practice Manual (as detailed in ARM B) after the participant has consented to

the trial and at the end of participation in the study. There is no minimum or maximum number of sessions; however, median number of sessions is anticipated to be 15.

6.4.2 Arm B (Control)

6.4.2.1 Enhanced Standard Care (ESC) alone

The control is Enhanced Standard Care (ESC) alone. There will be no restriction on access to existing NHS standard outpatient treatment for young people with non-psychotic severe and complex problems and social disability. ESC can include provision of short term individual and family psychological therapies within the Improving Access to Psychological Therapies (IAPT) and medication management, support and monitoring provided by Adult and Child and Adolescent Mental Health Services. Participants may also receive a range of education, training, vocational, and youth work interventions from a variety of statutory and non-statutory service providers (including social services, voluntary agencies, employment and education providers). ESC also involves the provision of a Best Practice Manual for standard treatment from the trial team. This manual summarises good practice including referral to IAPT services and medication management where appropriate. The Best Practice Manual has been produced by monitoring and mapping service contacts received across a range of services in both arms of the feasibility trial using the Health Service Resource Use Questionnaire (Thornicroft et al., 2006).

All service contacts are monitored during the trial duration. In addition, assessments identify any risks to self or others and this is communicated to the referring clinicians to facilitate appropriate management. As identified by the reports from the qualitative study, participation in the study in both control and treatment arms is experienced by participants as beneficial and an enhanced intervention. The Best Practice Manual and the approach of the trial team has been supported by service user groups and steering groups overseeing youth mental health provision in each of the regions and its delivery has been very well received by participating services, with referrers very keen to involve participants in both treatment and control arms.

6.4.2.2 Treatment Schedule

The Best Practice Manual will be provided to participants and referrers following pre-trial assessments with the Research Assistants and at the end of participation in the study. The participants will receive no contact with the Trial Therapists providing the intervention as described in ARM A.

6.4.2.3 Dispensing

The Best Practice Manual will be given to the referrers by the Research Assistants following pre-trial assessments and consent to participate at baseline and again at the end of participation.

6.4.3 Compliance and Adherence

Young people with severe and complex mental health problems who are socially withdrawn often present challenges to clinical services and they may disengage from treatment. Intervention and assessment procedures have been designed to be flexible and work in an outreach way to deliver the intervention and conduct assessments wherever most suitable for the participant. A full accountability trail of the invention and control participants will be maintained via the patient study number and captured on the study database. Trial Therapists will record sessions with clients and to rate the use of specific treatment techniques in notes and recording sheets. Assessments are delivered as flexibly as possible whilst minimising measurement error, for example, self-report questionnaires may be completed in the presence of the Research Assistant or as 'homework' in between

assessment sessions. Self-report questionnaires may be read aloud for participants with literacy issues.

The primary outcome assessment, Time Use, is a useful estimate of time in constructive economic activity (work, education, voluntary work). If participants are unwilling or unable to meet face to face, the Time Use Survey can be assessed by telephone contact, with additional triangulation with mental health or other professionals and/or participant relatives. Consent will be sought from participants for permission to be contacted by telephone, and for professionals/relatives to be contacted, to maximise follow-up opportunities. Intervention requires face to face meetings and therefore cannot be delivered over the telephone.

6.4.4 Concomitant Care

There will be no restriction on access to existing NHS standard outpatient (or inpatient) treatment for young people with non-psychotic severe and complex problems and social disability in either Arm A (Intervention) or Arm B (Control).

6.4.5 Protocol Treatment Discontinuation

In consenting to the trial, participants are consenting to trial treatments, trial follow-up and data collection. However, an individual participant may stop treatment early or be stopped early for any of the following reasons:

- Adverse event
- Inter-current illness that prevents further treatment
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
- Withdrawal of consent for treatment by the participant
- Disengagement or inability to maintain contact

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of data collected, follow up and data analysis.

6.5 Outcomes

6.5.1 Primary Outcomes

The primary outcome is hours per week engaged in structured activity (Time use) measured at 15 months post randomisation. This assessment of social functioning is derived from the Office of National Statistics Time Use Survey interview (Short, 2006). Number of hours per week engaged in structured activity includes time spent both constructive economic activity: e.g. paid and voluntary work, education, childcare, housework and chores; and in structured activity: structured social activity, including leisure and sports. This is the standard Time Use Survey interview as used in the Office of National Statistics UK Time Use Survey which provides extensive normative data to matched non-clinical controls.

6.5.2 Secondary Outcomes

Clinical Outcomes:

- Levels of attenuated psychotic symptoms and associated psychopathology using the Comprehensive Assessment of At Risk Mental States (CAARMS) interview (Yung et al., 2002);
- Change in difficulties experienced by participants in the study using the Structured Clinical Interview for DSM-IV (Spitzer et al., 1995);
- Emotional disturbance using self-report questionnaires; Social Interaction Anxiety Scale (Mattick & Clarke, 1989) and Beck Depression Inventory-II (Beck, Steer, & Brown, 1996),
- Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1989).

Health Economic Outcomes:

- Resource use will be calculated from the perspective of the NHS and personal social services (PSS) using a modified version of the Health Service Resource Use Questionnaire (Thornicroft et al., 2006) and the Time Use Survey (Short, 2006);
- Quality of life will be assessed via the EQ-5D (Brooks, 1996).

Role of cognitive function and motivational factors on mediation hypotheses will be evaluated by:

- Beck Hopelessness Scale (Beck & Steer, 1988);
- Meaning in Life Questionnaire (Steger et al., 2006);
- Trait Hope Scale (Snyder et al., 1991);
- Schizotypal Symptoms Inventory (Hodgekins et al., 2012);
- Brief Core Schema Scales (Fowler et al., 2006);
- Acceptance and Avoidance II (Hayes et al., 2004).

Role of cognitive function and premorbid adjustment in mediating effects on therapy a short neuropsychological assessment will be performed comprising of:

- Logical Memory I subtest of the Wechsler Memory Scale, Third Edition (Wechsler, 1987);
- Controlled Oral Word Association Test (COWAT; Benton, Hamsher, & Sivan, 1994).
- Premorbid Adjustment Scale (Cannon-Spoor et al., 1982)
- National Pupil Database data (Department for Education)

Levels of harmful drug and alcohol use will be evaluated using:

- Alcohol Use Disorders Identification Test (Babor et al., 2001);
- Drug Use Disorders Identification Test (Berman et al., 2005).

6.6 Participant Timeline

All participants will be invited to undergo screening, baseline and three post allocation follow-up assessments at 9, 15 and 24 months as detailed in the table below (Table 1).

Table 1: Screening and Assessment Timeline.

	Screening	Baseline	Allocation	Intervention (months)	Follow Up (months)	
TIMEPOINT	*-t_1	**-t_2	0	*9*	*15*	*24*
ENROLMENT:						
Informed consent	X					
Eligibility screen	X					
Global Assessment of Functioning score	X			X	X	X
Time Use Survey	X			X	X	X
Comprehensive Assessment of At Risk Mental States (CAARMS).	X			X	X	X
Randomisation			X			
INTERVENTIONS:						
SRCBT +ESC			←	→		
ESC alone			←	→		
ASSESSMENTS:						
Health Service Resource Use Questionnaire		X		X	X	X
Scale for the Assessment of Negative Symptoms		X		X	X	X
Structured Clinical Interview for DSM-IV		X		X	X	X
Social Interaction Anxiety Scale		X		X	X	X
Beck Depression Inventory-II		X		X	X	X

EQ-5D		X		X	X	X
Beck Hopelessness Scale		X		X	X	X
Meaning in Life Questionnaire		X		X	X	X
Trait Hope Scale		X		X	X	X
Schizotypal Symptoms Inventory		X		X	X	X
Brief Core Schema Scale		X		X	X	X
Acceptance and Avoidance II		X		X	X	X
Logical Memory I subtest of the Wechsler Memory Scale		X			X	
Controlled Oral Word Association Test		X			X	
Alcohol Use Disorders Identification Test		X		X	X	X
Drug Use Disorders Identification		X		X	X	X
Premorbid Adjustment Scale* **				**X**	**X**	**X**
National Pupil Database * **				**X**	**X**	**X**
Adverse events		X	X	X	X	X

*-t_1: The duration between the screening visit and the allocation of treatment is anticipated to be 2 weeks. This allows time for clinician review of the screening information and confirmation of eligibility. Once eligibility has been confirmed, a date (-t_2) will be arranged with the participant to complete the remaining assessments. Once remaining assessments have been completed, treatment allocation will be performed.

**-t_2: Remaining assessments will be completed as soon as possible after the confirmation of eligibility, however no restrictions are placed on whether these should be completed in a single visit

or two visits. This is to allow participants to complete the assessments at their own pace and according to their own availability.

***** These measures will be administered at only one of the 9, 15 or 24 month time points, or at a separate time point post-24 months for participants who have already completed study participation.**

6.6.1 Early Stopping of Follow-up

If a participant chooses to discontinue their trial treatment, they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole trial, even though they no longer receive the trial treatment. If, however, the participant exercises the view that they no longer wish to be followed up either, this view must be respected and the participant withdrawn entirely from the trial. NCTU should be informed of the withdrawal in writing using the appropriate PRODIGY trial documentation. Data already collected will be kept and included in analyses according to the intention to treat principle for all participants who stop follow up early.

Participants who stop trial follow-up early will not be replaced.

6.6.2 Participant Transfers

If a participant moves from the area every effort is made to complete as many assessments over the telephone and by post. It is not anticipated that the participant's care would be taken on by another participating trial centre.

6.6.3 Loss to Follow-up

Contact details will be stored for both patients and (and parent/relative if appropriate). In the internal pilot study, combined loss to follow-up and withdrawal of consent was 8%, which is lower than the anticipated 10%. Loss to follow up will be monitored by the Trial Management Group.

6.6.4 Trial Closure

The end of the trial is defined as 12 months following the last follow-up visit of the last patient randomised, to allow for data entry and data cleaning activities to be completed.

6.7 Sample Size

170 participants will be recruited to the trial. Together with the 100 participants of the pilot study, this will provide 135 participants in each of the trial arms. The primary outcome is hours per week in structured activity on the Time Use Survey (Short, 2006). The trial team has conservatively taken account of the possibility this may not follow a normal distribution but could have a positive skew and the analyses may use logarithmically transformed data. The sample size is based on a 'unit free' effect size of 0.4 standard deviations being considered a minimum clinically significant benefit. A total of 270 participants would provide greater than 90% statistical power to detect a 0.4 standard deviation effect size; a total of 200 participants (i.e. even accounting for greater than 25% loss to follow-up) would provide 80% statistical power for the same effect size.

6.8 Recruitment and Retention

6.8.1 Recruitment

Recruitment will be via established referral pathways. All sites have existing services which have built on referral pathways to recruit participants with At Risk Mental States.

The trial team in each site will continually liaise with primary care, secondary care and voluntary services which can refer to the project. These services then make referrals directly to the trial team. Services are asked to discuss all referrals with the trial team. If appropriate, staff familiar to the young person, or their care coordinator, will inform the young person about the study. These staff will ask the young person for permission to be contacted by a member of the trial team (usually Research Assistant). A Research Assistant will then invite the young person to a screening assessment. Specific recruitment will include, but not be limited to:

- Youth Mental Health services across the three regions; meaning voluntary, secondary, primary care, and social service partners, including Not in Education, Employment or Training (NEET) services and also those monitored as drop outs from schools, colleges and universities
- Improving Access to Psychological Therapies (IAPT), Child and Adolescent Mental Health Services (CAMHS), and Children and Young People's Services (CHYPS) across the three regions

6.8.2 Retention

Retention in the pilot study was 92% at 9 months. Intervention and assessment procedures have been designed to be flexible and are based on assertive outreach principles, which involves the delivery of assessments and the intervention wherever most suitable for the participant. Participants will also be consented to receive assessments by telephone as well as face to face, and providing consent for their mental health or other professionals and/or relatives to provide assessment data on their behalf; thereby improving the likelihood for retention. Intervention requires face to face meetings and therefore cannot be delivered over the telephone.

6.9 Assignment of Intervention

6.9.1 Allocation

6.9.1.1 Sequence generation

Following pre-trial assessments, consenting participants will be randomised to study arms stratified by age (16-19, 20-25); site (Sussex, East Anglia, Manchester); severity of social disability (withdrawn = 16 to 30 hours of structured activity per week; and extremely withdrawn = 0-15 hours of structured activity per week) and meeting symptomatic criteria for an At Risk Mental State or not. Both groups will receive standard treatments as applicable. A remote randomisation service will assign allocation to groups coordinated by the NCTU. Allocation is by pre-set lists of permuted blocks with randomly distributed block sizes (agreed with the trial statistician). The lists are generated by the Data Management Team in Norwich CTU.

6.9.1.2 Allocation concealment mechanism

The allocation process is web-based, managed as part of the Trial Data Management System (TDMS). The sequence is hidden from TDMS users. Once allocated the details are emailed to nominated individuals at the study site to enable the allocation of treatment to be implemented. The allocation is not exposed to any other users of the database or other individuals.

6.9.1.3 Allocation Implementation

Following completion and scoring of all baseline assessments, site staff will enter participant information (pertaining to stratification information) on the 'Add a new participant' section of the electronic database. Once submitted, an email is generated to the site staff to issue a participant number and inform that a participant has been randomised. Nominated members of the team (Trial Manager and Coordinators in the individual site) will receive an email detailing the allocation of said participant. This is then logged by the Site Coordinator (locally) / Trial Manager (centrally) and the allocated Trial Therapists are informed to contact participant (for those randomised to the intervention). Research Assistants do not have access to the allocation at any time during the study.

6.9.2 Blinding

Research Assistants (RAs) collecting baseline and follow-up data are blinded to group allocation. This has successfully been maintained in the pilot using a range of procedures, which will also be used in the definitive trial. Following allocation to the treatment or control arm, all participants in the study, their care coordinator/ referrer and clinical team (if applicable) are asked not to reveal the group to which the participants were randomised to the RA. Participants are also asked at the beginning of each assessment interview not to disclose the group to which the individual was allocated. Outside of the assessments, RAs are shielded from discussion of participants in study forums where the possibility of determining the allocation group of the participants could occur. A system of web based data entry ensures that RAs will not have access to information in the database that would reveal the allocation group. Data entered into TDMS by Trial Therapists that might inadvertently lead to unblinding is hidden from non-Trial Therapist users. To test the success of blinding, the blind assessor is asked to guess the allocation group for each participant at the end of the final assessment.

Reported blind breaks will be managed to maintain blind outcome assessments by reallocating 'blind' RAs to collect and score study data, therefore not biasing results. Within the internal pilot, five of these have occurred at either mid—point contact or when arranging follow-up assessments, irrespective of reminding participants, referrers and parents of the importance of blinding. Six have been administrative and/or referrer errors. The Trial Manager ensures that where blind breaks occur 'blind' assessors are allocated to participants to ensure blind outcome assessment. 'Blind' awareness/education continues throughout the study communicating to administrative staff and referrers to minimise the occurrence of accidental blind breaks. Participants, referrers and parents/relatives are also explicitly reminded of this at contact points.

6.9.3 Emergency Unblinding

As the intervention and control are delivered unblinded, and responsible clinicians are aware as to whether participants are randomised to intervention or control, no emergency unblinding procedures are required for this study.

6.10 Data Collection, Management and Analysis

6.10.1 Data Collection Methods

Each participant will be given a unique trial Participant Identification Number (PIN). Data will be collected at the time-points indicated in the Trial Schedule (see Table 1, section 6.6).

Data will be entered onto paper Case Record Forms (CRFs) or assessment packs prior to entry onto the database. Data will be entered onto the central database, stored on servers based at NCTU by members of the PRODIGY trial team working within each research site. Training on paper CRF completion, use of the online system, and storage for site staff listed on the delegation of responsibilities log will be provided at the site initiation meeting(s). Research Assistants will also receive weekly supervision, and will engage in monthly telephone conferencing and yearly cross-site training; all of which will have a continual focus on paper CRF completion and use of the online database system.

Data collection, data entry and queries raised by a member of the PRODIGY trial team will be conducted in line with the NCTU and trial specific working practice documents. Identification logs, screening logs and enrolment logs will be kept at the trial site in a locked cabinet within a secured room. Trial team members will receive trial protocol training. All data will be handled in accordance with the Data Protection Act 1998 and sponsor guidance.

6.10.2 Data Management

The database will be password protected and only accessible to members of the PRODIGY trial team at NCTU, the participating local trial teams and external regulators. The server is in a secure room, which is protected by CCTV, where access is restricted to members of the UEA Information Systems team by security door access. The study database will be built using Microsoft SQL Server tools and direct access will be restricted to NCTU data management staff. Data entry will be via web pages created using Microsoft.NET technology. All internet traffic will be encrypted using the standard TLS (Transport Layer Security) methodology. The data entry system will validate data on entry to ensure it is of the expected type (e.g. integers, dates etc.) and range of values. Periodically and at database lock the data will be further validated for errors and inconsistencies. The database is linked to an audit tool where all data additions, modifications and deletions are recorded with date/time and the user ID of the person making the change. The database is designed to comply with the ICH Guideline for Good Clinical Practice (GCP), within the Standard Operating Procedures for Data Management in NCTU and also where appropriate with UEA IT procedures.

The database and coding values have been developed by the Head of Data Management in conjunction with the study Statistician and other NCTU members. The database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data. Further details can be found in the PRODIGY Trial Data Management Plan. After completion of the trial the database will be retained on the servers of UEA for 10 years for on-going analysis of secondary outcomes.

6.10.3 Non- Adherence and Non-Retention

Adherence to the intervention is a secondary outcome. All data will be recorded irrespective of participant adherence. Should a patient withdraw consent or be lost to follow-up, all data will be included in the study dataset up to the point of consent withdrawal or loss to follow-up and will be included in the study database.

6.10.4 Statistical Methods

6.10.4.1 Statistical Analysis Plan

A full statistical analysis plan (SAP) will be written and agreed with the independent Data Monitoring and Ethics Committee and Trial Steering Committee. This will be prior to database lock and any data analysis. This plan will be amended only with agreement of the former two committees.

6.10.4.2 Statistical Methods – Outcomes

Primary analyses will compare SRCBT plus ESC with ESC alone on Time Use at 15 months post randomisation. The primary analysis will be on the intention to treat principal: i.e. all participants will be followed up for data collection irrespective of adherence to treatment and will be analysed according to group allocation rather than intervention received. Assuming a normal distribution (potentially of transformed values), a linear model will be constructed. This will include recruiting site (as a random factor), 'Time Use' at baseline (as a covariate) and any factors considered prognostic and determined in advance of any analysis, together with treatment arm as a fixed effect.

The primary intention to treat analysis is intended to provide inferences regarding the effectiveness of the intervention overall not to provide inferences regarding the causal effect of the intervention itself, but on the intervention as deployed in 'real life'.

Statistical significance will be set at the conventional (2-tailed) 5% level and all parameter estimates will be presented with 95% confidence intervals. Analyses will be carried out by the trial Statistician blinded to group identity, (i.e. 'subgroup' blind). There are no plans for formal interim efficacy or subgroup analyses. Analyses will be carried out in SAS (currently version 9.3).

6.10.4.3 Additional Analyses - Subgroup

No subgroup analyses are planned. During the trial, specific sub-groups may be suggested possibly as the result of new information becoming available, but any analyses will be agreed and stated in the statistical analysis plan.

6.10.5 Analysis Population and Missing Data

For both the primary and secondary outcomes the extent and patterns of missing data will be checked and multiple imputation will be used if it is deemed appropriate. Factors to include in the imputation model will be those that are likely to be related to the outcomes (a clinical decision) and those related to missingness (a statistical decision). The analysis using imputed data will be a secondary, sensitivity analysis with complete case analysis being the primary analysis.

6.10.5.1 Economic evaluations

An economic analysis will be conducted alongside the trial. In line with guidance by the National Institute of Health and Clinical Excellence (NICE, 2013c) costs will be calculated from the perspective of the NHS and personal social services (PSS). Resources associated with the provision of multisystemic SRCBT will thereby be monitored (in order to maintain blinding this will be

undertaken by those who deliver the specific activity). This includes the costs associated with training (including the manual, workshops for Trial Therapists, etc.), supervision (expected to be weekly) and therapy sessions. In addition to the contact time for each session, non-contact time (preparation, travel time, discussions with other professionals, report writing, etc.), travel and other costs associated with outreach work (e.g. organising a work placement) and home visits will also be recorded. The Health Service Resource Use Questionnaire (Thornicroft et al., 2006), a modified version of the Client Service Receipt Inventory (Beecham & Knapp, 1992), will be used to monitor other items of resource use, including health professional contacts, admissions to hospital / other units of care, medication and any support provided. Appropriate unit costs (Curtis, 2012) will subsequently be attached to all items of resource use. This will enable the total cost per participant to be estimated for both multisystemic SRCBT and ESC (15 month follow-up constitutes the primary analysis; 24 month follow-up is also planned).

The main measure of outcome in the economic analysis will be the EQ-5D (Brooks, 1996). This will enable a cost-utility analysis to be conducted, where the incremental QALY (Quality Adjusted Life Year) gain associated with SRCBT compared to ESC will be estimated over the 15 month trial period. Cost-effectiveness analyses will also be performed, where the effectiveness of SRCBT compared to ESC will also be assessed in relation to activity (Time Use) and symptoms (CAARMS).

Analyses will be undertaken in order to estimate both the incremental cost and incremental effect associated with SRCBT compared to treatment as usual (this within trial analysis will be undertaken for a 15 month follow-up period as part of the primary analysis, a 24 month follow-up is also planned). The primary analysis will be a complete case analysis. Assuming dominance does not occur (where one option is estimated to be more effective and less costly than the other option), the incremental cost-effectiveness ratio associated with SRCBT will be estimated and assessed in relation to a range of cost-effectiveness thresholds e.g. £20,000-£30,000 per QALY is recommended by NICE (NICE, 2013c). The associated level of uncertainty will also be characterised by estimating cost-effectiveness acceptability curves. Sensitivity analysis will also be undertaken to assess the robustness of conclusions to changes in key assumptions. Multiple imputation will be undertaken if deemed appropriate. In line with the outcome analysis, all analysis will initially be conducted on an intention to treat basis. A per protocol, analysis will also be conducted where (based on the adherence checklist) only those who have received competent and adherent therapy will be included.

6.10.5.2 Health Economic Analysis Plan

A health economics statistical analysis plan (SAP) will be developed between the trial Health Economist and Chief Investigator and agreed with the trial's governance committees.

6.11 Data Monitoring

6.11.1 Data Monitoring Committee

The Data Monitoring and Ethics Committee (DMEC) for the PRODIGY Pilot will continue for the full trial. The DMEC has access to all trial data and meets bi-annually to review safety data.

6.11.2 Interim Analyses

No efficacy interim analyses are planned. However, analysis of recruitment rates, withdrawal rates, etc. will be conducted at intervals during the study.

6.11.3 Data Monitoring for Harm

Any unfavourable and intended sign, symptom or illness that develops or worsens during the period of the study will be classified as an adverse event (AE), whether or not it is considered to be related to the study treatment. Adverse events will include unwanted side effects, sensitivity reactions, abnormal laboratory results, injury or inter-current illnesses, and may be expected or unexpected. These will be recorded on the CRF and electronically on the NCTU database.

The period for adverse event reporting will be from the time of first exposure until last follow-up assessment 24 months after randomisation.

6.11.3.1 Safety reporting

Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial.

Table 2: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorised product or summary of product characteristics (SPC) for an authorised product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that at any dose: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition***

* the term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g. a silent myocardial infarction)

** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AEs or ARs that may not be immediately life threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one

of the other outcomes listed in the table (e.g. a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation, or development of drug dependency).

Adverse events include:

- an exacerbation of a pre-existing illness
- an increase in the frequency or intensity of a pre-existing episodic event or condition
- a condition (regardless of whether PRESENT prior to the start of the trial) that is DETECTED after trial intervention administration. (This does not include pre-existing conditions recorded as such at baseline – as they are not detected after trial drug administration.)
- continuous persistent disease or a symptom present at baseline that worsens following administration of the trial treatment

Adverse events do NOT include:

- Medical or surgical procedures: the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisation where no untoward or unintended response has occurred e.g. elective cosmetic surgery
- Overdose of medication without signs or symptoms

6.11.3.2 Other Notifiable Adverse Events

None

6.11.3.3 Investigator responsibilities relating to safety reporting

All non-serious AEs and ARs, whether expected or not, should be recorded in the patient's medical notes (if applicable) and reported in the SAEs and AEs on the database within 7 days.

6.11.3.3.1 Seriousness assessment

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 2. If the event is classified as 'serious' then an SAE form must be completed and the Trial Manager notified within one working day.

6.11.3.3.2 Severity or grading of Adverse Events

The severity of AEs and/or ARs (serious and non-serious) are not being graded in this trial. .

6.11.3.3.3 Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 3.

Table 3: Causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant treatment)	SAR
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	SAR
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

If an SAE is considered to be related to trial treatment, and treatment is discontinued, interrupted or the dose modified, refer to the relevant Interventions sections of the protocol.

6.11.3.3.4 Expectedness

If there is at least a possible involvement of the trial procedures (including any comparators), the investigator and sponsor must assess the expectedness of the event. If a SAR is assessed as being unexpected it becomes a SUSAR (suspected, unexpected, serious adverse reaction) and REC reporting guidelines apply (see Notifications sections of the protocol).

6.11.3.4 Notifications

6.11.3.4.1 Notifications by the Investigator to PRODIGY Trial Manager

The Trial Manager must be notified of all SAEs within 1 working day of a member of the trial team becoming aware of the event. Trial team members should notify the Trial Manager of any SAEs occurring from the time of randomisation until the last follow-up assessment.

The SAE form must be completed by the trial team member notified of the SAE in conjunction with the local site coordinator or person with delegated responsibility. The responsible investigator should check the SAE form at the earliest opportunity, make any changes necessary, sign and then email to the Trial Manager (or delegated persons in absence of Trial Manager) within one working day for review. The Trial Manager / delegated person will review the SAE form and disseminate to the CI, PIs and sponsor representative within 72 hours of being informed to assess relatedness. The sponsor representative will also send out the SAE form for independent clinical review. The trial team member who identified the SAE should enter the report into the PRODIGY database as instructed by the Trial Manager (or delegated persons). The DMEC, REC and NCTU will be informed of SAEs periodically unless the CI or sponsor's representative escalates the SAE or deems necessary.

The minimum criteria required for reporting an SAE are the trial number and date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available. Follow-up SAE forms (clearly marked as follow-up) should be completed and sent to the trial team, as per above procedure. The participant must be identified by trial number, date of birth and initials only. The participant's name should not be used on any correspondence.

6.11.3.4.2 Chief Investigators responsibilities

The Chief Investigator (CI or a clinically qualified delegate) will review all SAE reports received. In the event of disagreement between the causality assessment given by the local investigator and the CI, both opinions and any justifications will be provided in subsequent reports.

The delegated staff within the trial team will review the assessment of expectedness and, based on possible wider knowledge of the reference material for the treatment or comparator, and after discussion with the CI, may over-rule the investigator assessment of expectedness for the purposes of onward reporting.

The Chief Investigator is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs and other SARs to the REC as appropriate. Fatal and life threatening SUSARs must be reported to the competent authorities within seven days of the Chief Investigator becoming aware of the event; other SUSARs must be reported within 15 days.

The Chief Investigator will keep investigators informed of any safety issues that arise during the course of the trial.

6.11.3.4.2 NCTU responsibilities

NCTU will submit annual reports to the REC. .

6.11.4 Quality Assurance and Control

6.11.4.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the PRODIGY trial are based on the standard NCTU Quality Management procedures which include a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

6.11.4.2 Central Monitoring at NCTU

Participants are asked to provide consent to central monitoring of their consent forms which will be shared via a confidential process. When consent is provided, NCTU staff will review consent forms for errors and missing data. When consent is not provided, sites will monitor own consent forms following NCTU guidance. The trial database will also be programmed to generate reports on errors and error rates. Essential trial issues, events and outputs, including defined key data points, will be detailed in the PRODIGY trial Data Management Plan.

6.11.4.3 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the PRODIGY Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by the Sponsor or R and D office of a participating site, theNCTU must be notified as soon as possible.

6.11.4.3.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including sponsor audits and REC review by providing access to source data and other trial related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

6.11.4.4 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent trial oversight complies with the NCTU procedures.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the PRODIGY Quality Management and Monitoring Plan.

6.11.4.4.1 Trial Management Team

The Trial Management Team (TMT) will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be decided by the TMT.

6.11.4.4.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

6.11.4.4.3 Independent Trial Steering Committee

The independent Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the CI, NCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

6.11.4.4.4 Data Monitoring and Ethics Committee (DMEC)

The DMEC is the only oversight body that has access to unblinded accumulating comparative data. The DMEC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the DMEC terms of reference. The DMEC will consider data in accordance with the statistical analysis plan and will advise the TSC through its Chair.

Membership of the DMEC is completely independent of the study and comprise of two clinical academics with experience of trials, Professor Andrew Gumley, Glasgow (Chair) and Professor Richard Bentall, Liverpool and independent Statistician (Professor John Norrie, Aberdeen).

Further details of the roles and responsibilities of the DMEC, including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in PRODIGY DMEC Terms of Reference (ToR).

6.11.4.4.5 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. Sussex Partnership NHS Foundation Trust is the trial sponsor. Sussex Partnership NHS Foundation Trust has delegated some activities to NCTU via the Sponsor's Delegation of Activities log.

7 Ethics and Dissemination

7.1 Research Ethics Approval

Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant will be submitted to the relevant REC for approval. Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents will be submitted for local Research and Development (R&D) approval.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so must be recorded. After randomisation the participant must remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

7.2 Other Approvals

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site or to other local departments for approval as required in each country. A copy of the local R&D approval (or other relevant approval as above) and of the Participant Information Sheet (PIS) and consent form on local headed paper must be forwarded to the co-ordinating centre before participants are randomised to the trial.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the NCTU Protocol Review Committee.

7.3 Protocol Amendments

Substantial protocol amendments (e.g. changes to eligibility criteria, outcomes, sample size calculations, analyses) will be decided by the Chief Investigator. Each site-PI will be informed of the potential changes. Such amendments will be submitted to NREC for approval. Once approved, the protocol amendments will be circulated to trial personnel.

7.4 Consent

Potential participants will be provided with a Patient Information Sheet (PIS) and given time to read it fully. The participant and professional information sheets include information about possible benefits and risks. Staff familiar to the young person, or their care coordinator, are involved in informing young people about the study, in collaboration with a Research Assistant who are all carefully trained by the applicants in procedures for eliciting informed consent from young people with mental health problems. Young people are supported as required throughout their involvement

in the study (e.g. post assessment or interview). Time for them to consider their participation in the study is factored in and we do not include individuals who do not have capacity to consent to participation or who are currently detained in hospital.

During the consent process it will be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the patient information sheet and the participant will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use.

A copy of the approved consent form is available from the PRODIGY trial team.

7.4.1 Consent or Assent in Ancillary Studies

There is no current intention to perform any ancillary studies but should plans emerge they will require additional funding and ethics applications to be made.

7.5 Confidentiality

Any paper copies of personal trial data will be kept at the participating site in a secure location with restricted access. Consent will be sought for a copy of the consent form to be sent to NCTU by secure fax for centralised monitoring. Receipt of the consent form will be logged and the form checked for errors or missing data. Once reviewed and confirmed correct, the consent form will be destroyed by secure document destruction.

Confidentiality of patient's personal data is ensured by not collecting patient names on CRFs or eCRFs. Any data sent to NCTU via entry into the trial database is anonymised. At trial enrolment (i.e. randomisation), the participant will be issued a patient identification code and this will be the primary identifier for the participant.

The patient and carer's consent forms will carry their name and signature but these will be kept at the trial site and not with any additional participant data at NCTU. The participant consent forms will only be accessed by NCTU staff for purposes of monitoring the consent procedure at the site.

7.6 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

7.7 Indemnity

Sussex Partnership NHS Foundation Trust holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can

prove that Sussex Partnership NHS Foundation Trust has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant in the clinical trial.

SPT holds insurance to cover participants for injury caused by the design of the protocol. SPT does not accept liability for any breach in a hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

NHS Trust sites selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to NCTU, upon request.

7.8 Finance

PRODIGY is fully funded by an NIHR Health Technology Assessments grant number 10/104/501.

7.9 Archiving

The investigators agree to archive and/or arrange for secure storage of PRODIGY trial materials and records for 10 years after the close of the trial unless otherwise advised by the Sponsor.

7.10 Access to Data

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG and TSC. Considerations for approving access are documented in the TMG and TSC Terms of Reference.

7.11 Ancillary and Post-trial Care

The sponsor does not intend to provide any interventions or other care to patients after trial completion.

7.12 Publication Policy

7.12.1 Trial Results

The results of the trial will be disseminated regardless of the direction of effect. Ownership of the data arising from the study resides with the sponsor. The publication policy will be in line with rules of the International Committee of Medical Journal Editors. The TMG will decide on authorship with any difficulties being resolved by the TSC.

7.12.2 Authorship

The TMG will nominate a writing group, which will consist of members of the TMG and will be responsible for drafting the manuscript for publication. These individuals will be named on the final publication.

7.12.3 Reproducible Research

The PRODIGY Trial Protocol will be published and made available for public access.

8 Ancillary Studies

No ancillary studies are currently planned. Any that are proposed during the lifetime of the trial will require funding applications to be made, and will be submitted for ethical approval prior to initiation.

9 Protocol Amendments

This is the first version of the protocol and no amendments have yet been made to it.

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11 Appendices

1. Appendix One: Project Gantt Chart