RADAR
Research into Antipsychotic Discontinuation And Reduction

PROTOCOL

Research into Antipsychotic Discontinuation and Reduction (RADAR) randomised controlled trial

Trial details	Randomised Controlled trial, schizophrenia and psychotic disorders
Short title of trial	RADAR Trial
Version and date of protocol	V12.0 27-April-2021
Sponsor	Priment
Sponsor protocol number	15/0947
Funder (s)	National Institute for Health Research
Trial registration number	ISRCTN90298520
EudraCT number	2016-000709-36
Active IMP(s)	Licensed antipsychotic drugs
Phase of trial	IV
Sites	Multi site
Chief investigator:	Dr Joanna Moncrieff j.moncrieff@ucl.ac.uk
Sponsor Representative:	Charlene Griffith Priment Clinical Trials Unit Primary Care & Population Health Royal Free Campus, Rowland Hill Street London, NW3 2PF Email: sponsor.priment@ucl.ac.uk

Signatures:

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

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

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

Chief Investigator: Dr Joanna Moncrieff

Sign:

Date: 27.04.2021

Sponsor Representative: Charlene Griffith, Priment Clinical Trials Unit

Sign:

Date: 27.04.2021

For the purposes of this document, Priment is representing the Sponsor.

This Protocol template is intended for use with UK sites only.

VERSION HISTORY

Version	Author	Date	Reason for Revision
0.1	Joanna Moncrieff		First draft
1.0	Joanna Moncrieff	12-Jul-2016	Updated following review
2.0	Joanna Moncrieff	19-Sept-2016	Updated following REC meeting
3.0	Charlene Griffith	11-Nov-2016	Updated following comments from the MHRA
4.0	Ruth Cooper	14-Dec-2016	Updated following review
5.0	Zoe Haime	05-Sept-2017	Updated following review
6.0	Charlene Griffith / Nadia Crellin	08-Jan-2018	Updated following review and discussion with MHRA
7.0	Nadia Crellin	01-Feb-2019	Updated and clarified information on data collection and conduct of qualitative interviews aspect of the substudy.
8.0	Nadia Crellin	04-April-2019	Updated to include all established antipsychotic drugs that are licensed for use within Europe and used in the NHS, to add Melperone to the list of IMPs, and to add the SIX to the outcome measures.
9.0	Nadia Crellin	01-June-2019	Updated to correct error to remove reference to antipsychotics licensed in the United States.
10.0	Jacki Stansfeld	14-April-2020	Updated to outline arrangements for participant follow-ups and the qualitative sub-study in light of the COVID-19 pandemic.
11.0	Jacki Stansfeld	14-July-2020	Updated to include interviews with participants from the maintenance group in the qualitative sub-study
12.0	Jacki Stansfeld	27-April-2021	Updated to include a clinician survey and remove maintenance group interviews for the qualitative sub-study

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DSMB	Data Safety and Monitoring Board
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
NIMP	Non Investigational Medicinal Product
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug

RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Document Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TRG	Trial Review Group

3 TRIAL PERSONNEL

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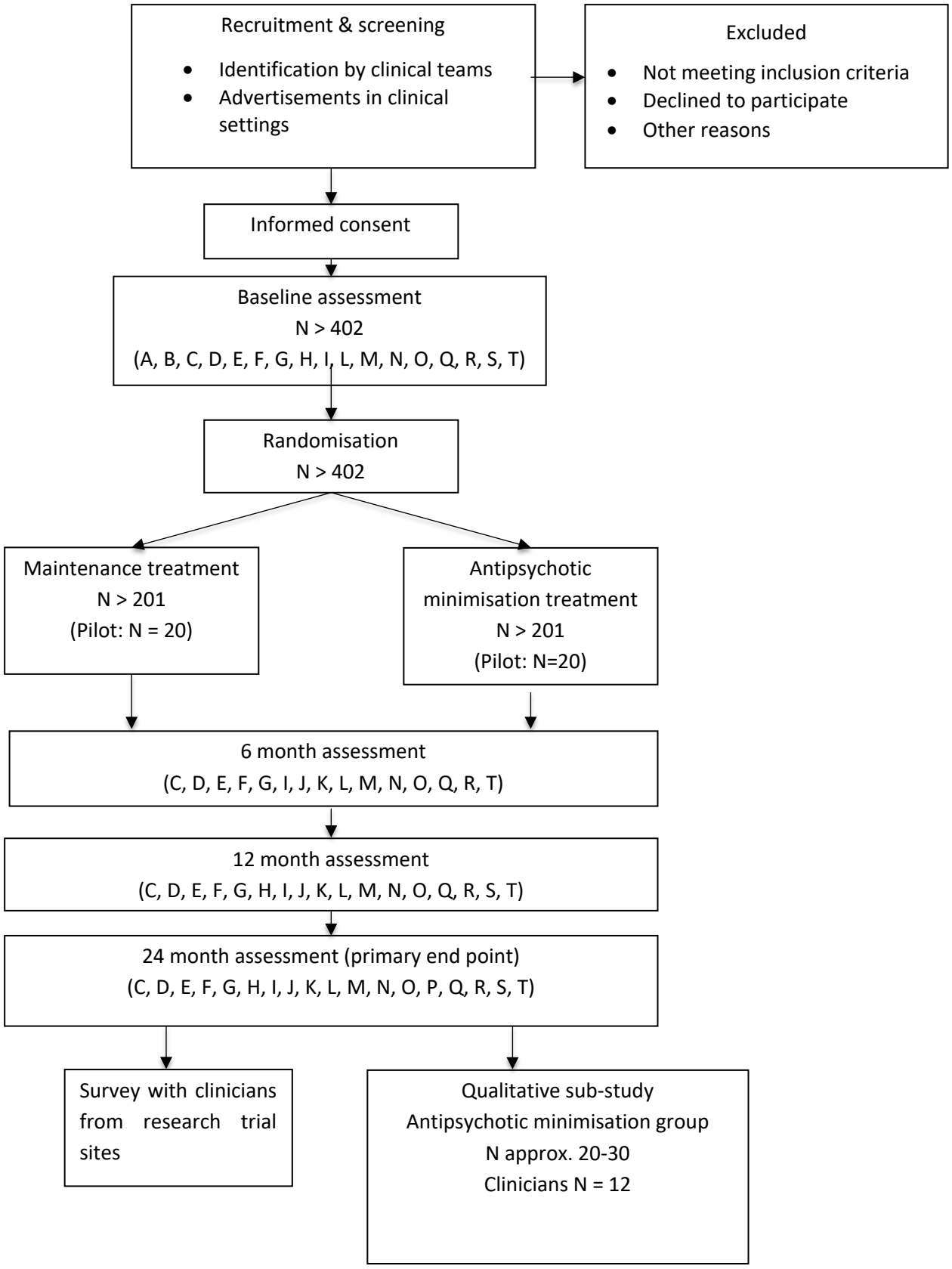
4 SUMMARY

Title:	Research into Antipsychotic Discontinuation and Reduction randomised controlled trial.
Short title:	RADAR Trial
Trial medication:	The experimental intervention consists of a flexible and gradual antipsychotic reduction and discontinuation strategy, based on best practice, and leading to discontinuation where feasible, but not in every case. The control condition will consist of continuous antipsychotic maintenance treatment.
Phase of trial:	IV
Objectives:	To evaluate the benefits and risks of a supported programme of antipsychotic dose reduction and discontinuation compared with continuous, maintenance antipsychotic treatment in adults with multiple episode schizophrenia spectrum disorders and psychotic disorders. To evaluate trial processes using quantitative and qualitative methods.
Type of trial:	Open, parallel group, multi-centre randomised controlled trial.
Trial design and methods:	The trial will compare a flexible and gradual antipsychotic reduction programme, with maintenance antipsychotic treatment. In the reduction group, a guideline reduction schedule will be devised by the research team for each participant, taking into account starting dose and number of antipsychotics prescribed. This may be adjusted by treating clinicians in discussion with participants. Antipsychotics will be discontinued in cases where reduction progresses well. The reduction schedule will be flexible, and will include guidance on monitoring and treating symptoms and signs of early relapse. Participants will be individually randomised to the two treatment strategies, which will be administered by treating clinicians. They will be followed up for two years. Main outcome is social functioning, and secondary outcomes include relapse, symptoms, side effects, employment and medication adherence.

	There will be a qualitative interview study involving a sample of participants in the antipsychotic reduction group, and a sample of treating clinicians.
Trial duration per participant:	2 years
Estimated total trial duration:	54 months
Planned trial sites:	Multi-site. Five sites at least.
Total number of participants planned:	402
Main inclusion/exclusion criteria:	Inclusion criteria: aged over 18 years; a diagnosis of schizophrenia, schizoaffective disorder, delusional disorder or other non-affective psychosis; more than one previous episode or a single episode lasting over a year; prescribed ongoing antipsychotic medication. Exclusion criteria: lacking capacity to consent to the trial; has insufficient command of spoken English to understand trial procedures; subject to a Community Treatment Order (CTO) that includes a requirement to take antipsychotic medication; admitted to hospital or had treatment from the Home Treatment or Crisis Team within the last month; clinician considers there is a serious risk of harm to self or others; females who have a confirmed pregnancy or are breastfeeding.
Statistical methodology and analysis:	The primary outcome (social functioning scale) will be analysed using generalised mixed models, accounting for baseline and treatment periods. Relapse will be compared between the randomised groups using Cox constant proportional hazards models. Secondary outcomes will be analysed using analogous methods. Demographic and clinical predictors of recovery and relapse will be explored within the data, using prognostic models.

5 TRIAL FLOW CHART



A	Demographic information (including weight in kgs)
B	Diagnosis (established from clinical records)
C	Social Functioning Scale (SFS)
D	Positive and Negative Syndrome Scale (PANSS)
E	Modified Glasgow Antipsychotics Side-effects Scale (GASS)
F	Client Satisfaction Questionnaire (CSQ 8)
G	Manchester Short Assessment of quality of life (MANSA)
H	Neuropsychological function tests
I	Medication Adherence Rating Scale (MARS-5)
J	Relapse questionnaire
K	Serious Adverse Events
L	EQ-5D-5L
M	ICECAP-A
N	Client Service Receipt Inventory
O	Work Productivity and Activity Questionnaire
P	Schedule for economic data from patient records
Q	Questionnaire about the Process of Recovery (QPR)
R	Arizona Sexual Experiences Scale (ASEX)
S	Social Cognition Battery
T	The Social Outcomes Index (SIX)

6 INTRODUCTION

6.1 BACKGROUND

Schizophrenia and related conditions are common and associated with long-term disability, premature death, physical illness and high costs. Priorities for long-term management include improving functioning, physical health and patient autonomy.

Recommended treatment for people with recurrent episodes consists continuous antipsychotic medication (NICE, 2014; Hasan et al, 2013), yet despite this many people remain functionally impaired. In one study, 25% of people with schizophrenia had severe social disabilities after 15 years, and only 14% had none (Wiersma et al, 2000).

Schizophrenia and related disorders are a common source of long-term disability. Schizophrenia alone accounted for 30% of expenditure on adult mental health and social care in 2007 (McCrone et al, 2008). In 2011, the total cost of schizophrenia was estimated to be £11.8 billion in England (Andrews et al, 2012).

Drug treatment is also expensive with medicines constituting around 16% of non-pay Mental Health Trust expenditure (Healthcare Commission, 2007) and medication-related adverse effects are a significant source of distress, illness and disability.

Antipsychotics reduce positive symptoms and risk of relapse in the short-term. They have little effect on negative symptoms, however, and they can cause serious physical and mental side effects, including diabetes, tardive dyskinesia, heart disease (Osborn et al, 2007; Ray et al, 2009) and possibly early death (Joukamaa, 2006). Mental side effects, including sedation, emotional blunting and akathisia, are debilitating and unpleasant (Moncrieff et al 2009; Barbui et al, 2005).

Rates of non-adherence with antipsychotics are high, with many patients stopping abruptly and without support (Byerly et al, 2007). This may lead to adverse events, including withdrawal reactions and withdrawal-induced relapse (Moncrieff, 2006; Baldessarini & Viguera, 1995).

Evidence on long-term antipsychotic treatment

The evidence base for long-term antipsychotic treatment consists of studies showing lower relapse rates with maintenance treatment compared to discontinuation (Gilbert et al, 1995; Adams et al, 2001; Leucht et al, 2012). However, there are acknowledged problems with these studies (Leucht et al, 2008). First, most focus on relapse and neglect other outcomes. Second, follow-up is generally short (only six of 65 studies followed people up for more than a year in the Leucht et al meta-analysis) and longer duration is associated with less difference between maintenance and discontinuation (Leucht et al, 2012; Gilbert et al, 1995). Third, relapse rates may have been inflated by abrupt discontinuation and

misidentification of withdrawal-related adverse effects (Baldessarini & Viguera, 1995; Whitaker, 2010).

It has been suggested that repeated relapse may worsen prognosis (Lieberman et al, 1996), but follow-up of placebo-controlled trials indicates that symptoms return to previous levels following relapse (Curson et al, 1986; Govinsky et al, 1992; Wyatt et al, 1999), although they may remain mildly elevated for some months (Emsley et al, 2012). Moreover, suggestions that relapse is indicative of an active neurotoxic process are not supported by clinical or neurobiological evidence (McGlashan, 2006; Moncrieff, 2012; Zipursky et al, 2012). Indeed, recent evidence suggests long-term antipsychotic treatment itself produces progressive reduction in brain volume (Ho et al, 2011; Dorph-Petersen et al, 2005), although the clinical significance of this remains unclear.

Moreover, some evidence suggests gradual discontinuation may reduce risk of relapse compared with abrupt discontinuation (Viguera et al, 1997), although this difference was not confirmed in Leucht et al's (2012) meta-analysis. However, the average taper of 28 days may not have been gradual enough for people who have been taking antipsychotics for many years.

Therefore, although continuous antipsychotic treatment has become the norm, we are not certain that this treatment represents the best balance of benefits and harms. In particular, we need more evidence on the effects of gradual reduction of antipsychotics on outcomes other than relapse, with longer term follow up.

6.2 PRECLINICAL DATA

This is not relevant, since all drugs that will be used in the trial are fully licensed and in routine clinical use.

6.3 CLINICAL DATA

A recent study conducted in the Netherlands suggests that antipsychotic reduction and discontinuation, if conducted in a gradual and supported manner, may be advantageous in terms of social recovery in the medium to longer term. Participants randomised to a strategy of gradual and flexible antipsychotic reduction and discontinuation over 18 months were twice as likely to show a full social recovery compared with people who had been randomised to maintenance treatment at seven-year follow-up, with no difference in relapse (Wunderink et al, 2013). At the 18-month follow-up relapse rates were higher in the discontinuation group, but relapses were generally benign, and there was no increase in hospitalisation. Although global social functioning did not differ between groups at 18 months, there was a non-significant increase in being in work (p=0.05), and statistically significant improvements in neurocognitive function in the discontinuation group (Wunderink et al, 2007a; Faber et al, 2012).

Meta-analysis has found no difference in relapse between first and multiple episode patients after antipsychotic discontinuation (Leucht et al, 2012), but there is no comparable study using gradual and flexible reduction in the latter. A non-randomised cohort study, which indicated worse outcomes for those on continuous antipsychotic treatment 15 to 20 years after onset, may also suggest the Dutch findings are more widely applicable, although confounding by severity or indication cannot be ruled out (Harrow et al, 2012).

6.4 RATIONALE AND RISKS/BENEFITS

The proposed trial will assess the benefits and risks of a flexible, supported strategy for antipsychotic dose reduction and possible discontinuation. In particular, it will evaluate effects on social functioning as well as relapse.

The trial will establish whether a strategy of supported and flexible antipsychotic reduction and discontinuation improves social functioning in people with schizophrenia and related disorders compared with maintenance antipsychotic treatment, without producing a clinically significant increase in the risk of severe relapse.

The evidence base for long-term antipsychotic treatment is flawed, as described above, and antipsychotic drugs have serious side effects including neurological damage, cardiac toxicity and diabetes, as well as causing subjective impairment and depression. An intervention that helps people to reduce and stop these drugs safely is likely to have advantages over current maintenance treatment in terms of reducing side effects, improving functioning, quality of life and neuropsychological functioning.

All antipsychotic drugs (IMPs) that participants take during the study will be licensed products within Europe and used within their licensed indication.

6.5 ASSESSMENT AND MANAGEMENT OF RISK

Intervention:

The principal risk associated with the intervention is a higher risk of deterioration and relapse of ‘positive’ symptoms of psychosis. We cannot be certain of the level of risk, since this is the first study of its kind to be conducted with this particular population. In the Dutch study, conducted with first-episode patients, ‘relapses’ occurred in 43% of those randomised to reduction and discontinuation, compared with 21% randomised to maintenance treatment at 18 month follow-up. However, relapses were broadly defined and generally mild. In particular there was no difference in time spent in hospital between the groups. At long-term follow-up, relapses had equalised.

The risk of relapse has to be balanced against the well-recognised risks of continuous, long-term antipsychotic treatment, which include some serious adverse effects such as sudden cardiac death, tardive dyskinesia, weight gain, diabetes, hyperlipidaemia and hyperprolactinaemia. The Dutch first-episode study also suggested it could cause

impairment of social and neuropsychological functioning (Wunderink et al, 2013; Faber et al, 2011).

Risk minimisation in the intervention group will be achieved by the slow and gradual nature of the antipsychotic reduction and by the close monitoring of symptoms, and early identification of relapse and other adverse events. Participants in the intervention group will have their antipsychotic medication reviewed and their mental state monitored every two months by a psychiatrist. They will be seen more frequently if problems occur or symptoms emerge.

All participants will draw up a personalised relapse prevention plan at the start of their randomised treatment, which will include listing early symptoms and indicators of relapse.

The intervention protocol will include guidance on how to manage increased symptoms and relapse and there will be close liaison between research staff and clinical staff about monitoring and managing symptoms and relapse. The protocols suggest a number of interventions for treating emerging symptoms and early signs of relapse, based on current clinical practice, other research (Gaebel et al, 2011) and the clinical expertise of the research team.

Measures suggested include:

- More regular appointments with their psychiatrist, care-coordinator or other professional
- Advice on anxiety management techniques and sleep hygiene
- Temporary treatment with a general sedative or hypnotic
- An increase in their antipsychotic dose

Pregnancy:

Participants who have a confirmed pregnancy at baseline will be excluded. Pregnancy is uncommon among people with severe, long-term mental illness. Since the antipsychotic drugs (IMPs) have been in widespread clinical use for many years, and will all be used within their licensed indications, we are not planning to take measures to detect and exclude people who are planning to become pregnant. Questions about participants' plans to become pregnant, and pregnancy testing, are likely to be perceived as overly intrusive, and might be upsetting for this population. We will, however, exclude any participants who become pregnant during the course of the trial from further randomised treatment. They will revert to treatment as usual.

Conduct and completion of trial:

The study will be a multi-site study involving several mental health Trusts and possibly primary care centres as well. Clinical personnel from different teams at the sites will be

involved in identifying potential participants and implementing the intervention with participants. Good communication between sites, and between researchers and clinicians will ensure that sites follow the trial protocol, and that treating clinicians implement the intervention and maintenance protocols. The research team and members of Priment Clinical Trials Unit will ensure all involved personnel at all sites are familiar with trial procedures and are informed of any changes made in a timely manner.

The Patient in this trial will only take antipsychotic drugs that are licensed for use in the patient population within Europe and used within their licensed indication. Therefore the potential risk associated with the IMP is considered to be low and no greater than standard medical care.

This trial is categorised as Type A, in accordance with MHRA guidance.

7 OBJECTIVES

Principal objectives: to evaluate the benefits and risks of a supported programme of antipsychotic dose reduction and discontinuation compared with continuous maintenance antipsychotic treatment in adults with a multiple episode schizophrenia spectrum disorder or non-affective psychotic disorders. Main outcomes are social functioning and relapse rates, and follow-up is 2 years.

Hypothesis: A supported programme of antipsychotic reduction and discontinuation will improve social functioning, with no increase in severe relapses at two year follow-up.

Secondary objectives: to evaluate trial processes using quantitative and qualitative methods.

8 OUTCOMES

8.1 PRIMARY OUTCOME

The primary outcome is social functioning, as measured by the Social Functioning Scale (SFS Birchwood et al., 1990) at 2-year follow-up. The Social Functioning Scale has good psychometric properties (Birchwood et al, 1990), is widely used, easy to administer and sensitive to change in intervention studies (Koshikawa et al, 2016; Cuidad et al, 2006; Barrowclough & Tarrier, 1990).

8.2 SECONDARY OUTCOMES

The principal secondary outcome will be severe relapse, which will be assessed for the duration of the study period. Thus any event that occurs during the period of active follow up of the trial (minimum follow up 24 months) will be included.

Relapse will be assessed in the following ways, each of which will be reported:

1) Admission to inpatient care.
2) Any acute care: admission to inpatient care or episode of treatment with Crisis Team or Home Treatment Team.
3) Patient report during scheduled follow-up assessments.
4) Information from clinical notes: episodes of relapse will be identified from clinical notes by a member of the research team.

A blinded 'endpoint committee' will judge relapse based on information from these different sources.

Other secondary outcomes will be:

- Symptoms as measured by PANSS (Kay et al, 1987)
- Subjective quality of life as measured by the MANSA (Priebe et al, 1999)
- Adverse effects of antipsychotics measured by a modified version of the Glasgow Antipsychotic Side-effect Scale (GASS) (Waddell & Taylor, 2008)
- Body weight
- Sexual dysfunction as measured by the ASEX (McGahuey et al, 2000)
- The process of recovery as measured by the QPR (Law et al, 2014)
- Employment
- Neuropsychological function (measured by a brief battery of tests designed for this trial)
- Economic analysis
- Social outcomes as measured by the SIX (Priebe et al, 2008)
- Social cognitive function - measured by a brief battery of tests designed for this trial (Corcoran et al, 1995; Combs et al, 2007; Bell & Lysaker, 1997; Bell et al, 2010; Baron-Cohen et al, 2004; Cooper & Petrides, 2010)

All antipsychotic side effect scales were reviewed and none were found to be both comprehensive and suitable for self-administration or administration by non-specialist research assistants. The GASS was therefore modified by adding 11 items to improve coverage of adverse mental effects, extra-pyramidal effects and other common adverse effects using items from other validated scales namely the Liverpool University Neuroleptic Side-Effect Rating Scale (LUNSERS) (Day et al, 1995) and the Antipsychotic Non-Neurological Side-Effects Rating Scale (ANNSERS) (Ohlsen et al, 2008). The wording of the introduction was also slightly amended so the questionnaire can be administered to people who have discontinued antipsychotics, as well as those who are still taking them.

Process measures are:

- Dose of antipsychotic medication (in haloperidol equivalents)
- Patient satisfaction as measured by the CSQ (Atkisson & Zwick, 1982)
- Antipsychotic medication adherence as measured by MARS-5 (Mahler et al, 2010)

8.3 SAMPLE SIZE AND RECRUITMENT

8.3.1 SAMPLE SIZE CALCULATION

The primary outcome is social functioning, which will be measured by the Social Functioning Scale (Birchwood et al, 1990). We estimate that a difference of 4 points or more would be clinically significant since this appears to differentiate between patients with good and poor outcomes (Hellvin et al, 2010; Leeson et al, 2012; Jaracz et al, 2015). Moreover, onset of psychosis was associated with a 4 point decline in SFS scores in a recent study (Jang et al, 2011).

The trial has also been powered to establish the safety of the antipsychotic reduction strategy by powering it to detect whether there is a difference in rates of severe relapse between the intervention arms. We believe that an increased risk of severe relapse of up to 10% would be acceptable to many clinicians and patients if it is balanced by the important outcomes of an improvement in social functioning and reduced side effects. Other comparative trials such as the large CATIE study used a larger non inferiority boundary of 12% for the related outcome of treatment failure or drop-out. We used hospitalisation as the proxy for severe relapse, and derived event rates for hospitalisation from those reported in the Leucht et al, 2012 meta-analysis of antipsychotic discontinuation studies.

We conducted a non-inferiority calculation using a 10% margin of difference. Using a strict non inferiority boundary for 10% event rates (severe relapse), with an alpha of 0.05, requires a sample size of 372 for 90% power to exclude a difference of 10% between groups. Adding 15% for attrition brings this up to 402. The lower confidence interval on the absolute scale would exclude a difference of 10% in the situation where non inferiority was achieved.

Therefore the current sample size could be used to address non inferiority between the groups with a margin of 10%. However, the study will endeavour to recruit a larger number of subjects in order to be able to detect even smaller differences in rates of severe relapse. Indeed we are aware that our non-inferiority boundary may reasonably differ from other patients and clinicians, and prioritise achieving a precise estimate of the relative hazard of severe relapse with narrow confidence intervals to inform clinical decision making.

Using a conventional α of 5% (two sided) and taking a SD of 8.8 derived from the literature, a sample size of 402 will provide 90% power to detect a difference of 3.2 points on the primary efficacy outcome (the SFS).

The sample size of 402 is large enough to provide precise estimates of important secondary outcomes such as symptoms, side effects and quality of life. If successfully recruited, the trial will be the largest study of antipsychotic reduction strategy conducted to date.

8.3.2 PLANNED RECRUITMENT RATE

We plan to recruit participants from Community Recovery Teams, Assertive Outreach teams, Early Intervention in Psychosis teams, Older Adults teams and Learning Disability teams within participating Trusts. A Recruitment Study (a separate study) is being

conducted currently to establish the proportion of patients who are likely to be eligible and willing to participate, and how many Trusts will be required to achieve required numbers.

Depending on the results of the Recruitment Study, we may also recruit patients from local General Practices using methods adapted from trials of people diagnosed with depression.

The timeline for the trial allows 4 months for recruitment in the pilot trial, at a rate of 10 participants per month. In the full trial there are 26 months for recruitment, which assumes an average recruitment rate of 14 participants per month. We believe it is a realistic estimate and takes account of eventualities such as poor recruitment at one or two sites.

The research team has extensive experience of successfully undertaking trials in this patient population, of achieving planned recruitment rates, and achieving high retention rates.

9 TRIAL DESIGN

9.1 OVERALL DESIGN

The trial will consist of an open, parallel group trial with individual randomisation to the intervention: antipsychotic reduction and discontinuation; and the control group: antipsychotic maintenance treatment.

The RADAR PPI group will be involved at key stages in particular development of recruitment materials, training materials and problem solving.

Interventions:

An individualised antipsychotic reduction schedule will be devised for each patient randomised to the intervention group by the research team, based on the participant's initial antipsychotic regime. Dose will be reduced incrementally every two months, with flexibility to speed up or slow down the schedule in discussion with the patient. Feedback from the RADAR PPI group highlights that reduction of antipsychotics has to be flexible to accommodate individual circumstances and response to reduction.

The antipsychotic reduction and maintenance protocols will be administered by treating psychiatrists, who will also monitor participants' mental state. Participants will also be regularly monitored by other members of their usual care team, as per usual clinical care. The antipsychotic reduction manual will contain guidance on action to be taken in the case of deterioration of symptoms or signs of early relapse.

The antipsychotic reduction protocol will extend over a period of between six to 12 months, although this may be extended according to individual circumstances.

The control group protocol will allow for increases or minor adjustments to antipsychotic medication, but discourage significant dose reduction.

Psychiatrists will receive training on administering the intervention protocols. Throughout the trial there will be close contact between the research team and treating clinicians to ensure adherence to protocols and to monitor participants for adverse effects.

Blinding:

Participants and treating clinicians will not be blinded because participants will start on different antipsychotic regimes, and those within the intervention group will follow an individualised reduction protocol.

Members of the research team conducting outcome assessments will be blinded to treatment allocation.

A number of procedures will be in place in order to assess and maintain the integrity of the blinding, as recommended by Minns Lowe and colleagues (2011):

- Research staff carrying out outcome measures, statisticians, health economists, the Programme Steering Committee (PSC) and the 'endpoint committee' (see below) will be blind to participant allocation.
- Participants will be asked not to tell research staff who visit what arm they have been allocated to and not to mention the antipsychotic reduction process, if they are in that arm. The importance of this will be stressed to participants at baseline assessment and before each visit by research staff who organise the appointments.
- If staff are inadvertently unblinded by participants or staff then they will record any knowledge of arm allocation.
- Where possible, blinded research staff will not be in contact with treating clinicians.
- Clinicians will be made aware of which members of staff to speak to with queries regarding antipsychotic treatment schedules and the treatment-related issues.
- Blinded research staff will have no access to any study data that could compromise blinding.
- Blinded research staff will have no access to treatment notes, or participant identifying data, except necessary names and addresses.
- Following each assessment point blinded research staff will record if they guessed arm allocation, based on the same procedure as Minns Lowe et al. (2011), selecting one of the statements below:
    - "I do not know which arm the participant is in"
    - "I have guessed the participant is in the antipsychotic reduction arm"
    - "I have guessed the participant is in maintenance treatment arm"
    - "The participant has told me they are in the antipsychotic reduction arm"
    - "The participant has told me they are in the maintenance treatment arm"
    - "I have been told that the participant is in the antipsychotic reduction arm"
    - "I have been told that the participant is in maintenance treatment arm"
- If blinded research staff have been made aware of allocation the reasons for unblinding will be recorded. This information will be stored and blinded staff will not have access to it.
- Research staff will complete field diaries to record any useful information regarding blinding that may be referred to if unblinding occurs.

Internal Pilot:

The main trial will be preceded by an internal pilot trial that will evaluate the methods and design of the proposed trial, ensuring the trial is achievable and provisionally safe. The pilot

will evaluate the recruitment strategy, the mechanism of randomisation, baseline assessments, adherence to intervention protocols, effectiveness of monitoring procedures, retention rates and relapse assessment. It will consist of a four month recruitment period. Process data will be collected at three-months following randomisation and there will be a six-month participant follow-up assessment and collection of process data.

The pilot trial will immediately precede the main trial, with information from the initial stages being used to inform recruitment strategies, and later information being used to inform outcome assessments and methods of follow up.

The pilot study will be conducted in two sites, NELFT and ELFT, which are geographically close to maximise the efficiency of the study, and economise on researcher time. It is estimated that 20 participants per group will be sufficient to address the issues involved, recruited over a four-month recruitment period.

Outcome assessment and follow-up:

The current study is designed to provide as long a follow-up period as possible within the constraints of the funding stream. Efforts will be made to follow-up all participants (including those withdrawn from the interventions) for two years.

Participants who wish to withdraw from further follow-up assessment will be asked to provide verbal consent for continuing permission for the research team to access their clinical records to obtain data on some outcomes (such as relapse). This will be recorded in writing by the research team.

Relapse will be assessed by an 'endpoint committee,' based on blinded information about episodes of acute treatment, patient report and episodes identified from case notes. The Committee will identify episodes of 'severe relapse' and 'any relapse' according to pre-set criteria.

Qualitative evaluation:

There will also be a Qualitative evaluation. Qualitative data will be gathered from around 20-30 participants from the antipsychotic reduction group in a sub-study designed in collaboration with the RADAR Public and Patient Involvement (PPI) group. Interviews will be conducted with early participants following the 24-month follow-up interviews so as not to contaminate the main trial results.

The qualitative sub-study has two aims: to collect data on participant and clinician experience of trial processes. In the interviews with reduction participants we aim to explore in detail experiences of antipsychotic reduction and discontinuation from the patient perspective. Participants will be identified towards the end of follow up, using purposive sampling to obtain variation in clinical profile, experience of reduction,

completion of the antipsychotic reduction protocol and experience of relapse. We will aim to include participants who have successfully reduced or discontinued antipsychotics, those who have not managed to do this, and those who reduced or discontinued but had to increase or restart antipsychotics.

Participants who consent to undertake the qualitative study will have a semi-structured interview. In the interviews with participants from the antipsychotic reduction group we will focus on experiences of the intervention and its impact on their mental health and wider lives, the acceptability of the antipsychotic reduction programme, satisfaction with available support and responses to adverse events and experiences of follow procedures. We will also attempt to interview a small number of patients who have withdrawn from the study during the follow-up period to investigate reasons for this. Interviews will be conducted by research assistants, with supervision from the qualitative lead, NM. Interview schedules will be drawn up by applicants with PPI group input. Interviews will be audio-recorded with participants' consent.

Further process data will be collected from a sample of around 12 practitioners involved in the study, using semi-structured interview schedules. Interviews will focus on experiences of implementing different aspects of the antipsychotic reduction strategy, relations with the research team, acceptability of medication monitoring procedures and responses to adverse events. Interviews will be audio-recorded if participants consent to this.

Data will also be collected from around 20-30 carers (friends/relatives) of patients who meet the trial eligibility criteria, some of whom will have taken part in the antipsychotic reduction programme. Family members/friends who consent will take part in a semi-structured interview exploring their views of antipsychotic medication for their relative/friend, as well as their views and experiences of alterations in antipsychotic dose (particularly any reductions and/or stoppages). For those who have a family member/friend taking part in the antipsychotic reduction programme the interviews will focus on experiences of the intervention and its impact on their relative/friends mental health and wider lives, satisfaction with available support and responses to adverse events.

Clinician survey

Further to the qualitative interviews with clinicians, we will conduct an online survey with practitioners from the research sites and NHS Trusts involved in the trial. This brief online survey will focus on clinician views regarding antipsychotic reduction and discontinuation and facilitators and barriers to this.

9.2 RECRUITMENT

Potential participants will be identified initially by clinical teams or recruited by advertisements placed in clinical settings. Potential participants will also be identified through community groups and networks, social media and the RADAR website.

Depending on the results of the recruitment study, some participants may be identified from primary care.

10 SELECTION OF SUBJECTS

10.1 INCLUSION CRITERIA

1. Aged over 18 years
2. A clinical and/or ICD10 diagnosis of schizophrenia, schizoaffective disorder, delusional disorder or other non-affective psychosis
3. More than one previous episode of relapse or psychotic exacerbation, or a single episode lasting more than one year
4. Taking antipsychotic medication

10.2 EXCLUSION CRITERIA

1. Participant lacks capacity to consent to the trial.
2. Participant has insufficient command of spoken English to understand trial procedures
3. Participant subject to section 37/41 of the Mental Health Act (MHA) or a Community Treatment Order (CTO) that includes a requirement to take antipsychotic medication
4. Clinician considers there will be a serious risk of harm to self or others
5. Participant has been admitted to hospital or had treatment from the Home Treatment or Crisis Team within the last month
6. Females who have a confirmed pregnancy
7. Females who are breast-feeding
8. Involvement in another IMP trial
9. No contraindications to continuing on antipsychotic medication

11 STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

11.1 PATIENT IDENTIFICATION

Team caseloads will be screened to identify potential participants according to inclusion and exclusion criteria. Clinical staff will then contact potential participants from among their caseload to ask if they would be willing to be contacted by the research team to receive further information. They may do this in person, by telephone or by sending out a brief leaflet about the study in the post. If clinicians see or speak to patients they will obtain verbal consent from potential participants to be sent further information about the study, and to be contacted by the research team. Consent will be documented by clinical staff. If clinical staff send out information in the post, participants will be asked to contact the

research team by telephone if they are interested in taking part, or to return a reply slip to the research team by post, indicating their agreement to be contacted and sent further information. Research staff will not have access to clinical records or contact information until patients have provided verbal consent to be contacted.

When potential participants agree to receive further information about the study, they will be sent the Participant Information Sheet by post (both in short and long versions with the option to listen to the information sheet in audio for those with visual impairment or difficulties with reading), and will then be telephoned by a member of the research team. If researchers are unable to make contact by telephone, the potential participant will be sent a letter about the study by post, asking them to make contact with the research team if they are interested in taking part.

Advertisements will be placed in clinical settings, describing the study and the study will be presented to community groups or networks. Potential participants will be invited to discuss the study further with their clinical team, or to contact the research team directly for further information.

The local PI of the study or a delegated medical practitioner will confirm eligibility.

A screening log will be used by the research team to record all potential participants who have expressed interest in the study, whether they meet the eligibility criteria and reasons for exclusion.

11.2 INFORMED CONSENT PROCEDURE

Trial consent procedure:

Potential participants will be contacted initially by a member of their clinical team, as described above. If they give consent to receive further information about the study, they will be sent the standard Patient Information Sheet, which will have been approved by the Research Ethics Committee. The date of sending the PIS will be recorded in the screening log. They will be telephoned by a member of the research team at least three days after having been sent the information. During this conversation, potential participants will have an opportunity to ask questions about the study, and if they agree an interview will be scheduled.

Written informed consent will be obtained during the interview prior to participation in the trial, following a full explanation of the aims, methods, anticipated benefits and hazards of the trial. Consent will be taken by a delegate of the principal investigator who will be GCP trained and named on the delegation log.

The designee who conducts the consent procedure will explain that the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason. The designee will complete a formal assessment of each participant's capacity to provide informed consent, which will be documented and stored with study documents. No clinical trial procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into the trial.

A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes, along with the capacity assessment form. General Practitioners, consultant psychiatrists and care-coordinators or clinical team managers (in the case of patients who do not have care-coordinators) will be informed that their patients have consented to participate in the trial. A letter will be sent to General Practitioners and consultant psychiatrists, and care-coordinators and team mangers will be informed by e-mail.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and participants will be re-consented as appropriate. Consent is an ongoing process and researchers will ask participants for verbal consent at each follow-up time-point.

Qualitative sub-study:

A selected sample of antipsychotic reduction intervention participants in the trial will be asked whether they agree to be contacted to take part in an in–depth interview study following the end of the main trial. Further information will be provided to eligible participants during or shortly after the final trial follow-up assessment, including a participant information sheet. An interview time will be set up with those participants who agree.

Written informed consent will be obtained during the interview appointment prior to participation in the research procedures, following a full explanation of the aims, methods, anticipated benefits and hazards of the sub-study. Consent will be taken by a delegate of the principal investigator who will be named on the delegation log.

The designee who conducts the consent procedure will explain the patients are under no obligation to enter the sub-study and that they can withdraw at any time during the interview, without having to give a reason. The research interview will not start until the participant has given consent. No audio-recording will take place until full informed consent is obtained.

A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes.

A sample of clinical staff, including psychiatrists, who have been involved in administering the antipsychotic reduction protocol will also be approached and asked to take part in the qualitative interview sub-study. A Participant Information Sheet will be provided outlining what taking part will involve and written informed consent will be obtained from participating clinicians by a member of research staff prior to the commencement of the research interview. All participants will be provided with a copy of their signed consent form.

A sample of carers (friends/relatives) of patients who meet the trial eligibility criteria, some of whom will be taking part in the antipsychotic reduction programme will be asked if they are willing to take part in a semi-structured interview about their views of antipsychotic medication for the person they care for. A Participant Information Sheet will be provided

outlining what taking part will involve and written informed consent will be obtained prior to the interview. No audio-recording will take place until full informed consent is obtained.

Qualitative sub-study COVID-19 arrangements:

During the COVID-19 pandemic, arrangements will be made for the qualitative sub-study consent procedures and interview to be completed remotely, in order to comply with social distancing measures. These arrangements will be in place only for the duration of this pandemic or if participants, carers or clinicians prefer to be seen remotely even if the risk is low. If participants have access to the internet, a consent form will be emailed to them. If participants do not have access to internet, a consent form will be sent in the post with a freepost envelope for its return once completed. We will ask all participants to complete the consent form (either electronically or on hard copy) whilst on the phone or other communication platform (e.g. Skype) with the researcher. This will ensure that the researcher has explained each point on the consent form to the participant. This process will be audio-recorded (with the participant's verbal consent to do so) to evidence that the consent was fully informed and will be stored on the NHS Trust secure shared drive. The researcher will counter-sign the consent form and return a copy to the participant in the post.

Clinician survey

Clinicians will be contacted via email through relevant Trust channels, R&D department contacts and site Principal Investigators.

11.3 RANDOMISATION PROCEDURES

Randomisation will be performed using a remote computerised system with allocation 1:1, described in a separate randomisation protocol. Random allocations will be issued on completion of the baseline eligibility criteria confirmed by the PI or delegate. There will be no replacements for subjects who drop out or otherwise cannot comply with study procedures, but randomisation will continue with the aim to achieve 402 randomised participants.

11.4 UNBLINDING

Not applicable

11.5 BASELINE ASSESSMENTS

For baseline assessments with participants, the following data will be collected:

A	Demographic information (including weight and use of illicit drugs and alcohol)
B	Diagnosis (established from clinical records, using OPCRIT system for psychotic and affective illness)
C	Social Functioning Scale (SFS)
D	Positive and Negative Syndrome Scale (PANSS)
E	Modified Glasgow Antipsychotic Side-effect Scale (GASS)
F	Client Satisfaction Questionnaire (CSQ 8)
G	Manchester Short Assessment of quality of life (MANSA)
H	Neuropsychological function tests
I	Medication Adherence Rating Scale (MARS-5)
L	EQ-5D-5L
M	ICECAP-A
N	Client Service Receipt Inventory
O	Work Productivity and Activity Questionnaire
Q	Questionnaire about the Process of Recovery (QPR)
R	Arizona Sexual Experiences Scale (ASEX)
S	Social Cognition Battery
T	The Social Outcomes Index (SIX)

11.6 TREATMENT PROCEDURES

Intervention group: Antipsychotic Minimisation

Treating psychiatrists will be advised to aim to reduce antipsychotic medication over a period of up to 18 months approximately.

A suggested individualised antipsychotic reduction schedule will be provided for each participant. This will be devised by the research team following baseline assessment and randomisation, taking account of each participant's initial antipsychotic regime.

Antipsychotic doses will be reduced by small decrements approximately once every two months.

The aim of the reduction will be to discontinue antipsychotics when possible. If this is not possible, then the aim will be to reduce to a minimum dose (equivalent to 2mg of haloperidol or 100mg of chlorpromazine). This is twice the dose that was considered 'low dose' treatment for those in the Dutch First Episode antipsychotic reduction and discontinuation study (equivalent to 2mg of haloperidol). Evidence suggests that effective doses in people with multiple episodes are roughly twice those of people following a first episode (McEvoy et al, 1991).

The following table presents some examples of suggested reduction schedules for common antipsychotic regimes (these will vary, however, depending on participants' individual circumstances):

Time schedule (Month)	Risperidone 8mg	Aripiprazole 30mg daily	Haloperidol 15mg daily	Olanzapine 20mg daily	Zuclopentixol 600mg 2-weekly
1	6mg	25mg	10mg	15mg	400mg 2-weekly
3	4mg	20mg	7mg	10mg	300mg 2-weekly
5	2mg	15mg	5mg	7.5mg	200mg 2-weekly
7	1.5mg	10mg	3mg	5mg	100mg 2-weekly
9	1mg	5mg	1.5mg	2.5mg	100mg 4-weekly
11	Stop if possible	Stop if possible	Stop if possible	Stop if possible	Stop if possible

Treating psychiatrists will be advised that they can vary the reduction schedule in discussion with the participant, and in response to individual participant response and circumstances. However they should aim to complete the reduction and discontinuation process within 12 to 18 months if possible. The research team will provide ongoing support to clinicians in implementing the reduction protocol.

The intervention manual will include instructions on making a relapse prevention plan in conjunction with participants to identify early signs of relapse.

The intervention manual will also contain guidance on responding to an increase in symptoms or an early relapse, in line with current practice, existing literature and expert consensus. Suggested measures consist of:

- More regular appointments with their psychiatrist, care-coordinator or other professional
- Advice on anxiety management techniques and sleep hygiene
- Temporary treatment with a general sedative or hypnotic
- An increase in their antipsychotic dose

Once the situation has stabilised, the patient may be encouraged to continue with the antipsychotic reduction schedule.

Other drug treatment (including antidepressants and 'mood stablisers') may be used as indicated throughout the trial. Other interventions such as psychological therapy may be used as indicated throughout the trial.

All participants will be free to decide they no longer wish to reduce their antipsychotic medication. In this case, they will not be withdrawn from the trial, but will be followed up, with their permission, according to the follow-up assessment schedule.

Control group: Antipsychotic Maintenance Treatment

The control group will be prescribed continuous, maintenance antipsychotic treatment. This will involve participants continuing on their current dose of antipsychotic medication. Minor dose adjustments can be made to manage side effects, according to usual clinical practice. Increase in antipsychotic dose, and changes to different antipsychotic agents at equivalent doses will be permitted, but significant dose reduction will be discouraged.

Participants in this group will be monitored according to usual clinical practice. The intervention manual will include instructions on making a relapse prevention plan to identify early signs of relapse.

Other drug treatment (including antidepressants and 'mood stabilisers') may be used as indicated throughout the trial. Other interventions such as psychological therapy may be used as indicated throughout the trial.

All participants will be free to decide that they want to reduce or stop their antipsychotic medication. In this case, they will not be withdrawn from the trial, but will be followed up, with their permission, according to the follow-up schedule.

Participant information

Following randomisation, participants from both groups will be provided with information about their treatment condition, which will also include general advice about local support services. Information for participants in the antipsychotic reduction group will include a copy of their individualised reduction schedule, unless the treating psychiatrist objects to this being included in a particular case.

11.7 SUBSEQUENT ASSESSMENTS

Follow-up assessments with participants will be conducted at 6 months, 12 months and 24 months with all participants. This will either be conducted at the participant's home, clinic or completed via phone if the participant is unwilling to complete a face-to-face assessment. Data on relapse in early recruits will be collected from medical records after the two year follow-up, up until the end of the study period (the last follow-up interview with the last recruit). Data on antipsychotic medication use, service use and adverse events will be collected from medical records throughout the course of the study.

Due to the lack of long-term data from trials of antipsychotic maintenance and discontinuation, it is extremely important to facilitate the collection of data after the current study officially ends. Data from other studies suggests that differences in functional outcome may only emerge after four years or more, and that early differences in relapse attenuate after two to three years of follow-up (Harrow et al, 2012; Wunderink et al, 2013). Consent will therefore be sought to access participants' clinical records and information collected by the NHS Health and Social Care Information Centre, following the end of the trial. This will enable us to assess important outcomes such as relapse to provide long-term data. Consent will also be sought to contact participants after the end of the study for further follow-ups should funding become available.

Follow-up assessments will involve the completion of the following questionnaires (see visit schedule in section 11.8 for the measures to be used at each follow-up):

A	Demographic information (selected sections including weight and use of illicit drugs and alcohol)
C	Social Functioning Scale (SFS)
D	Positive and Negative Syndrome Scale (PANSS)
E	Glasgow Antipsychotic Side-effect Scale (GASS)
F	Client Satisfaction Questionnaire (CSQ 8)
G	Manchester Short Assessment of quality of life (MANSA)
H	Neuropsychological function tests
I	Medication Adherence Rating Scale (MARS-5)
J	Relapse questionnaire
K	Serious Adverse Events
L	EQ-5D-5L
M	ICECAP-A
N	Client Service Receipt Inventory
O	Work Productivity and Activity Questionnaire
P	Schedule for economic data from patient records
Q	Questionnaire about the Process of Recovery (QPR)
R	Arizona Sexual Experiences Scale (ASEX)
S	Social Cognition Battery

T	The Social Outcomes Index (SIX)

Follow-up assessments during COVID-19 pandemic.

Follow-up assessments will be completed remotely with participants over the phone or other communication platform (e.g. Skype). Questionnaires that cannot be completed remotely will be completed in person once business as usual resumes. All researchers will receive additional guidance regarding completing questionnaires over the phone.

Qualitative sub-study

A semi-structured interview will be conducted with a subgroup of consenting trial participants from the intervention and maintenance group, a sample of clinicians with experience of delivering the antipsychotic reduction programme and a sample of carers (friends/relatives) some of whom will be taking part in the antipsychotic reduction programme. A Topic Guide created for this purpose will be used for these interviews.

11.8 FLOWCHART OF STUDY ASSESSMENTS

	Baseline	Follow-up				
Visit #	1	2 Pilot trial 3 month data collection	3 6 month follow-up	4 12 month follow-up	5 24 month follow-up	6 Qualitative evaluation
Informed Consent	X					X
Eligibility determination	X					
Protocol Assessments	A-I, L-O, Q, R, S, T	K,	C-G, I-O, Q, R, T	C-O,Q, R, S, T	C- T	Indicative topic guide with sample of participants and psychiatrists
Randomisation	X					
IMP administration	X	X	X	X	X	
Adverse Events review	X	X	X	X	X	
Medical notes review for prescribing information and fidelity to intervention protocols	X	X	X	X	X	
Concomitant Medication review	X	X	X	X	X	
Physician's Withdrawal Checklist		X	X	X		

11.8 METHODS

11.8.1 LABORATORY PROCEDURES

Not applicable

11.9 DEFINITION OF END OF TRIAL

The trial will end 24 months after the randomisation of the last study patient.

11.10 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS AND 'STOPPING RULES'

The Chief Investigator will consider whether any participants need to be withdrawn from randomised treatment on a case by case basis.

Stopping rules:

The Programme Steering Group and the DSMB will continually review all adverse events data. The DSMB will derive a prospective monitoring plan, including sequential stopping rules, which will be described in a separate charter.

12 NAME AND DESCRIPTION OF ALL DRUGS USED IN THE TRIAL

12.1 TREATMENT OF SUBJECTS

Please see Section 11.6

All participants will use currently licenced antipsychotic drugs, defined as first and second generation for the purposes of the trial.

Concomitant medication:

Concomitant medication will be prescribed as indicated as per usual clinical practice.

Use of concomitant medication will be measured at follow-up and compared between groups, as one measure of the outcome of the trial.

13 INVESTIGATIONAL MEDICINAL PRODUCT

13.1 NAME AND DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

Please see Appendix (below).

The Appendix lists anti-psychotic drugs which may be considered investigational medicinal products (IMPs) in this trial, irrespective of which arm the participant is randomised to. This list is not exhaustive as new antipsychotics drugs/preparations may come onto the market and established antipsychotic drugs that are licensed for use in other countries may be prescribed in the UK. Any anti-psychotic drug that patients take as their trial medication will be used for the treatment of schizophrenia and related psychotic conditions in the NHS and used within their licensed indication.

13.2 NAME AND DESCRIPTION OF EACH NIMP

There are no NIMPS

13.3 SUMMARY OF FINDINGS FROM NON-CLINICAL STUDIES

Not applicable

13.4 SUMMARY OF FINDINGS FROM CLINICAL STUDIES

This can be found in the Summary of Product Characteristics for each drug.

13.5 SUMMARY OF KNOWN AND POTENTIAL RISKS AND BENEFITS

Side effects of first generation antipsychotics include: sedation, weight gain, Parkinsonism, akathisia, tardive dyskinesia, cardiac arrhythmias, sudden cardiac death, hypotension, hyperprolactinaemia, impotence, menstrual disturbances, galactorrhea, jaundice, blood dyscrasias, constipation, photosensitisation.

Side effects of second generation antipsychotics include: sedation, weight gain, diabetes, Parkinsonism, akathisia, tardive dyskinesia, cardiac arrhythmias, sudden cardiac death, hypotension, hyperprolactinaemia, impotence, menstrual disturbances, galactorrhea, blood dyscrasias, constipation, hypersalivation and epileptic fits with clozapine.

Please see Summary of Product Characteristics for each individual drug for more details.

13.6 DESCRIPTION AND JUSTIFICATION OF ROUTE OF ADMINISTRATION AND DOSAGE

Route of administration of antipsychotic medication during the trial will be determined by the route of administration before the trial starts. It may be changed during the trial depending on participant preference and clinical indication.

13.7 DOSAGES, DOSAGE MODIFICATIONS AND METHOD OF ADMINISTRATION

Please see section 11.6 for dose adjustment suggestions and 11.11 for stopping criteria.

13.8 PREPARATION AND LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCT

Trial specific labelling will not be used for this study as standard NHS stock will be used.

13.9 DRUG ACCOUNTABILITY

There are no formal accountability measures required for this trial. Medication will be prescribed by treating psychiatrists and dispensed from community and hospital pharmacies as it would usually be.

Types and doses of antipsychotic drugs currently prescribed will be recorded at baseline and at each follow-up assessment.

13.10 SOURCE OF IMPS INCLUDING PLACEBO

Medication will be prescribed by treating psychiatrists and dispensed from community and hospital pharmacies as it would usually be. There is no placebo in this trial.

13.11 DOSE MODIFICATIONS

Please see section 11.6 for dose adjustments protocols and 11.11 for stopping criteria.

13.12 ASSESSMENT OF COMPLIANCE

Medication adherence will be assessed in both groups using the MARS-5, a validated and simple instrument.

Adherence to treatment protocols in the intervention and control group will be assessed regularly by comparing current dose of treatment with that recommended in the treatment protocol. Where there are differences, the research team will contact the clinical team to discuss the reasons for these.

Participants will not be excluded due to non-compliance with the protocol, and antipsychotic dose will be one of the outcomes of the trial, which will be compared between groups.

13.13 POST-TRIAL IMP ARRANGEMENTS

Not applicable. All IMPS are routinely available.

14 DATA MANAGEMENT AND QUALITY ASSURANCE

14.1 CONFIDENTIALITY

All personal data will be handled in accordance with the UK Data Protection Act 1998.

The Case Report Forms (CRFs) will not bear the participant's name. The subject's initials, date of birth and trial identification number, will be used for identification.

14.2 DATA COLLECTION TOOLS AND SOURCE DOCUMENT IDENTIFICATION

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The study delegation log will identify all personnel with responsibility for data handling and data entry, including those who have access to the trial database.

Data collected during assessments will be recorded on CRFs in electronic form and stored in a secure online data management system provided by Priment.

Data on potential relapses will be recorded on a 'relapse information recording form'. This information will be blinded for review by the Trial Endpoint Committee and will be stored in the secure online data management system after review by the committee.

For the qualitative sub-study, interviews will be audio-recorded, with participants consent. The recordings will be encrypted and will be sent to the transcriber via secure means. Transcriptions will not contain any identifying data and will be stored securely at NELFT and UCL.

14.3 DATA HANDLING AND ANALYSIS

The trial database will be provided by Sealed Envelope with support from Priment CTU that will include facility for data entry. This will be accessed via a secure website to allow data to be entered from all sites.

Data management activities will be described in a trial specific Data Management Plan.

All data will be handled according to the Data Protection Act 1998 as well as UCL Information Security Policy and Trust Information Governance Policy.

Data analysis will be performed under the supervision of the trial statistician. Data analysis will be completed independently from data entry. A data analysis plan will be agreed by the Programme Steering Committee before the database is locked.

14.4 DATA OWNERSHIP

At the end of the trial, the data belongs to North East London Foundation Trust and University College London.

15 RECORD KEEPING AND ARCHIVING

Archiving will be authorised by the Sponsor following submission of the end of study report. Chief Investigators are responsible for the secure archiving of essential trial documents (for each site, if multi-site trial) and the trial database as per their trust policy. All essential documents will be archived for a minimum of 5 years after completion of trial.

Destruction of essential documents will require authorisation from the Sponsor.

16 STATISTICAL CONSIDERATIONS

Professor Nick Freemantle is the trial statistician who will be responsible for all statistical aspects of the trial from design through to analysis and dissemination, which will be conducted according to the relevant Priment SOPs.

There will be an a priori Statistical Analysis Plan.

16.1 STATISTICAL ANALYSES

16.1.1 SUMMARY OF BASELINE DATA AND FLOW OF PATIENTS

A consort flow diagram will be produced (http://www.consort-statement.org/). Randomised groups will be compared on demographics and baseline characteristics.

16.1.2 PRIMARY OUTCOME ANALYSIS

The primary outcome measure is the Social Functioning Scale (SFS).

The primary outcome will be analysed using generalised mixed models, accounting for baseline and treatment periods and in supportive analyses exploring the effect of community teams as random intercept terms. The principal analysis will be undertaken using the intention to treat population (defined as all patients randomised, analysed according to their randomised group regardless of treatment received). The principal analysis will include all available data, without imputation. Supportive analyses will include analysis of different time periods, analysis using repeated measurements (where all subjects with data at one or more post intervention assessment will be included), exploring potential community team effects and making pessimistic assumptions by group on the patient outcome (to assess the thresholds to the impact of 'missingness') because of the likely pattern of missing not at random.

It seems highly likely that the missing at random assumption will not be tenable in this setting. For the SFS (primary efficacy variable) we will undertake a complete case analysis for the primary analysis, and contrast if appropriate with multiple imputation strategies (based upon the patient characteristics and the array of available end point data since participants provide the outcome at a range of different times). A complete case analysis will be unbiased in the context of missingness that it not related to the outcome of treatment. The reasons for any differences in the results of these analyses will be explored.

16.1.3 SECONDARY OUTCOME ANALYSIS

Severe relapse will be compared between the randomised groups using Cox constant proportional hazards models including community teams as marginal frailty terms. Levels of medication use and successful withdrawal in both groups will be described and compared using analogous statistical methods. Demographic and clinical predictors of recovery and

relapse will be explored within the data, using prognostic models, including factors derived from other studies plus expert clinical opinion, such as symptom severity and length of treatment. In general, a randomised trial with a high rate of censorship will often meet the assumptions required for a Cox model even in the presence of more complex underlying data patterns. However the extent to which there is a departure from constant proportional hazards will be assessed statistically using analyses derived from cumulative sums of martingale residuals over follow-up times and Kolmogorov-type supremum tests. As departure from constant proportional hazards is possible given the early reduction in neuroleptics followed by appropriate clinical management and such departure leads to biased effect estimates, these will be addressed by fitting time dependent explanatory variables. In the unlikely event that departure from constancy exists and cannot be reasonably addressed through modelling strategies, other survival based models (fully flexible parametric models) or categorical models (e.g. binomial mixed) will be adopted based upon explicit criteria in the statistical analysis plan. The p value for the comparison of relapse will be derived from the log rank test which is not biased in the context of departure from constant proportional hazards.

We will minimize missing data by design and implementation, since there are no unbiased strategies to account for missing data. In previous studies conducted by Priment we have achieved follow up rates in the high 90%s for patients with severe mental illness. By supplementing face to face interviews with routine data we will increase the follow up for outcomes such as hospitalisation, and possibly also 'severe relapse' (depending on how this is defined). Baseline characteristics required for the principal analyses will be a requirement for randomisation so will not be missing by design.

We will undertake supportive threshold analyses where any loss to follow up will be considered according to extreme data patterns – e.g. assuming all those who were lost in the antipsychotic withdrawal group had a relapse and all those in the maintenance group did not, and thus quantifying the extent of possible effects of missingness and thus the robustness of the main result. These threshold analyses are similar to those required by regulatory agencies considering applications for marketing authorisation for new pharmacologic products.

Proposed analysis of secondary outcomes associated with the economic evaluation is described below in section 17.

16.1.4 SENSITIVITY AND OTHER PLANNED ANALYSES

A full statistical analysis plan (SAP) will be produced a priori, describing planned subgroup analyses and with detailed description of the statistical processes to be used.

16.2 INTERIM ANALYSIS

There will be no formal interim analysis, but the Programme Steering Group and the DSMB will continually review all adverse events data. The trial will be stopped if it is judged that there is a substantial increase in serious adverse events that are likely to be related to the intervention.

16.3 OTHER STATISTICAL CONSIDERATIONS

The SAP will be developed a priori. Any necessary deviation from the SAP will be described in the Clinical Study Report.

17 ECONOMIC EVALUATION

An economic analysis plan will be completed prior to the completion of the trial by the trial health economist, Rachael Hunter.

The economic evaluation will evaluate the cost-effectiveness of antipsychotic minimisation strategy compared to maintenance treatment over 24 months. The principal analysis will be the incremental cost per quality adjusted life year gained from the health and social services cost perspective using the EQ-5D-5L to calculate quality adjusted life years (QALYs) (EuroQol Group, 1990). The EQ-5D has been included given that it is the measure recommended by NICE when calculating the incremental cost per QALY, but there is contradictory evidence that that the EQ-5D is a valid and reliable measure for patients with psychosis. Instead measures such as the ICECAP-A have better face validity, capturing outcomes that are important to patients (Brazier et al 2014). As a result a secondary analysis will include the cost per capability adjusted life year (CALY) gained of antipsychotic minimisation strategy compared to maintenance treatment over 24 months. Additional sensitivity analyses will explore the cost-effectiveness of minimisation compared to maintenance capturing the QoL loss associated with antipsychotics side effects using specific disutility values for antipsychotic side effects from the published literature (Briggs et al, 2008).

Resource use data will be collected from two sources: mental health resource will be collected from patient files; physical health and social care resource use will be collected using a self-completed questionnaire. This will also collect information on employment, benefits, housing, impact on family and close others and criminal justice contacts. The Work Productivity and Activity Impairment- General Health (WPAI) questionnaire and associated formula (Reilly et al, 1993) will be used to give a monetary value to impact on employment. Health and social care data costs using published sources will be used to calculate costs for the primary health and social care analysis. A secondary analysis will be conducted from a societal perspective to capture the impact on employment, criminal justice, benefits, family and close others. Extensive data will be collected as part of the trial on antipsychotic prescriptions include frequency of appointments, prescriptions, monitoring and physician time to allow for calculating the costs associated with antipsychotics in the two arms of the trial.

All costs and outcomes will be discounted in line with NICE guidance at 3.5% per year.

Bootstrapping will be used to construct confidence intervals for total mean costs, QALYs and CALYs and to construct cost effectiveness acceptability curves and cost-effectiveness planes. Missing data will be handled in the same way as stated by the statistical analysis plan.

18 NAME OF COMMITTEES INVOLVED IN TRIAL

There will be a Trial Management Group (TMG), a Data Safety and Monitoring Board (DSMB) and Programme Steering Group (PSG), which will provide independent oversight of the trial along with other aspects of the research programme. A PPI group will provide advice throughout the trial.

19 RECORDING AND REPORTING OF ADVERSE EVENTS AND REACTIONS

19.1 DEFINITIONS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	Any untoward and unintended response in a subject to an investigational medicinal product which **is related** to any dose administered to that subject. *This includes medication errors, uses outside of protocol (including misuse and abuse of product)*
Serious adverse event (SAE), serious adverse reaction (SAR) or unexpected serious adverse reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results in death, • is life-threatening, • requires hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect
Important Medical Event	These events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'.
Unexpected adverse reaction	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: (a) in the case of a product with a marketing authorization, in the summary of product characteristics for that product. (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
SUSAR	Suspected Unexpected Serious Adverse Reaction

19.2 RECORDING ADVERSE EVENTS

All adverse events will be recorded in the medical records and CRF. All symptoms of schizophrenia and psychotic disorders (as per clinical decision and section 19.2D) and other mental disorders will be captured in the CRF as endpoints (relapse) unless considered related to the IMPs not the underlying mental disorder. However, those meeting the criteria for serious events will be captured as such and recorded in the medical records and AE log.

In the medical records, all adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

All adverse events will be recorded until 30 days after the last protocol treatment administration. Where applicable, all adverse events will be reported to Priment until 30 days after the last protocol treatment administration.

Each adverse event will be assessed for the following criteria A-D (severity, causality, expectedness and seriousness).

A. SEVERITY

Category	Definition
Mild	The adverse event does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

B. SERIOUSNESS

Seriousness as defined for an SAE in section 19.1.

C. CASUALTY

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

D. EXPECTEDNESS

Category	Definition
Expected	An adverse event that is listed in the applicable reference information for the drug.
Unexpected	An adverse event the nature and severity of which is not consistent with the applicable reference information for the drug.

Reference Safety Information

To determine expectedness, Investigators will be supplied with a list of SPC's for all the IMPs involved in the trial, so they can refer to the section 4.8 of an SPC relating to the IMP that the patient is taking.

Where there is more than one pharmacologically identical preparation of the IMP, one SPC for one preparation of the IMP will be selected as the reference document. A list of IMPs that may be used in this trial is provided in the Appendix.

In instances where the name of the drug that the patient is taking is known but the formulation is unknown, the SPC relating to the name of the IMP will be used to determine expectedness.

19.3 PROCEDURES FOR RECORDING AND REPORTING SERIOUS ADVERSE EVENTS

In addition to being recorded in the medical notes and the CRF, all serious adverse events (SAEs) must be recorded on the Priment SAE log. The SAE log will be reported to Priment annually.

All reportable SAEs occurring at any of the trial sites must be reported to Priment (see SAE reporting criteria section 19.3.1). Within 24 hours of becoming aware of a SAE, the Principal Investigator or delegate, must complete the RADAR SAE form and email the form to Priment at the following address:

primentsafetyreport@ucl.ac.uk

The TM (jacki.stansfeld@nelft.nhs.uk) must be copied in to the email. The Principal Investigator will respond to any SAE queries raised by Priment as soon as possible.

19.3.1 SAE reporting criteria:

- Hospital admissions that were planned prior to patient randomisation will not be reported as SAEs.
- Expected events related to schizophrenia and psychotic disorders and other co-existing mental disorders will not be reportable to the Sponsor unless the PI assess the event as more severe than expected. Relapse is a disease related expected event.

SAEs unrelated to IMPs will not be reportable to the Sponsor as the IMPs are well established drugs used within their licensed indication. All reportable serious events will be reviewed by the TMG at their regular meetings. All reportable serious events will be reported to PRIMENT within 24 hours of the investigator becoming aware of the event.

19.3.1 NOTIFICATION OF DEATHS

All deaths of trial patients must be reported to the Principal Investigator. Within 24 hours of becoming aware of a death, the Principal Investigator must complete the RADAR SAE form and email the form to Priment at the above email address.

19.3.2 REPORTING SUSARS

The Priment will notify the REC and MHRA of all SUSARs occurring in the trial within the required regulatory timelines.

The Chief Investigator is responsible for dissemination of all SUSARS to all participating Principal Investigators.

19.3.3 DEVELOPMENT SAFETY UPDATE REPORTS

Priment will provide the REC and the MHRA with Development Safety Update Reports (DSUR), which will be written in conjunction with the trial team. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

19.3.4 ANNUAL PROGRESS REPORTS

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The chief investigator will prepare the APR.

19.3.5 PREGNANCIES

Pregnancies that occur in female patients should be reported to Priment. Within 24 hours of becoming aware of a pregnancy, Principal Investigators should complete the Priment pregnancy form and email the form to Priment at the following address:

primentsafetyreport@ucl.ac.uk

The CI (j.moncrieff@ucl.ac.uk) and TM (jacki.stansfeld@nelft.nhs.uk) must be copied in to the email. The Principal Investigator will respond to any queries raised by Priment or the CI as soon as possible.

Pregnancies will be followed up until term or termination provided that consent has been given by the mother.

Pregnant women will be withdrawn from randomised treatment and treated according to normal clinical practice for pregnant women.

There will be no follow-up of children born to pregnant patients, since all IMPs are in routine clinical use. Patients will be followed-up according to the trial protocol.

19.3.6 OVERDOSES

Overdoses which require admission to hospital or where there is clear intent to endanger life must be reported to Priment using the RADAR SAE form following the guidance given in sections 19.1-19.3.

Where this involves a participant in the antipsychotic minimisation group, the TMG will consider whether to maintain the participant in the intervention group or to withdraw them from treatment.

Other overdoses that do not require admission to hospital and where there is no clear intent to endanger life will not be considered as an SAE, but will be recorded in the CRF and medical notes as per other adverse events.

All participants will be followed up according to the trial protocol, whether or not they continue their randomised treatment.

19.4 PATIENT FOLLOW-UP AFTER ADVERSE EVENTS

All patients that experience an adverse event will be followed-up until the event has resolved. Where an adverse event results in an ongoing medical condition the patient should be followed-up until the condition has stabilised.

19.5 REPORTING URGENT SAFETY MEASURES

If any urgent safety measures are taken, the Chief Investigator and Priment shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

19.6 NOTIFICATION OF SERIOUS BREACHES OF GCP AND/OR THE PROTOCOL

A "serious breach" is a breach which is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

Priment will notify the MHRA and EC in writing of any serious breach of:

(a) the conditions and principles of GCP in connection with that trial; or (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

Priment must be notified immediately of any case where the above definition applies during the trial conduct phase. Priment SOP 25 – Serious breaches of GCP or trial protocol must be followed.

20 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

21 ETHICS AND REGULATORY REQUIREMENTS

Priment, in its role as delegate of the Sponsor, will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body (MHRA in UK) and a main research ethics committee, prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

For a research site to begin recruitment, confirmation of capacity and capability will be confirmed following the HRA approval process.

It is the responsibility of the Chief Investigator/ Principal Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section 20.4.7 for reporting urgent safety measures).

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the MHRA and main REC within 1 year after the end of the trial.

21.1 PUBLIC AND PATIENT INVOLVEMENT

There has been extensive Public and Patient Involvement (PPI) during the development of the present protocol, including several focus groups of service users and carers. Patients and carers throughout the country are strongly supportive of the research. An outline proposal of the research programme was reviewed in detail by a service user panel recruited through McPin (PPI organisation). These participants were also strongly supportive of the importance of the programme, including the trial.

The research team includes a PPI co-ordinator, a service user representative, who has additional research experience, a carer and a representative from National Mind who has extensive experience of providing accessible information for the general public and has worked with the research team in the past. They have all been involved in developing the trial design and they will be involved in advising on all aspects of the trial. They will be members of the Programme Management Group for the overall research programme.

In addition, a PPI group has been set up for the purposes of the research programme, consisting of 8 service users. This group has been advising on various aspects of the trial design, and has helped produce trial information for participants. The group is chaired by the PPI co-ordinator. The group will also be involved in publicising the trial and disseminating results and will help design the qualitative interview schedule for the qualitative sub-study.

22 MONITORING REQUIREMENT FOR THE TRIAL

A trial-specific monitoring plan will be established for the trial based on the risk assessment. The trial will be monitored with the agreed plan, in line with the Sponsor's SOPs.

Consistency of trial and treatment protocol delivery across study sites will be achieved through regular contact between the study team and the clinical teams.

23 FINANCE

The trial is funded by the NIHR Programme Grants for Applied Research funding stream for 5 years from the start of the trial.

24 INSURANCE

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in an NHS organisation or an organisation contracted to the NHS, the NHS organisation or an organisation contracted to the NHS continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the NHS organisation or an organisation contracted to the NHS's duty of care, or any negligence on the part of NHS organisation employees. This applies whether the NHS organisation is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

NHS organisation selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees.

25 PUBLICATION POLICY

All proposed publications will be discussed with Sponsor prior to publishing other than those presented at scientific forums/meetings. Please refer to UCL publication policy.

26 STATEMENT OF COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the UK Regulations, EU GCP and the applicable regulatory requirement(s).

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Appendix: Investigational Medicinal Products (IMPs) and Summary of Product Characteristics (SMPCs)

ROT= Date of revision of text of SMPC

	Name	Common formulations	SMPC to be used to determine expectedness
1	AMISULPRIDE	Tablets (Solian®) Oral Solution (Solian®)	AMISULPRIDE Tablets (Solian) SMPC ROT 25 June 2019
2	ARIPIPRAZOLE	Tablet (Abilify®) Orodispersible tablet (Abilify®) Oral solution (Abilify®) Injection (Abilify®) Injection, powder for reconstitution (Abilify Maintena®)	ARIPIPRAZOLE Tablet (Abilify®) SMPC ROT 01 September 2020
3	BENPERIDOL	Tablet (Anquil®)	BENPERIDOL Tablet (Anquil®) SMPC ROT 28 May 2015
4	CHLORPROMAZINE HYDROCHLORIDE	Oral solution (25mg/ml only) Oral syrup 100/5ml Injection (Largactil®) Tablet (Chloractil®)	CHLORPROMAZINE HYDROCHLORIDE Tablet (Chloractil®) SMPC ROT 28 July 2020
5	CLOZAPINE	Tablet - Clozaril® Denzapine®, Zaponex® Suspension (Denzapine®)	CLOZAPINE Tablet - Clozaril® (25 and 100mg) SMPC ROT 16 August 2019
6	FLUPENTIXOL	Tablet - Fluanxol® Tablet - Depixol®	FLUPENTIXOL Tablet - Fluanxol® SMPC ROT 13 May 2014
7	FLUPENTIXOL DECANOATE	Injection - Depixol Inj 20mg and Depixol Concentrated inj.® 100mg/ml Injection - Depixol Low Volume® 200mg/ml	FLUPENTIXOL DECANOATE Injection - Depixol Inj 20mg and Depixol Concentrated inj.® 100mg/ml SMPC ROT 28 February 2017
8	FLUPHENAZINE DECANOATE	Modecate concentrate 100mg/ml injection Modecate 25mg/ml injection	FLUPENTIXOL DECANOATE - Injection (Modecate®) SMPC ROT 06 January 2014
9	HALOPERIDOL	Oral liquid (Haldol®) Injection Oral liquid (Dozic®) Injection, oily (Haldol Decanoate®) Tablet Capsule (Serenace®)	HALOPERIDOL Tablet 5mg SMPC ROT 22 November 2017
10	LEVOMEPROMAZINE	Tablet (Nozinan®) Injection (Nozinan®)	LEVOMEPROMAZINE Tablet (Nozinan®) SMPC ROT 25 February 2015

11	LURASIDONE HYDROCHLORIDE	Tablet (Latuda®)	LURASIDONE HYDROCHLORIDE Tablet (Latuda®) SMPC ROT 23 July 2020
12	OLANZAPINE	Tablet (Zalasta®)	OLANZAPINE Tablet (Zalasta®) SMPC ROT 01 October 2014
		Tablet (Zyprexa®)	
		Tablet (Olanzapine Accord)	
		Orodispersible tablet (Zyprexa Velotab	
13	OLANZAPINE EMBONATE	Injection, powder for reconstitution (ZypAdhera®)	OLANZAPINE EMBONATE Injection, powder for reconstitution (ZypAdhera®) SMPC ROT 23 February 2017
14	PALIPERIDONE	Tablet (Invega®)	PALIPERIDONE Tablet (Invega®) SMPC ROT 13 September 2018
		Injection (Xeplion®)	
15	PERICYAZINE	Tablet	PERICYAZINE Tablet SMPC ROT 25 June 2015
		Syrup	
16	PERPHENAZINE	Tablet (Fentazin®)	PERPHENAZINE Tablet (Fentazin®) SMPC ROT 21 March 2014
17	PIMOZIDE	Tablet (Orap®)	PIMOZIDE Tablet (Orap®) SMPC ROT 01 July 2016
18	PROCHLORPERAZINE	Tablet (Stemetil®)	PROCHLORPERAZINE Tablet (Stemetil®) SMPC ROT 10 February 2016
		Buccal tablet (Buccastem M®)	
		Oral solution (Stemetil®)	
		Injection (Stemetil®)	
19	PROMAZINE HYDROCHLORIDE	Oral solution	PROMAZINE HYDROCHLORIDE Tablet 25mg SMPC ROT 14 July 2015
		Tablet 25mg	
20	QUETIAPINE	Film-Coated Tablet (Seroquel®)	QUETIAPINE Film-Coated Tablet (Seroquel®) SMPC ROT 20 April 2018
		Modified release tablet (Seroquel® XL)	
		Modified release tablet (Tenprolide® XL)	
21	RISPERIDONE	Tablet (Risperdal®)	RISPERIDONE Tablet (Risperdal®) SMPC ROT 24 September 2018
		Orodispersible tablet (Risperdal Quicklet®)	
		Liquid (Risperdal®)	
		Injection, powder for reconstitution (Risperdal Consta®)	
22	SULPIRIDE	Tablet (Dolmatil®)	SULPIRIDE Tablet (Dolmatil®) SMPC ROT 07 September 2018
		Oral solution (Sulpor®)	
23	TRIFLUOPERAZINE	Tablets (Stelazine®)	TRIFLUOPERAZINE Tablets (Stelazine®) SMPC ROT 3 September 2012
		Oral solution	
24	ZUCLOPENTHIXOL	Tablet (Clopixol®)	ZUCLOPENTHIXOL Tablet (Clopixol®) SMPC

			ROT 12 May 2015
25	ZUCLOPENTHIXOL DECANOATE	Injection, oily (Clopixol®, Clopixol Conc.®)	ZUCLOPENTHIXOL DECANOATE Injection, oily (Clopixol®, Clopixol Conc.®) SMPC ROT 22 October 2015
26	MELPERONE	Film coated tablets (Buronil)	MELPERONE HYDROCHLORIDE (Buronil) 14 March 2018

In instances where the name of the drug that the patient is taking is known but the formulation is unknown, the SPC relating to the name of the IMP will be used to determine expectedness.