TRIAL PROTOCOL

ADEPP

Antidepressant for the prevention of DEPression following first episode Psychosis trial

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

Version Number: 11.0

Version Date: 7th December 2022

Protocol Amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version	Type of amendment	Summary of amendment
1	22-Jan-2021	5.0	Substantial amendment	Updated section 6.2.5 to include further details regarding emergency unblinding Updated section 7.2 to include details regarding reversible MAOIs Updated section 8.4. Updated 11.4.1 to include further clarification regarding self-evident corrections
2	18-May-2021	6.0	Substantial amendment	Rewording in section 7.2 Updated section 7.5.IMP is to be sent from manufacturer to sites Updated section 7.6 IMP will be sent to manufacturer for destruction
3	20-Oct-2021	7.0	Substantial amendment	Clarifying the RSI (section 9.5.2) Amending blood sample details (section 8.4) Changing eligibility period from 3 to 6 months
4	11-May-2022	8.0	Substantial amendment	Changing upper eligibility age limit from 35 to 65 years Changing eligibility period from 6 to 12 months Updates to section 5, 6, 7, 8, 9 for clarity.
5	22-Jun-2022	9.0	Non-Substantial amendment	Clarification that eligibility can be confirmed by medically qualified doctor with appropriate expertise Correction of typographical errors Update IMP vendor due to company name and address change Minor clarification in section 7.6.2

6	12-Oct-2022	10.0	Substantial amendment	Removal of vital sign, specific physical health assessment and routine blood monitoring at baseline. Clarifiaction that blood assessment at one month only required if possible. Update to approach process to allow research team to be involved in first approach to patients. Change to DMC member's organisation. Update to TMG. Clarification of eligbiltiy criterion Removal of unnecessary AE check at 12 months. Update to section 7.6.2 and 8.2.1 for clarity Update to section 14.1
7	09-Dec-2022	11.0	Non-Substantial amendment	Minor clarification to section 5.

Funding and Support in Kind	
Funder	**Financial and non-financial support given:**
National Institute for Health Research (NIHR)	£2,087,138.33
Funding Scheme	HTA Mental Health Themed Call
Funder's reference number	NIHR127700
The Funder of the trial has had no role in the trial design, data collection, data analysis or data interpretation This project is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (project reference 127700). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.	

CI Signature Page

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.

I agree to ensure that the 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 trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

This protocol has been approved by:

Trial Name:	ADEPP
Protocol Version Number: Protocol Version Date: Chief Investigator Name: Signature and date:	11.0 07/12/2022 Professor Rachel Upthegrove _____ __ __ / __ __ / __ __ __ __

Sponsor	
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Sponsor statement:

By signing the IRAS form for this trial, University of Birmingham, acting as Sponsor of this trial, confirms approval of this protocol.

Compliance statement:

This protocol describes the ADEPP trial only. The protocol should not be used as a guide for the treatment of participants not taking part in the ADEPP trial.

The trial will be conducted in compliance with the approved protocol, UK Policy Framework for Health and Social Care Research 2017, the Data Protection Act 2018, and the principles of Good Clinical Practice as defined by the European Good Clinical Practice (GCP) Directive and laid down in UK law by the Medicines for Human Use (Clinical Trials) Regulations (2004) and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

PI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol.

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.

This protocol has been approved by:

Trial Name:	ADEPP
Protocol Version Number: Protocol Version Date:	Version: 11.0 07/12/2022
PI Name:	
Name of Site:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

Reference Numbers	
EudraCT number	2020-002787-32
Sponsor number	RG_19-172
ISRCTN reference number	12682719
IRAS reference number	279574

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Trial website	www.birmingham.ac.uk/ADEPP

ABBREVIATIONS

Abbreviation	Term
ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
AR	Adverse Reaction
ANNSERS-e	Antipsychotic Non-Neurological Side Effects Rating Scale -extended
BARS	Barnes Akathisia Rating Scale
BCTU	Birmingham Clinical Trials Unit
CBT	Cognitive Behavioural Therapy
CBTp	Cognitive Behavioural Therapy for psychosis
CDSS	Calgary Depression Scale for Schizophrenia
CRN	Clinical Research Network
CTIMP	Clinical Trial of Investigational Medicinal Product
CV	Curriculum Vitae
DCF	Data Clarification Form
DMC	Data Monitoring Committee
EIP	Early Intervention in Psychosis service(s)
ECG	Electrocardiogram
EU	European Union
FEP	First Episode Psychosis
FROGS	Functional Remission Of General Schizophrenia
GAD7	Generalised Anxiety Disorder Assessment
GCP	Good Clinical Practice
GP	General Practitioner
HBRC	Human Biomaterials Resource Centre
HTA	Health Technology Assessment
ICECAP-A	ICEpop CAPability measure for Adults
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IT	Information Technology
HRA	Health Research Authority
MAOI	Monoamine oxidase inhibitors
MHRA	Medicines and Healthcare products Regulatory Agency
MINI	Mini International Neuropsychiatric Interview
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PANSS	Positive and Negative Syndrome Scale
PI	Principal Investigator
PIS	Participant Information Sheet
QALY	Quality-Adjusted Life Year
QIDS-SR	Quick Inventory of Depression Symptomatology (Self Report)
QTc	Corrected QT interval

REC	Research Ethics Committee
RGT	University of Birmingham Research Governance team
SBQ-R	Suicidal Behaviour Questionnaire-Revised
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SAS	Simpson-Angus Scale
SmPC	Summary of Product Characteristics
SOFAS	Social and Occupational Functional Assessment Scale
SSRI	Selective Serotonin Reuptake Inhibitor
STAI	State/train anxiety Inventory
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UK	United Kingdom
UoB	University of Birmingham

DEFINITIONS

Term	Description
Investigator	A suitably qualified person who appears on the delegation log
Depressive episode	An episode of moderate or severe depression as defined by International Classification of Disease - version 10 (ICD-10) and confirmed by standardised structural interview using the MINI-International Neuropsychiatric Interview

TRIAL SUMMARY

Title

Antidepressant for the prevention of DEPression following first episode Psychosis trial (ADEPP)

Objectives

To establish the effectiveness and cost-effectiveness of an antidepressant medication (sertraline) for the prevention of a depressive episode following first episode psychosis (FEP).

Trial Design

Multi-centre randomised, double-blind, placebo controlled trial with an internal pilot study.

Participant Population and Sample Size

452 participants will be recruited from Early Intervention in Psychosis services (EIP) in England and Wales within 12 months of FEP treatment onset.

Setting

NHS Early Intervention in Psychosis Services (EIP) in England and Wales.

Inclusion Criteria

- Diagnosis of first episode psychosis (FEP)
- Within 12 months of initial treatment for FEP (as defined by onset of care provision by an Early Intervention Team)
- Positive and Negative Syndrome Scale (PANSS) individual positive item scores all ≤4
- Sufficiently recovered from acute psychotic episode with capacity to consent
- Male and females aged 18-65 years
- Currently prescribed antipsychotic medication at a stable dose
- Female participants must be willing to use one form of highly effective contraception

Exclusion Criteria

- Current moderate or severe depression as indicated by a Calgary Depression for Schizophrenia Scale (CDSS) score >7
- Currently prescribed antidepressant medication (or within 2 weeks of stopping if previously prescribed a monoamine oxidase inhibitor)
- Previous history of mania
- Contraindications to SSRI antidepressant treatment: e.g. recurrent thrombotic illness, previous adverse reaction, confirmed pregnancy or planning to become pregnant (although risk in pregnancy is low), prescribed pimozide. (See sertraline SmPC)
- Serious medical or neurological illness (as identified by a medically qualified doctor)
- Hypersensitivity to the active substance or any of the excipients or placebo
- Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs)
- Patient with any other systemic dysfunction (e.g. gastrointestinal, renal, respiratory, cardiovascular, neurological or psychiatric) or significant disorder which, in the opinion of the investigator would jeopardize the safety of the patient by taking part in the trial
- Electrocardiogram (ECG): QTc interval >450 ms recorded in the last 12 months
- Aged below 18 years
- Aged over 65 years
- Female participants that do not agree to follow the protocol contraception requirements

Interventions

Sertraline 50mg vs placebo once a day for 6 months in addition to usual treatment (antipsychotic medication).

Primary outcome measure

The primary outcome will be the number of new cases of depression as indicated by a CDSS score >5 and confirmed by MINI diagnostic interview in each treatment arm over the 6-month intervention phase.

Secondary outcome measures

- Positive and Negative Syndrome Scale (PANSS)
- Suicidal Behaviours Questionnaire-Revised (SBQ-R)
- State-Trait Anxiety Inventory (STAI)
- Generalised Anxiety Disorder Assessment (GAD-7)
- Relapse of psychosis as defined by a hospital admission or acute community care provided by a Home Treatment/Crisis Intervention team
- Functioning: Functional Remission of General Schizophrenia (FROGS) and Social and Occupational Functioning Assessment Scale (SOFAS)
- Quality of life: EQ-5D-5L and ICEpop CAPability measure for Adults (ICECAP-A)
- Quick Inventory of Depression Scale (Self Rating) (QIDS-SR)
- Side effect measures: Barnes Akathisia Rating Scale (BARS), Antipsychotic Non-Neurological Side Effects Rating Scale-extended (ANNSERS-e) and Simpson-Angus Scale (SAS)
- Adverse Events
- Healthcare Resource Usage (Client Service Receipt Inventory – CSRI)

Trial Schema

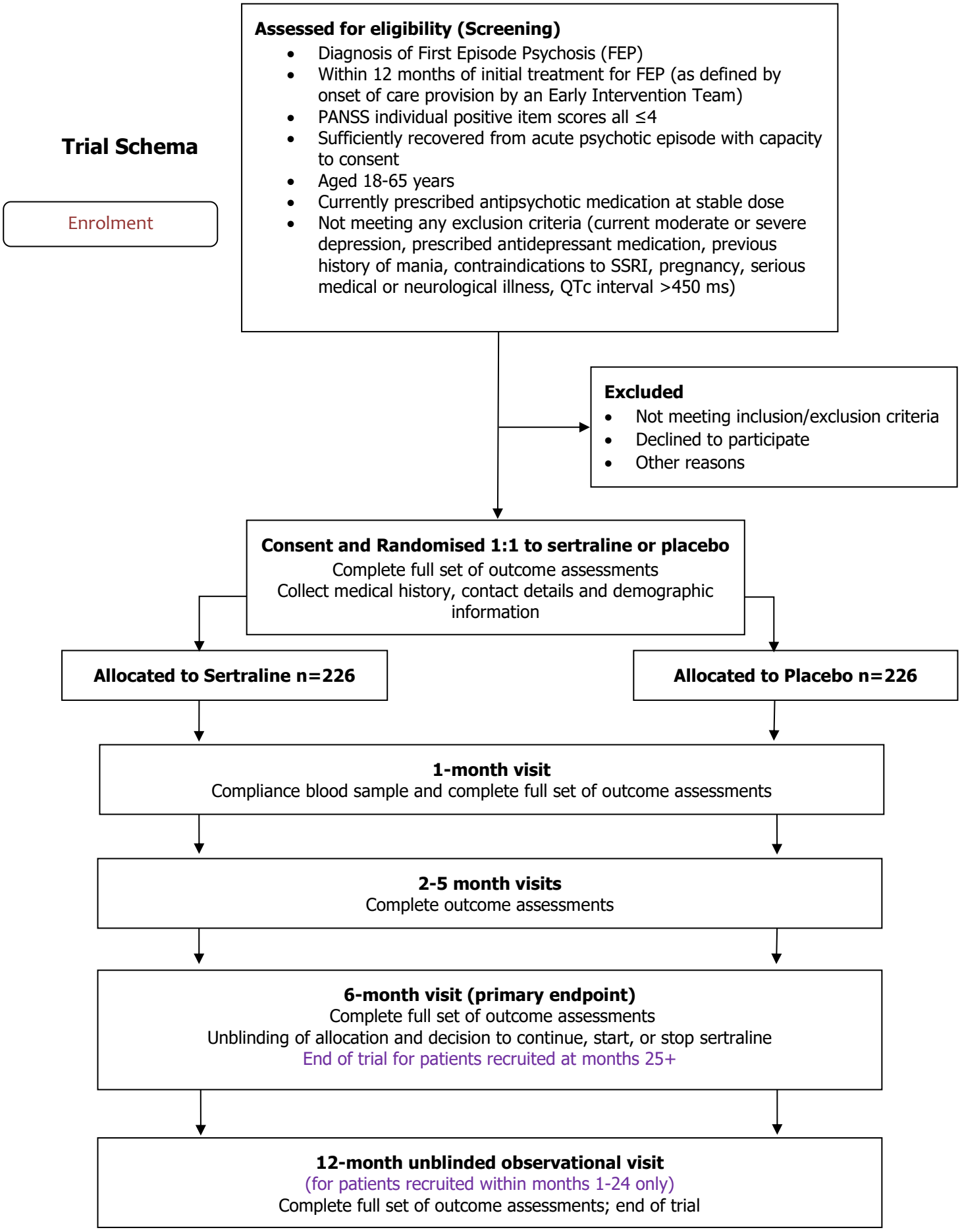


TABLE OF CONTENTS

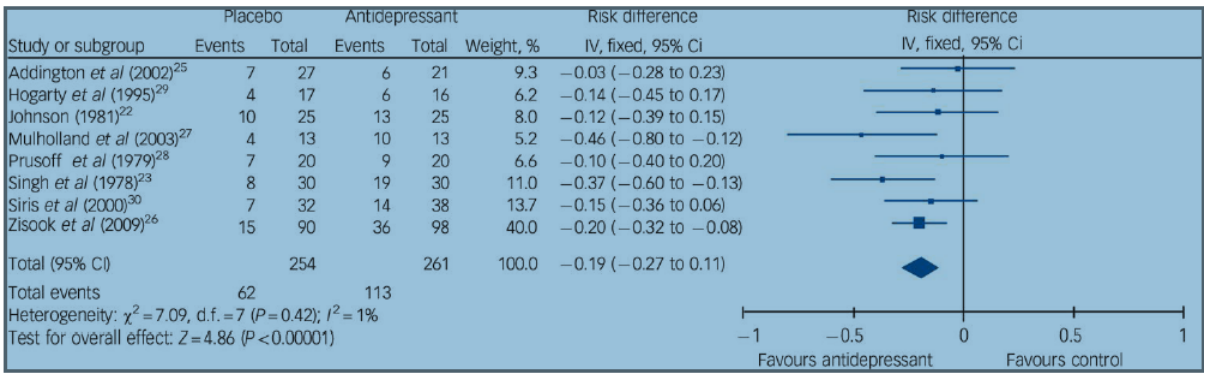
1. BACKGROUND AND RATIONALE

1.1 Background

Psychotic disorders including schizophrenia are highly disabling conditions that begin in adolescence or early adulthood and affect around 3% of the population at a cost to the UK economy of more than £11 billion per year [1]. Around 40% of young people experience a moderate or severe depressive episode in the six months following treatment of first-episode psychosis (FEP) [2, 3], and this is linked to poor outcomes with a high personal and economic burden. Depression after FEP is the most significant risk factor for suicidal behaviour and completed suicide; 35 out of every 100 patients with FEP will attempt suicide, and completed suicide is most common in these early years of illness [2, 4, 5]. We have recently shown that depression after FEP has a long-term impact on the likelihood of suicidal behaviour, lasting up to 7 years [6]. Depression after FEP also has adverse consequences for social and occupational recovery, quality of life and risk of relapse [7-9]. Only a minority of patients who experience FEP will achieve full recovery, with up to 70% of people having poor occupational and social functioning even with existing, intensive intervention [8, 10-12]. Our recent systematic review and meta-analysis, which included 7 longitudinal studies [13-19], with a mean follow-up of 3 years, demonstrated the clear and significant association of depression after FEP with poor functional outcome and reduced quality of life [20].

Furthermore a number of studies have found that depression and anxiety tend to increase before the onset of a psychotic relapse, suggesting that affective dysfunction, rather than being seen and treated as a co-morbidity, may be more causally related to psychosis [21]. Thus, whilst depression after FEP may be similar to non-psychotic depression, the complex psychosis related aetiological processes mean that specific evidence for its prevention is needed. However, there is good indication that antidepressants may be effective in the prevention of depression following FEP. Our 2017 systematic review and meta-analysis of antidepressant medication to treat an established depressive episode in schizophrenia identified 15 studies reporting the effect of antidepressant medication; 8 studies investigated selective serotonin reuptake inhibitors (SSRIs), with the majority of all studies showing effectiveness with an overall number needed to treat of 5 [23]. See figure 1.

Figure 1. Forest plot of response (recovery from depression) to antidepressant medication in schizophrenia [23]



Prevention of depression using antidepressant medication is an established strategy in other branches of medicine for groups at equally high risk of depression. Evidence exists for the

use of low dose antidepressant medication to reduce the incidence of depression post stroke [24], after cardiovascular event [25, 26], with liver disease [27], in post-partum women [28] and after traumatic brain injury [29]. SSRIs are the most frequently studied medication in these groups, with a reduction in incidence of depression ranging from 20 to 50% [25-29].

In summary, given the high rate of depression following FEP and the short and medium term impact of this depression on suicide risk, poor outcomes and functioning, we argue that *preventing* this by using a prophylactic antidepressant is a strategy that clinicians and patients would consider adopting if the evidence base was available. While there is evidence that this clinical strategy is effective in other serious (physical) disorders, we do not know the effectiveness of this intervention after FEP. ADEPP will address this question. Given the costs involved for people with psychosis, and to the NHS and society, if this low cost pharmacological prevention strategy proves to be effective, it is likely also to be a cost-effective intervention.

1.2 Trial Rationale

1.2.1 Justification for participant population

The introduction of Early Intervention in Psychosis services (EIP) prompted a major change in the treatment of psychotic illnesses, as highlighted by the Five Year Forward View [30].

Current treatments for FEP delivered in EIP result in high levels of remission from positive symptoms, such as hallucinations and delusions, yet the level of occupational and social recovery remains low, suggesting that current treatments that target positive symptoms alone are not sufficient to improve outcome [9, 31].

There is substantial meta-analytic evidence that antidepressants are well-tolerated in psychosis when prescribed in combination with continuing antipsychotic medication. In addition to our meta-analysis of the use of antidepressants to treat depression in schizophrenia [23], Helfer et al reviewed the co-prescribing of antidepressants with antipsychotic medications for any clinical indication in 3068 participants with schizophrenia [36] and both reviews showed an overall beneficial effect with a low risk of adverse effects.

In summary, the evidence base upon which young people can make a choice about treatments in FEP remains limited, despite a large increase in investment and NHS services to assertively treat this crucial stage of illness. Whilst evidence exists for the use of antidepressants to treat depression in schizophrenia, and for the prevention of depression in other groups at high risk, no studies have specifically focused on preventing depression after FEP, despite this being the period of very high rates of depression associated with significant poor outcomes including suicidal behaviour, relapse and impaired quality of life.

1.2.2 Justification for design

A new therapy or intervention should generally be tested against an established effective therapy or a placebo control. This trial involves combining two established treatments (antipsychotic medication and antidepressant medication) to test if this is an effective treatment targeted at reducing depression after FEP, and if so what additional benefits this may bring in terms of functional outcome and risk of relapse during the study and 6 months

after the intervention has stopped. ADEPP plans to use a placebo in a scientifically and methodologically sound way to establish efficacy and safety of the active intervention in this population.

1.2.3 Choice of intervention

The SSRI sertraline 50mg is a commonly used antidepressant and the standard dose for men and women age >18 years. Sertraline has clear evidence of efficacy in the treatment of moderate depression [38], and in the prevention of depression in other conditions [24]. It has a better safety profile in combination with antipsychotic medication compared to other effective SSRIs such as citalopram [39]. There is some evidence that in chronic depression women respond more favourably than men to sertraline [40]. FEP occurs more often in men (around 1.4 times higher) [41] and thus our stratification procedures will adjust for gender.

1.2.4 Safety

While there is robust evidence of tolerability and safety for a combination of antidepressant and antipsychotic medications [36, 42], there is the potential for such a combination to lead to prolongation of the QTc interval, measured on electrocardiogram (ECG). This risk is primarily associated with older patients on high doses of citalopram [39]. This knowledge has informed our choice of sertraline, rather than citalopram.

2. AIMS AND OBJECTIVES

The main objective is to establish if, compared with placebo, the addition of sertraline to continuing antipsychotic medication following FEP reduces the likelihood of developing depression over a 6 month intervention period. We will also investigate whether this intervention reduces the likelihood of developing anxiety or suicidal behaviour, reduces the risk of psychotic relapse, and improves the level of functional recovery achieved.

We will additionally gather evidence as to whether the prescription of antidepressant medication after FEP is cost-effective and whether any clinical benefit and cost-effectiveness continue beyond the 6 month intervention, up to a year.

2.1. Internal Pilot Stage of Study Objectives

- Accrual of 138 participants in 12 months
- Percentage of eligible patients that are recruited
- Percentage of first 50 randomised participants with usable data
- Percentage of participants not withdrawn or lost to follow up
- Adherence to trial medication based on self-report and pill count

See section 8.1 for further details of these objectives which will determine continuation of the trial beyond the pilot stage.

2.2. Main Trial Objectives

2.2.1. Clinical Aims and Objectives

To establish the effectiveness of an antidepressant medication (sertraline) for the prevention of a depressive episode following FEP and whether any clinical benefit continues beyond the 6-month intervention, up to a year.

2.2.2. Economic Aims and Objectives

To establish the cost-effectiveness of the prescription of antidepressant medication after FEP and whether any cost-effectiveness continues beyond the 6-month intervention, up to a year.

3. TRIAL DESIGN AND SETTING

3.1. Trial Design

Multi-centre randomised, double-blind, placebo-controlled trial of sertraline 50 mg once a day for 6 months. Following the 6-month primary outcome assessment, all participants and their research team will be unblinded and treatment as usual continues. Those participants recruited within the first 24 months of recruitment will undergo an additional 12-month follow-up visit (unblinded and observational). We include an internal pilot with clear stop-go criteria focussing on recruitment, completeness of the assessment data and retention.

3.2. Trial Setting

EIP are community-based multidisciplinary teams that manage all patients with FEP in England and Wales. Patients with FEP are required to be assessed and taken on by EIP within 2 weeks of presentation. In England and Wales around 26,000 young people will be treated for FEP within EIP, with an estimated 8,668 new cases each year [37]. We will recruit from large EIP including those in the West Midlands, North West England and in South Wales. As well as the larger hubs that will be led by the co-applicants we will identify a number of smaller sites; this will make our recruitment more feasible and results more generalizable.

3.3. Identification of participants

EIP team referrals are highly monitored by NHS England as part of the Access and Waiting Time Standards, thus our initial inclusion criteria (diagnosis of FEP and within 12 months of treatment onset) will be straightforward to pre-screen from electronic (or paper, where this is unavailable) EIP team caseload information including research registers: the clinical team and/or research nurses/assistants will do this. Screening of potential participants for detailed inclusion/exclusion criteria will then be conducted by the site PI, research nurses/assistants/clinical study officers and/or the EIP team (including nurses, psychiatrists and psychologists), who will identify potential participants. A medically qualified doctor with

appropriate expertise will confirm inclusion/exclusion criteria, capacity and eligibility of the potential participants.

3.3.1. Participant Identification Centres

At some sites, participants will be recruited via participant identification centres (PICs) and referred to the main randomising centre.

3.4. Sub-studies

Blood samples (9ml) will be taken at 4 weeks for analysis to check concordance with trial medication. These blood samples will not be analysed until the trial intervention is complete for all participants to remove the risk of unblinding. If the participant consents to it, additional research blood samples (18ml) will be taken and stored at the same time to be included at a later date in genomic and biomarker studies (see section 8.4 for further details).

3.5. Assessment of Risk

All clinical trials can be considered to involve an element of risk and in accordance with BCTU standard operating procedures this trial has been risk assessed, to clarify any risks relating uniquely to this trial. A risk assessment has concluded that this trial corresponds to the following categorisation: Type A in accordance with a risk-adapted approach to Clinical Trials of Investigational Medicinal Products (CTIMPs).

- Type A = No higher than the risk of standard medical care
- Type B = Somewhat higher than the risk of standard medical care
- Type C = Markedly higher than the risk of standard medical care

4. ELIGIBILITY

4.1. Inclusion Criteria

- Diagnosis of first-episode psychosis (FEP)
- Within 12 months of initial treatment for FEP (as defined by onset of care provision by an Early Intervention Team)
- Positive and Negative Syndrome Scale (PANSS) individual positive item scores all ≤4
- Sufficiently recovered from acute psychotic episode with capacity to consent
- Males and females aged 18-65 years
- Currently prescribed antipsychotic medication at a stable dose
- Female participants must be willing to use one form of highly effective contraception

4.2. Exclusion Criteria

- Current moderate or severe depression as indicated by a Calgary Depression for Schizophrenia Scale (CDSS) score >7
- Currently prescribed antidepressant medication (or within 2 weeks of stopping if previously prescribed a monoamine oxidase inhibitor)
- Previous history of mania
- Contraindications to SSRI antidepressant treatment: e.g. recurrent thrombotic illness, previous adverse reaction, confirmed pregnancy or planning to become pregnant (although risk in pregnancy is low), prescribed pimozide. (see sertraline SmPC)
- Serious medical or neurological illness (as identified by a medically qualified doctor)
- Hypersensitivity to the active substance or any of the excipients or placebo
- Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs)
- Patient with any systemic dysfunction (e.g. gastrointestinal, renal, respiratory, cardiovascular, neurological or psychiatric) or significant disorder which, in the opinion of the investigator would jeopardize the safety of the patient by taking part in the trial
- Electrocardiogram (ECG): QTc interval >450 ms recorded in the last 12 months
- Aged under 18 years
- Aged over 65 years
- Female participants that do not agree to follow the protocol contraception requirements

4.3. Co-enrolment

Participants in ADEPP cannot join other CTIMPs. They may be recruited to non-interventional trials such as observational or qualitative studies.

5. CONSENT

It will be the responsibility of the Principal Investigator (PI) or delegate to obtain informed consent for each participant prior to performing any trial related procedure. Any delegation of this duty will be captured on the **Site Delegation Log**.

All eligible patients will be approached about the trial by EIP team members which includes members of the research team. Participating sites are research active trusts with research embedded as part of their clinical care. Patients would therefore expect to be contacted about research studies they would be eligible for.

Potential participants will be approached and informed of the trial by telephone call or at a routine clinical visit. They will be informed that their participation is voluntary and choosing not to participate will not affect their care.

The research team will arrange for a visit for any further questions about the trial to be answered or to be consented into the trial. There is a two stage information provision and consent process: (1) screening assessments and (2) the main trial. To facilitate this there are separate screening and main trials PISs and Informed Consent Forms (ICFs). PIs or delegate(s) will ensure that they adequately explain the aim, trial intervention, anticipated

benefits and potential hazards of taking part in the trial to the participant. They will be given a copy of the Screening Patient Information Sheet (PIS) and sufficient time to consider the trial, and discuss with friends and family.

If the participant expresses an interest in participating in the trial they will be asked to return for a screening visit, where they will be asked to sign and date the latest version of the Screening ICF before any trial screening assessments are carried out. The participant will be asked for explicit consent for the regulatory authorities, members of the research team and/or representatives of the Sponsor to be given direct access to the participant's medical records.

The PI or delegate(s) will then sign and date the ICF. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes, and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial, the participant's trial number will be entered on the ICF. In addition, if the participant has given explicit consent, a copy of the signed ICF will be sent to the Birmingham Clinical Trials Unit (BCTU) trials team for review.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant, version number of ICF signed and date consent received. Where consent is obtained on the same day that trial related assessments start, a note should be made in the medical notes of the time the consent was obtained and what time the assessments started.

Following screening assessments if the patient is eligible for the trial they will be provided with the main trial PIS. If they wish to continue into the trial then they will sign and date the latest version of the main trial ICF.

The same process, as outlined above, should be followed for both screening and main trial consent.

At each visit the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial the participant will have the opportunity to ask questions about it. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF will be available from the Trial Office and will be printed or photocopied onto the headed paper of the local institution. Anonymised details of all participants approached about the trial will be recorded on the ADEPP **Participant Screening Log**.

We will request consent for access to mental health NHS records and GP contact for health service usage data to complete our health economics analysis.

We will also request optional consent to allow linkage to patient data available in NHS routine clinical datasets, including primary care data (e.g. Clinical Practice Research

Datalink, The Health Improvement Network, QResearch) and secondary care data (Hospital Episode Statistics) through NHS Digital and other central UK NHS bodies. The participant will consent to the Trial Office sending their name, address, date of birth and NHS number to the relevant national registry and then for the national registry to link this to their data and send the information back to the Trial Office. The consent will also allow access to other new central UK NHS databases that will appear in the future. This will allow us (subject to receipt of additional funding via another grant application) to assess longer-term impact and health service usage data without needing further contact with the trial participants.

5.1. Covid-19 and trial process resilience

Visits throughout the informed consent process will take place in person at the clinic or participant's home, or by telephone or video call as per local practice where patient and/or public health circumstances dictate. Signed informed consent forms will be on paper, completed in person or by post if the circumstances dictate. However, if a suitable secure electronic consent system is introduced by BCTU in future then this will be considered as an alternative for remote consent.

6. ENROLMENT AND RANDOMISATION

6.1. Enrolment and Screening

Pre-screening of potential participants will be conducted by the clinical team and/or research nurses/assistants for EIP patients. A medically qualified doctor with appropriate expertise will confirm capacity and eligibility. Patients will be asked to consent to screening for the trial.

Potential participants will complete screening with CDSS, the full PANSS and a pregnancy test if female of childbearing potential (fertile, following menarche and until becoming post-menopausal unless permanently sterile). Pregnancy test must be negative within 7 days before eligibility is confirmed and treatment initiation.

If they meet all the eligibility criteria and confirm they are still willing to take part in the study, they will be asked to formally consent to participate in the trial and randomisation. After consent, the full baseline battery of questionnaires and CRFs will be completed and they will be randomised into the trial.

Participants will be free to withdraw from either the intervention and/or follow-up assessments at any time should they wish to do so.

6.2. Randomisation

6.2.1. Randomisation Methodology

Participants will be individually randomised on a 1:1 basis between sertraline and placebo via a secure online randomisation system based at Birmingham Clinical Trials Unit (BCTU).

A minimisation algorithm will ensure that the predetermined stratification variables are balanced between trial arms. A minimisation algorithm will be used within the randomisation system to ensure equal distribution of the most commonly prescribed antipsychotics in this population (olanzapine, risperidone, aripiprazole and quetiapine), and gender.

Allocation concealment will be ensured via remote allocation of trial codes. The trial medication will be blinded (encapsulated sertraline 50mg or placebo to match) with all clinical team members blind to allocation. Participants, care-providers and researchers will also be blinded to the treatment allocation.

A 'random element' will be included in the minimisation algorithm, so that each participant has a probability (unspecified here), of being randomised to the opposite treatment that they would have otherwise received.

Full details of the randomisation specification will be stored in a confidential document at BCTU.

6.2.2. Allocation Concealment

Allocation concealment will be ensured via remote allocation of trial codes.

6.2.3. Blinding

This is a double-blind trial.

6.2.4. Blinded Personnel

The trial medication (thus the allocation) will be blinded (encapsulated sertraline 50mg or identical placebo capsules) to all clinical team members. Participants, care-providers and researchers will also be blind to the treatment allocation.

6.2.5. Unblinding

Participants and their clinical teams will be unblinded at the primary endpoint (at 6 months), if a depressive episode is identified (primary objective) before the primary end point, or if a reported event indicates that either treatment withdrawal or prescription of antidepressant medication is necessary.

At the primary endpoint (at 6 months) investigators (with the unblinding role on the delegation log) will be able to unblind participants at their site using the ADEPP database. **NOTE: the 6 month assessments must be completed prior to the research team and participant being unblinded.**

If emergency unblinding is required this can be done by all investigators involved in patient care either using the ADEPP database which is available 24/7 or by contacting the Trial Office Monday to Friday, 9:00 to 16:00 UK time, except for bank holidays and University of Birmingham (UoB) closed days. All investigators responsible for patient care will be delegated the duty for conducting emergency unblinding on the delegation log. The reason for unblinding and person requesting this will be recorded on the database and an email will be sent confirming that unblinding has occurred. Full details are given in the ADEPP unblinding instructions.

6.2.6. Randomisation Process

After participant eligibility has been confirmed and informed consent has been received, the participant can be randomised into the trial. Randomisation Notepad will be provided to investigators to collate the necessary information for minimisation prior to randomisation. All questions and data items on the Randomisation Notepad must be answered before randomisation can be completed and a Trial Number given. If data items are missing, randomisation will be suspended, but can be resumed once the information is available.

Randomisation will be provided by a secure online randomisation system at Birmingham Clinical Trials Unit (BCTU) (available at https://trials.bham.ac.uk/adepp). Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants as detailed on the Site Signature and Delegation Log. These unique log-in details must not be shared with other staff and in no circumstances should staff access the randomisation process using another person's login details. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance.

6.2.7. Randomisation Records

Following randomisation, a confirmatory email will be sent to the local PI, person carrying out the randomisation, pharmacist, and the Trial Office.

PIs will be provided with the ADEPP **Participant Recruitment and Identification Log** which will be used to record the participants with their allocated trial number. The PI must maintain this document, which is **not** for submission to the Trial Office. The PI will also keep and maintain the ADEPP **Participant Screening Log**. Both of these documents will be kept in the ISF. The ADEPP **Participant Screening Log** should be available to be sent to the Trial Office upon request. The ADEPP **Participant Recruitment and Identification Log** and ADEPP **Participant Screening Log** should be held in strict confidence.

6.3. Informing Other Parties

The participants' Early Intervention Care-Coordinator and Consultant Psychiatrist will be informed they are in the trial (using medical records for EIP staff), and if the patient agrees their GP will also be notified using the ADEPP **GP Letter.**

7. TRIAL TREATMENT / INTERVENTION

7.1. Intervention and Schedule

Sertraline is a serotonin reuptake inhibitor (SSRI). Participants in the trial will be randomised to receive 50mg of sertraline, or placebo, once a day for 6 months. Sertraline 50mg is the standard dose for men and women >18 years of age.

7.2. Drug Interaction or Contraindications

The intervention will be given in addition to stable antipsychotic medication. Usual practice of dose change or change in antipsychotic medication during the intervention will be documented. The combination of an SSRI and antipsychotic medication has the potential for an additional side effect burden. Sertraline has common side effects of drowsiness, dizziness, nausea, constipation and sexual dysfunction that will be monitored (see schedule of assessments: ANNSERS-e).

Sertraline is contra-indicated in patients with a known hypersensitivity to sertraline or to any of the excipients.

Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serotonin syndrome with symptoms such as agitation, tremor and hyperthermia. Sertraline must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI.

Concomitant treatment with reversible MAOIs (moclobemide and linezolid) is contraindicated due to the risk of serotonin syndrome. Sertraline must not be intitatied for at least 7 days after discontinuation of treatment with a reversible MAOI.

Sertraline must be discontinued for at least 7 days before starting treatment with an irreversible or reversible MAOI.

There is insufficient clinical experience in patients with significant hepatic dysfunction and accordingly sertraline should not be used in such patients.

Concomitant use in patients taking pimozide is contra-indicated.

Investigators must follow the local SmPC guidance for all interactions with other medicinal products and other forms of interaction.

Please see section 10 for details regarding pregnancy.

7.3. Treatment Modification

Any change to the allocated intervention dose or frequency of medication is not permitted.

7.4. Cessation of Treatment

If an episode of depression is identified (as defined by a CDSS score >5 and confirmed by the MINI diagnostic interview), this will be recorded as an event and the intervention will be discontinued and unblinded to allow the appropriate treatment. If the participant indicates their ongoing willingness to continue in the trial they will continue to be followed up as per protocol and an intention to treat analysis. Should a participant experience an adverse event (AE) as determined by the local PI or CI that needs unblinding, the intervention will be withdrawn and unblinded. This may include a new episode of mania, a serious episode of suicidal behaviour or relapse of psychotic illness. As above, the participant will be asked to remain in the trial for follow up.

On withdrawing from the intervention or trial, or completing the trial, participants will be asked to return any unused trial medication to the site.

7.5. Treatment Supply and Storage

The IMP manufacturer is Eramol (UK) Ltd who will source and re-encapsulate the sertraline 50mg and manufacture the matched placebo:

Eramol (UK) Ltd, Unit 9 North Downs Business Park, Sevenoaks, Kent, TN13 2TL, United Kingdom The authorised sertraline 50mg tablets will be sourced from appropriate Marketing Authorisation holders within the UK/EEA or equivalent. Eramol (UK) Ltd will source the authorised sertraline tablets in accordance with EU GDP, the CTA and the Wholesale Dealer's Authorisation held by Eramol (UK) Ltd.

7.5.1. Treatment Supplies

Eramol (UK) Ltd will supply the IMP directly to the site in treatment packs coded by treatment pack numbers supplied by BCTU. Treatment packs will be shipped to sites from Eramol (UK) Ltd when a request is received from BCTU. If the IMP needs to be recalled the Eramol (UK) Ltd recall procedure will be followed, and the IMP subsequently destroyed (see Section 7.6: Accountablity and Compliance Procedures).

7.5.2. Packaging and Labelling

Eramol (UK) Ltd will package and label the IMP.

7.5.3. Drug Storage

There are no special considerations needed for storage of sertraline which can be stored at ambient temperatures. The IMP will be delivered to and stored in the local site pharmacy department.

7.5.4. Covid-19 and trial process resilience

Delivery and receipt processes between site and participant may vary locally as participant and/or public health circumstances dictate. If face to face trial visits are not possible, it is envisaged that IMP will be distributed to participants by a research assistant visit, a member of the clinical team if face to face contact is planned as part of routine care, or courier. Local NHS site dispensing policies should be followed.

7.6. Accountability and Compliance Procedures

7.6.1. Compliance

Adherence to trial medication will be assessed using 3 methods:

a) Self-report at weeks 4 and 24
b) Blood levels of sertraline at 4 weeks
c) Monitoring of prescription usage (pill counting, pharmacy dispensing records, returned medication)

7.6.2. Accountability

The PI is responsible for ensuring that staff handling the IMP at site are appropriately trained and understand how to respond in the event of a deviation in line with trust policy and ADEPP IMP guidelines. Training will be provided by the Trial Office. Accountability logs will be provided for each participant.

IMP tracking

- IMP will be managed using a web-based system.
- This system will track treatment pack numbers sent to site. The treatment pack number list will be provided by BCTU and packed accordingly by Eramol (UK) Ltd.
- Upon delivery of IMP, the site pharmacy must access the web based system to confirm receipt; the treatment packs will not be available for allocation until this step is completed.
- The system will track the number of treatment packs at site and their expiry dates to ensure there are always sufficient treatment packs at site (providing there is sufficient stock held by the supplier).
- Re-ordering IMP for expired or allocated IMP to site will be triggered automatically by the system.
- The system will email sites twice before a treatment pack is due to expire. The system will prevent treatment packs due to expire being available for allocation.

IMP allocation

- At each randomisation, the site research team will access the system to reveal a treatment pack number to match the participant's randomised treatment.
- Email notification will automatically be sent to the local NHS pharmacy with details of the treatment pack.
- This notification must be printed out, checked against the treatment pack selected and signed by the pharmacy. The treatment pack will be recorded as allocated on the system.

IMP accountability

- The research team will collect the IMP pack for the previous month from the participant at each monthly visit and return it to pharmacy. If the participant has disposed of the pack then the research team should inform pharmacy so this can be documented on the accountability log.

IMP destruction

- If IMP needs to be destroyed, for example because it has expired, it must be returned to Eramol (UK) Ltd. Upon receipt of the IMP, Eramol (UK) Ltd will inform the Trial Office and the Trial Office will confirm IMP is unavailable on the system.
- The manufacturer will complete the trial destruction log.
- Once completed a copy of the trial destruction log will be returned to the Trial Office.

8. OUTCOME MEASURES AND STUDY PROCEDURES

Following consent for screening, participants will complete the screening assessments as described in section 6.1 (the CDSS and full PANSS, and a urine pregnancy test if female of childbearing potential).

All assessment visits will be carried out in person at the clinic or participant's home, or by telephone or video calls as per local practice where participant and/or public health circumstances dictate.

Baseline visit

- Following confirmation of eligibility and consent for randomisation, the following assessments/procedures will be performed:
- participant's contact details,
- medical history
- current medications
- demographic information
- The full baseline battery of assessments will also be completed. These include ANNSERS-e, BARS, CSRI, EQ5D-5L, FROGS, GAD7, ICECAP-A, QIDS-SR, SAS, SBQ-R, STAI, and SOFAS.

Participants will then be randomised as described in section 6.2.

A prescription will be provided to the site research pharmacy and medication dispensed to the participant at the baseline visit and monthly thereafter for a further 5 months. Participants and clinical teams will be given contact information for the research team to address any questions and to inform participants what to do in case of emergency regarding unblinding of the trial medication.

All follow up visits will be conducted either at home or in outpatient clinics, tied in with routine appointments as much as possible. Participants will be followed up once every month for 6 months from randomisation (and once at 12 months, if applicable). AE and SAE should be monitored throughout the AE reporting period and reported as per section 9.

Month 1 follow-up visit

- participants will be asked questions about compliance.
- The full battery of assessments that were completed at screening and baseline will be repeated. These include ANNSERS-e, BARS, CDSS, CSRI, EQ5D-5L, FROGS, GAD7, ICECAP-A, full PANSS, QIDS-SR, SAS, SBQ-R, STAI, and SOFAS. The MINI will need to be completed if the CDSS score is >5.
- If possible a blood sample will be taken for concordance monitoring and routine blood tests. Routine blood results will be reviewed for any relevant abnormality by the PI or delegate. If already performed within the previous month a repeat routine blood test isn't required and these should be reviewed for any relevant abnormality by the PI or delegate. Procedures for handling the blood sample will be detailed in the ADEPP laboratory manual.
- Vital signs (pulse, blood pressure and temperature) will also be recorded during this visit.

Month 2-5 follow-up visits

- CDSS, PANSS Positive subscale and GAD7 will be completed. The MINI will need to be completed if the CDSS score is >5.

Month 6 follow-up visit

- data on health service usage and compliance will be collected from participants and from health records.
- The full battery of assessments that were completed at screening and baseline will be repeated. These include ANNSERS-e, BARS, CDSS, CSRI, EQ5D-5L, FROGS, GAD7, ICECAP-A, full PANSS, QIDS-SR, SAS, SBQ-R, STAI, and SOFAS. The MINI will be completed if the CDSS score is >5.
- the intervention will be unblinded to allow the participants and their care team to decide whether to continue or start sertraline. **NOTE: the 6 month assessments must be completed prior to the research team and participant being unblinded.**
- Vital signs (pulse, blood pressure and temperature) will also be recorded during this visit.

For participants recruited within the first 24 months of the recruitment period, they will be followed up once at 12 months from randomisation. For participants recruited after 24 months of the recruitment period, this will be the end of the trial.

Month 12 follow-up visit

- data on health service usage will be collected from participants and health records.
- The full battery of assessments that were completed at screening and baseline will be repeated. These include ANNSERS-e, BARS, CDSS, CSRI, EQ5D-5L, FROGS, GAD7, ICECAP-A, full PANSS, QIDS-SR, SAS, SBQ-R, STAI, and SOFAS. The MINI will be completed if the CDSS score is >5.

The purpose is to chart the sustainability of any clinical benefit from sertraline. This will be the end of the trial for these participants.

We will also assess the acceptability of the intervention by the number of participants who received active intervention who request to stay on medication, and any clinical deterioration beyond the trial intervention period, assessed at 12-month outcome measures.

8.1. Internal Pilot Study Outcomes

We will have clear stop/go criteria assessed after 12 months of recruitment.

We will employ a traffic light system (**Green**, **Amber**, **Red**). Specifically, our internal pilot will report:

1. Recruitment: Recruitment will be reviewed after 12 months of recruitment, where we aim to have recruited 27% of the total sample size (n=138). **Green**: 25% or more, **Amber**: 15-25%, **Red**: <15%.
2. Percentage of eligible patients that are recruited: The denominator is the number of eligible patients invited into the study and the numerator is the number of those successfully recruited. **Green**: 50% or more of eligible participants approached agree to participate; **Amber**: between 25% and 50% and **Red:** less than 25%.

3. Percentage of first 50 randomised participants with usable data: This data will be collected 6 months after baseline. For the primary outcome measure CDSS this will be **Green**: 90% or more, **Amber**: 70-90% **Red**: <70%. For other secondary outcome measures: **Green**: 75% or more, **Amber**: 60-75% **Red:** < 60%.
4. Retention: those participants that have not withdrawn or are not lost to follow up or have an event that requires un-blinding: **Green** 80% or more, **Amber** 60-80% **Red**: 60% or less.
5. Adherence: (based on self-report and pill count) **Green:** 70% or more showing good adherence; **Amber:** between 40%-70%; **Red**: less than 40%). Note our final sertraline check on stored serum will be completed at the end of the study once final un-blinding is possible. Good adherence will be defined by >70% adherence on self-report, following our previous experience in BeneMin [56] and other trials in schizophrenia.

The success of the internal pilot will be determined by having all 5 criteria at green or amber. Any amber or red ratings will be discussed with the Trial Steering Committee (TSC) and funder and adjustments made and recommendations taken, including not proceeding with the trial if it is considered that there are irreconcilable red ratings.

8.2. Main Trial Outcomes

8.2.1. Primary Outcome

The primary outcome will be the number of new cases of depression, as indicated by a CDSS score of greater than 5 and confirmed by MINI diagnostic interview in each treatment arm, from the point of randomisation over the 6 month intervention phase.

8.2.2. Secondary Outcomes

8.2.2.1. Clinical

Positive and Negative Syndrome Scale (PANSS). PANSS is the established 30-item, semi-structured interview for assessment of the presence and change in symptoms of psychosis. In addition to a total score, subscale scores for positive, negative and general symptoms can be derived [57].

Suicidal Behaviours Questionnaire-Revised (SBQ-R): The SBQ-R is a 4-item validated tool to assess the presence of suicidal ideation and attempts in lifetime ever and preceding 12 months, together with current suicidal ideation and beliefs about future risk. It has established linear total and cut-off scores to identify those with and without the reported risk [46].

Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR) is a widely used brief general depression measure that will be rated alongside the CDSS, to allow comparison in secondary analysis with depression prevention trials in other disorders [55].

State-Trait Anxiety Inventory (STAI): The STAI is a commonly used 20 item self-report scale for the assessment of trait and current (state) anxiety [47].

General Anxiety Disorder (GAD7): a brief 7 item anxiety scale specifically assessing generalised anxiety [43].

Relapse of psychosis: as defined by a hospital admission or acute community care provided by a Home Treatment/Crisis Intervention team.

Functioning: Given the complexity of factors that may impact on functioning in emerging psychosis, the Social and Occupational Functioning Scale (SOFAS) [44] and the Functional Remission of General Schizophrenia (FROGS) [45] will both be rated.

CDSS: the number of new cases of depression beyond the intervention period, as indicated by a CDSS score >5 and confirmed by MINI diagnostic interview at 12 months, will be recorded.

Quality of life: EQ-5D-5L and ICECAP-A: EQ-5D-5L is a 5 item health related quality of life assessment scale with well-established reliability and population norms [48] and the Investigating Choice Experiments Capability Measure for Adults (ICECAP-A) is a measure of capability wellbeing, used to supplement economic evaluation where the benefits of healthcare interventions may relate to the patient's wellbeing more broadly defined [49].

In addition we include a number of side effect measures routinely used for patients on antipsychotic medication: Barnes Akathisia Rating Scale (BARS) [58], Antipsychotic Non-Neurological Side Effects Rating Scale-extended (ANNSERS-e) [59] which includes side effects of SSRI antidepressant medication, and Simpson-Angus Scale (SAS) [60].

8.3. Schedule of Assessments

Table 1. Schedule of assessments

	Visit					
	Screening	*Baseline*	*Month 1 ±7 days*	*Months 2-5 ±7 days*	*Month 6 ±7 days*	*Month 12 ±7 days*[1]
Eligibility check	*x*					
Pregnancy test	*x*					
Valid informed consent		*x*				
Relevant medical history		*x*			*x*	*x*
Concomitant medication		*x*			*x*	*x*
Randomisation		*x*				

[1] Month 12 visits only for participants recruited within the first 24 months of recruitment.

Blood sample for routine assessment			*x*			
Vital signs			*x*		*x*	
CDSS	*x*		*x*	*x*	*x*	*x*
MINI (if CDSS is >5)			*x*	*x*	*x*	*x*
GAD7		*x*	*x*	*x*	*x*	*x*
PANSS – Full scale	*x*		*x*		*x*	*x*
PANSS – Positive sub-scale				*x*		
QIDS-SR		*x*	*x*		*x*	*x*
STAI		*x*	*x*		*x*	*x*
SBQ-R		*x*	*x*		*x*	*x*
BARS		*x*	*x*		*x*	*x*
SAS		*x*	*x*		*x*	*x*
ANNSERS-e		*x*	*x*		*x*	*x*
SOFAS and FROGS		*x*	*x*		*x*	*x*
ICECAP-A		*x*	*x*		*x*	*x*
EQ-5D-5L		*x*	*x*		*x*	*x*
Resource use/CSRI		*x*			*x*	*x*
Dispensing of IMP		*x*	*x*	*x*		
Compliance self-report			*x*		*x*	
Compliance bloods			*x*			
Optional sub-study bloods			*x*			
Adverse event check		*x*	*x*	*x*	*x*	

8.4. Blood Samples

Full details of sample processing are described in the separate trial laboratory manual. It is the responsibility of the PI to maintain the **Research Sample Log** recording samples collected, stored, and sent. The Trial Office may request this log during the trial.

At 4 weeks, 1 x 9ml EDTA tube of blood will be taken to measure concordance. If the participant consents to it, additional research blood samples (1 x 9ml EDTA tube and 1 x 9ml BD tube) will be taken at the same time for future genomic analysis and biomarker studies.

The concordance blood samples will be sent directly to the trial research laboratory at UoB by overnight post at room temperature to arrive, be processed (centrifuged for 15 minutes and plasma pipetted off into 6 aliquots) and frozen in a -80°C freezer within 48 hours. They will then be stored at the trial research laboratory until they are analysed. Concordance blood samples will not be analysed until the trial intervention is complete for all participants to remove the risk of unblinding.

The **additional research blood samples** will be sent directly to the trial research laboratory at UoB to arrive by overnight post at room temperature. The BD tube will be processed and frozen in a -80°C freezer within 48 hours of being taken. The EDTA tube will be processed as peripheral blood mononuclear cells and then frozen in a -80°C or lower freezer within 48 hours of being taken. They will then be stored at the Human Biomaterials Resource Centre at UoB. Both samples will be stored until they are:

- Transferred on dry ice to the University of Cardiff for DNA extraction and genomic analysis; or
- Stored for future studies which will be funded and ethically approved separately from the ADEPP trial.

8.5. Participant Withdrawal and Changes of Status Within Trial

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation.

Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the trial at any time. A participant who withdraws from the trial does so completely (i.e. from trial treatment and all data collection). A participant who wishes to cease to participate *in a particular aspect of the trial*, will be considered as having changed their status within the trial.

The changes in status within the trial are categorised in the following ways:

- No trial intervention: The participant would no longer like to receive the trial intervention, but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis)
- No trial-related follow-up: The participant would no longer like to receive the trial intervention AND does not wish to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and if

applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes)

- No further data collection: The participant would no longer like to receive the trial intervention AND is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e. only data collected prior to the withdrawal can be used in the trial analysis)

The details of either withdrawal or change of status within trial (date, reason and category of status change) should be clearly documented in the source documents. Patients subsequently found to be ineligible will still have their data analysed.

9. ADVERSE EVENT REPORTING

9.1. Definitions

Table 2. Definitions for Adverse Events

Term	Abbreviation	Definition
Adverse Event	AE	Any untoward medical occurrence in a participant or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. This will include relapse of psychotic illness, new episode of mania, serious episode of self-harm, use of home treatment, inpatient psychiatric admission.
Adverse Reaction	AR	All untoward and unintended responses to an IMP related to any dose administered.
Serious Adverse Event	SAE	Any untoward medical occurrence or effect that: • Results in death • Is life-threatening[2] • Requires (medical) hospitalisation • Results in persistent or significant disability or incapacity • Is a congenital anomaly/birth defect

[2] The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.
[3] Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definitions above.

		• Or is otherwise considered medically significant by the Investigator[3]
Serious Adverse Reaction	SAR	An Adverse Reaction which also meets the definition of a Serious Adverse Event
Unexpected Adverse Reaction	UAR	An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or Summary of Product Characteristics for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction	SUSAR	A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.

9.2. Adverse Event Recording General Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care (2017), the Principles of GCP as set out in the UK Statutory Instrument (2004/1031 and subsequent amendments), the requirements of the Health Research Authority (HRA), and the Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments thereof.

Definitions of different types of AEs are listed in the table of definitions in section 9.1.

It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and also causality (relatedness to the intervention) in accordance with the protocol.

9.3.Adverse Event Reporting Requirements in ADEPP

The reporting period for AEs in ADEPP will be from the day of consent until 30 days after the last dose of trial treatment.

All medical occurrences which meet the definition of an AE during the reporting period should be reported on the AE log, with the exception of depressive episodes identified by CDSS score at scheduled trial visits, and returned to the Trial Office. This includes abnormal laboratory findings.

9.4. Serious Adverse Advent (SAE) Reporting in ADEPP

For all SAEs the PI (or any suitably qualified person on the delegation log) will do one of the following:

1. **Record safety reporting exempt SAEs** in the medical notes but **not report** them to the Trial Office as per section 9.4.1 below
2. **Report SAEs in a non-expedited manner**. This can only be done for the pre-defined subset of SAEs as per section 9.4.2 below
3. **Report all SAEs not covered by the above 2 categories in an expedited manner** (within 24 hours of the site research team becoming aware of the event) to the trial office as per section 9.5 below

Note: when an SAE occurs at the same hospital at which the participant is receiving trial treatment or is being followed up for trial purposes, processes must be in place to *make the research team at the hospital aware of any SAEs*, regardless which department first becomes aware of the event, *in an expedited manner*.

9.4.1. Serious Adverse Events not requiring reporting to BCTU

The following are not considered to be critical to evaluations of the safety of the trial:

1. Pre-planned hospitalisation

2. General hospital attendance lasting less than 24 hours, unrelated to a mental health event

All events which meet the definition of serious must be recorded in the participant notes, including the causality and severity, but for trial purposes these events do not require reporting. Such events are "safety reporting exempt".

9.4.2. Serious Adverse Events requiring non-expedited reporting to BCTU

Where the safety profile is well established, the causal relationship between either the intervention or the participant's underlying condition and the SAE may be known. That is, such events are protocol-defined as "expected" (see Section 9.5.2). Such events should still be recorded in the participant's notes and reported to BCTU on a trial specific SAE form within 4 weeks of becoming aware of the event. These events do not require expedited reporting since the assessment of expectedness for the specified events has been pre-defined. These include the following:

- Attendance at A&E for a mental health related reason
- Referral to mental health crisis team
- Referral to liaison psychiatry

9.4.3. Serious Adverse Events requiring expedited reporting to BCTU

All SAEs not listed in Sections 9.4.1. and 9.4.2 must be reported to BCTU on a trial specific SAE form within 24 hours of the site research team becoming aware of the event.

9.5. SAE Reporting process

On becoming aware that a participant has had an SAE which requires reporting on an SAE form, the PI (or any suitably qualified person on the delegation log) should report the SAE to their own Trust in accordance with local practice and to the Trial Office as per the requirements of sections 9.4.2 and 9.4.3 above.

To report an SAE to the Trial Office, the PI or delegate(s) must complete, date and sign the trial specific SAE Form. The completed form together with any other relevant, appropriately anonymised data should be scanned and emailed to the Trial Office at the address below:

To report an SAE:

Scan and email the SAE Form to: ADEPP@trials.bham.ac.uk

Where an SAE Form has been initially completed by someone other than the PI, the original SAE form should later be countersigned by the PI to confirm agreement with the causality and severity assessments.

On receipt of an SAE form, the Trial Office will allocate each SAE a unique reference number and return this via email to the site as proof of receipt. The site and the Trial Office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the ISF.

If the site has not received confirmation of receipt of the SAE from the BCTU or if the SAE has not been assigned a unique SAE identification number within 1 working day, the site should contact the Trial Office.

9.5.1. Assessment of causality of an SAE

When completing the SAE form, the PI (or, throughout this section 9.5.1, a medically qualified delegate) will be asked to define the causality (relatedness to the intervention) and the severity of the AE.

The PI must assess causality on case-by-case basis as per Table 3 overleaf. To define the causality the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which do not contribute to the event.

Table 3. Causality of SAEs

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
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 participant's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

On receipt of an SAE Form the Trial Office will forward it, with the unique reference number, to the Chief Investigator (CI) (or, throughout this section 9.5.1, their delegate) who will independently review the causality of the SAE. An SAE judged by the PI or CI to have a reasonable causal relationship with the intervention ("Related" as per Table 3) will be regarded as a serious adverse reaction (SAR). The causality assessment given by the PI will not be downgraded by the CI. If the CI disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting both opinions will be provided with the report.

9.5.2. Assessment of Expectedness of an SAE by the CI

The CI or their delegate will also assess all related SAEs for expectedness with reference to the criteria in Table 4 below.

Table 4. Expectedness of AEs

Category	Definition
Expected	An AE that is consistent with known information about the trial related procedures, psychosis, or that is clearly defined in the reference safety information (section 4.8 of the Summary of Product Characteristics for sertraline most recently submitted and approved by MHRA).
Unexpected	An AE that is not consistent with known information about the trial related procedures or clearly defined in the relevant safety information.

The CI or their delegate will not overrule the severity or causality assessment given by the site Investigator but may add additional comment on these. If an SAR is unexpected, it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

The CI or their delegate will undertake review of all SAEs and may request further information from the clinical team at site for any given event(s) to assist in this.

9.5.3. Provision of SAE follow-up information

Following reporting of an SAE, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the BCTU trials team. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, a final version of the SAE form completed at site must be returned to the Trial Office and a copy kept in the ISF.

9.6. Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) may review any SAEs.

BCTU will report details of all SARs (including SUSARs) to the MHRA, Research Ethics Committee (REC), and UoB Research Governance Team (RGT) annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).

Additionally, BCTU will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the MHRA, REC and RGT within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as non-life threatening SUSARs will be reported within 15 days.

The main REC and RGT will be notified immediately if a significant safety issue is identified during the course of the trial.

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to PIs. A copy of any such correspondence should be filed in the ISF and TMF.

9.7. Urgent Safety Measures

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

10. PREGNANCY MONITORING

Female potential participants of childbearing potential will be screened with a urine pregnancy test which must be negative within 7 days before eligibility is confirmed and treatment initiation.

Any participants that become pregnant between the start of protocol-defined treatment until 30 days after the last dose will be recorded on a notification of pregnancy form, and followed up to outcome of the pregnancy as per the applicable BCTU Standard Operating Procedure. The participant's GP will be notified that the participant is pregnant and taking

part in the ADEPP trial, and therefore potentially taking sertraline. However, there are no special interventions for patients taking sertraline in pregnancy.

Female participants of childbearing potential will be requested to use highly effective contraception throughout screening, whilst on trial treatment and 7 days after trial treatment is ceased.

At present there is no known risk to participant's partners of child bearing potential. They will not be asked to use contraception or have their pregnancies monitored.

11. DATA HANDLING AND RECORD KEEPING

11.1. Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

Table 5. Source data in ADEPP

Data	***Source***
Participant Reported Outcomes and Research Measures	*The original CRF is the source and will be sent to the Trial Office, whilst copies will be kept with the ISF.*
Lab results	*The original lab report (which may be electronic) is the source and will be kept and maintained in line with normal local practice. Information will be transcribed onto CRFs.*
Clinical event data	*The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g. phone calls), must be documented in the source documents. Information will be transcribed onto CRFs. Original CRFs will be sent to the Trial Office, whilst copies will be kept with the ISF.*
Health Economics data	*Often obtained by interview directly with the participant or from electronic or paper participant records for transcription onto the CRF. The CRF is source data in the first case; the participant records in the second.*

Recruitment	*The original record of the randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system.*
Drop out	*Where a participant expresses a wish to withdraw, the conversation must be recorded in the electronic or paper participant records.*
Electrocardiogram (ECG)	*The ECG recording will be automatically generated by the ECG machine and the output will be used as the source and will be kept and maintained in line with normal local practice.*

11.2. Case Report Form (CRF) Completion

ADEPP will use paper CRFs with data entry by the Trial Office.

The ADEPP **Site Signature & Delegation Log** will identify all those personnel with responsibilities for data collection.

The delegated staff completing the CRF should ensure the accuracy, completeness and timeliness of the data reported. This will be evidenced by signing and dating the CRF. In all cases it remains the responsibility of the PI to ensure that the CRF has been completed correctly and that the data are accurate.

Original completed CRFs or true copies should be sent to the Trial Office with copies filed in the ISF. Entries should be made in dark ink and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Only CRFs provided by the Trial Office should be used.

The CRFs will include (but will NOT be limited to) the following Forms *(Table 6):*

Table 6. Data collection forms in ADEPP

Form Name	***Schedule for submission***
Consent and Randomisation CRF	*At the point of randomisation*
Baseline and follow-up CRFs including participant reported outcome measures	*As soon as possible after each follow-up assessment time point*
Serious Adverse Event CRF	*If expedited: Emailed within 24 hours of site research team becoming aware of event*

	If non-expedited: emailed within 4 weeks of site research team becoming aware of event
Pregnancy notification CRF	*As soon as possible after becoming aware of a participant's pregnancy*
Change of status CRF	*As soon as possible after the point of withdrawal or death*

Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to ADEPP working instructions.

The following guidance applies to data and partial data:

- Time format and unknown times – all times should be in accordance with the 24hr clock
- Rounding conventions – rounding should be in the normal way: If the number you are rounding is followed by 5, 6, 7, 8, or 9, round the number up. **Example**: 3.8 rounded to the nearest whole number is 4. If the number you are rounding is followed by 1, 2, 3 or 4, round the number down. **Example**: 3.4 rounded to the nearest whole number is 3
- Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied
- Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible
- Missing/incomplete data – should be clearly indicated – all blank fields unaccounted for will be queried by the trial office
- Repeat laboratory tests – the data used to inform clinical decisions should always be supplied. If a test is repeated it is either to confirm or clarify a previous reading. Confirmatory tests should use the original test values. Protocol and GCP non-compliances should be reported to the Trial Office on discovery.

11.3. Participant completed Questionnaires

The STAI, GAD-7, EQ-5D-5L, SBQ-R, ICECAP-A and QIDS-SR are participant reported and will be completed with research nurses or assistants overseeing completion and providing support if necessary. Checks for missing data will be done before the participant leaves the visit by the research nurse or assistant reviewing the questionnaire for completeness.

11.4. Data Management

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan. Coding and

validation will be agreed between the trial manager, statistician and programmer, and the trial database will be signed off once the implementation of these has been assured.

Data entry will be completed by the Trial Office via a bespoke BCTU trial database. The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries will be raised using data clarification forms (DCFs) via the trial database, with the expectation that these queries will be completed by the site within 30 days of receipt. Overdue data entry and data queries will be requested on a monthly basis.

11.4.1. Self-evident corrections

The below self-evident corrections will be permitted by the Trial Office:

Contingent fields: When a response to a question determines, to a degree, the response required by a second question, then conflicts in the responses can be resolved by the data entry clerk. E.g. Has the person had procedure "x"? If yes, state type. If the response to the first question is "no", yet the type of procedure is stated, it is self-evidently true that the initial response was incorrect.

Changes to administrative notes and reference numbers: when new information becomes available such that a reference number does not accurately reflect the sequence of CRFs received e.g. an SAE form is received for an incident which occurred prior to an already reported incident, then it is appropriate to change the reference number provided no DCFs have been raised using the original number. Similarly, any notes relating to the patient care which have an impact on the administration process, but not the data fields themselves, can be changed as appropriate.

11.5. Data Security

The security of the System is governed by the policies of UoB. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at UoB have to be registered with the Data Protection Officer and data held in accordance with the Data Protection Act (2018) and subsequent amendments. UoB will designate a Data Protection Officer upon registration of the study. The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The System incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
- Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate storage of non-identifiable data etc.
- Network security measures: including site firewalls, antivirus software, separate secure network protected hosting etc.
- System Management: the System will be developed by the BCTU Programming Team and will be implemented and maintained by the BCTU Programming Team.

- System Design: the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- Operational Processes: the data will be processed and stored within the Trial Office.
- System Audit: The System will benefit from the following internal/external audit arrangements:
    - Internal audit of the system
    - Periodic IT risk assessments
- Data Protection Registration: The University's Data Protection Registration number is Z6195856.

11.6. Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, ISFs, Pharmacy Files, participants' hospital notes, CRFs etc.) at their site are securely retained for at least 25 years. Archiving will be authorised by BCTU on behalf of UoB following submission of the end of trial report. No documents should be destroyed without prior approval from the BCTU director or their delegate.

The TMF will be stored at BCTU under controlled conditions for at least 3 years after the end of the study. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored for at least 25 years. BCTU has standard processes for both hard copy and computer database legacy archiving.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Site Set-up and Initiation

All PIs will be asked to sign the necessary agreements including a **Site Signature and Delegation Log** between the PI and BCTU/Sponsor, and supply a current CV (signed) and GCP certificate to BCTU. All site staff who are performing trial specific tasks are required to sign the **Site Signature and Delegation Log**, which details which tasks have been delegated to them by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a meeting or a teleconference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF and a pharmacy file containing essential documentation, instructions, and other documentation required for the conduct of the trial. The BCTU trials team must be informed of any change in the site research team.

12.2. Monitoring

The monitoring requirements for this trial have been developed following trial specific risk assessment by BCTU and are documented in the monitoring plan.

12.3. Onsite Monitoring

For this trial we will monitor all sites in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the Trial Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of participant withdrawals or deviations (also defined in the monitoring plan). PIs and site research teams will allow the ADEPP trial staff access to source documents as requested. The monitoring will be conducted by BCTU/UoB staff.

12.4. Central Monitoring

The Trial Office will check incoming ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the Data Management Plan. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

Sites will be requested to send in copies of signed ICFs and other documentation for central review for all participants providing explicit consent for this. This will be detailed in the monitoring plan.

12.5. Audit and Inspection

PIs will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. PIs will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections or local audits.

12.6. Notification of Serious Breaches

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified may be reported to the TSC, DMC and the REC. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA.

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the Sponsor is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a "serious breach" is a breach which is likely to affect;

- the safety or physical or mental integrity of the subjects of the trial
- the scientific value of the trial

Sites are therefore requested to notify the Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trial Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

13. END OF TRIAL DEFINITION

The end of trial will be 6 months after the last data capture, including resolution of DCFs. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The Trial Office will notify the REC, MHRA and sponsor within 90 days of the end of trial. Where the trial has terminated early, the Trial Office will notify the MHRA and REC within 15 days of the end of trial. The Trial Office will provide the REC, MHRA and sponsor with a summary of the clinical trial report within 12 months of the end of trial.

14. STATISTICAL CONSIDERATIONS

14.1. Sample Size

To detect a reduction in the rate of depression from 40% to 25% and with power set to 90% and type I error rate of 5% would require 203 participants per arm to be randomised, 406 in total. Assuming and adjusting for a 10% drop-out rate 452 participants will need to be recruited in total.

A reduction in the rate of depression from 40% to 25% represents a risk reduction of just over 35% which although relatively large is average in the risk reductions seen in previous depression prevention trials (20-50%).

14.2. Analysis of Outcome Measures

A separate Statistical Analysis Plan (SAP) will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below. The primary comparison groups will be composed of those randomised to sertraline versus those randomised to placebo. In the first instance, all analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the treatment group to which they were randomised irrespective of compliance or other protocol deviations. For all outcome measures, appropriate summary statistics will be presented by group (e.g. proportions/percentages, mean/standard deviation or median/interquartile range). Intervention effects will be adjusted for the minimisation variables listed in section 6.2.1 where possible. A p-value <0.05 will be considered statistically significant, and there will be no adjustment for multiple testing.

14.2.1. Primary Outcome Measure

The primary outcome analysis will be the proportion of patients in the sertraline arm who become depressed compared with that in the placebo arm over 6 months. To capture all depressive episodes during the trial, if a participant scores 5 or more on the CDSS at any one point during the trial, the MINI will be completed to confirm a diagnosis of a depressive episode. These data will be summarised as a number and percentage in each arm. A log binomial model will be used to compare proportions of depression in each arm at 6 months with adjustment for stratification variables (antipsychotics and gender). Estimates of treatment effects will be shown as adjusted relative risk with 95% confidence intervals. The p-value as well as the 95% confidence interval from the associated model will be used to determine statistical significance. An unadjusted analysis will be done as a check using chi-squared or Fisher's exact test to compare proportions of depression events between arms. P-values will be reported at the 5% level of significance.

14.2.2. Secondary Outcome Measures

For the secondary outcome analysis, those variables that are on a binary scale will be analysed like the primary outcome measure. Those on a continuous scale will be summarised using mean and standard deviations. A linear regression model will be used to compare outcomes between the two arms adjusting for the stratification variables (antipsychotics and gender) in the model. Adjusted mean differences between groups and 95% confidence intervals will be presented.

14.2.3. Planned Subgroup Analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm (see section 6.2.1). Tests for statistical heterogeneity (e.g. by including the treatment group by subgroup interaction parameter in the statistical model) will be performed prior to any examination of effect estimate within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

14.2.4. Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. In brief, this will include multiple imputation methods. Full details will be included in the SAP. Further sensitivity analysis will include a per protocol analysis.

14.3. Planned Interim Analysis

Interim analyses of safety and efficacy for presentation to the DMC will take place during the study. The DMC will meet prior to trial commencement to agree the manner and timing of such analyses but this is likely to include the analysis of the primary and major secondary outcomes and full assessment of safety (SAEs) at least at annual intervals. Criteria for stopping or modifying the trial based on this information will be ratified by the DMC. Details of the agreed plan will be written into the SAP.

14.4. Planned Final Analyses

The primary analysis for the trial will occur once all participants have completed the 6 month assessment and corresponding outcome data has been entered onto the trial database and validated as being ready for analysis. This analysis will include data items up to and including the 6 month and 12 month assessment.

15. ECONOMIC EVALUATION

A separate Health Economic Analysis Plan will be produced and will provide a more comprehensive description of the planned economic analyses. A brief outline of these analyses is given below.

15.1. Trial-based economic evaluation

We will conduct a trial-based economic evaluation from a NHS/personal social services perspective based on the primary outcome for the trial, the cost per case of depression avoided, as well as the cost per Quality-Adjusted Life Year (QALY) gained.

Healthcare resource use will be collected at each follow-up assessment, when patients will be asked to recall visits to health professionals, medications and admissions. This will be recorded on a modified version of the Client Service Receipt Inventory (CSRI) [61], as is common in mental health evaluations. The information provided will be checked by searching patients' electronic patient records. Resource use will be costed using national sources [50-52] (i.e. PSSRU for healthcare contacts [50, 51]).

Health effects of the intervention will be estimated using EQ-5D-5L-based QALY estimates as favoured by NICE for assessing cost-effectiveness [49, 52], collected at baseline, 1, 6 and 12 months. EQ-5D-5L profiles will be scored using the cross-walk algorithm [62] and QALYs will be estimated using the area-under-the-curve method controlling for baseline characteristics [63].

Impacts on capability wellbeing will be assessed using ICECAP-A [49], which can offer additional insight into the quality of life of those with mental health conditions [53]. ICECAP-A data will also be collected at baseline 1, 6 and 12 months. ICECAP-A states will be scored using the UK value set [64] and 'Years of Full Capability' and 'Years of Sufficient Capability' will be estimated in a similar manner to QALYs [65].

Sensitivity analysis will be applied to data parameters and assumptions. Results will be expressed as incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves (CEACs) to represent the probability of the intervention being cost-effective at different willingness to pay thresholds.

15.2. Modelling

Psychosis is associated with long-term impacts on quality of life outcomes and treatment costs [66]. If the trial-based evaluation finds that the intervention improves functional recovery and reduces the likelihood of adverse outcomes including depression, anxiety or psychotic relapse, a model-based economic evaluation will be used to estimate the long-term cost-effectiveness of using sertraline for patients with FEP. Cost-effectiveness will be estimated from a healthcare and wider societal perspective as recommended in recent international guidelines for economic evaluation [67].

Health outcomes (survival and quality of life) will use data collected from the trial and literature on long-term outcomes associated with FEP [68]. Costs in the model will include those for the sertraline and placebo pathways derived from the trial-based analysis and literature-based estimates for long-term outcomes associated with FEP.

The model will have a lifetime horizon for a cohort of patients, with costs and benefits discounted at a rate of 3.5%. The model will be used to estimate long-term impacts of the intervention from a wider societal perspective. We will use the multiplier approach [69] and evidence on the long-term spill over effects of depression [70, 71] to model any carer QALYs, as recommended by NICE [72] for reference case economic evaluations. We will also use available literature to model other inter-sectoral effects on, for example, the criminal justice system, and lost productivity [73]. As with the trial-based analysis, the analysis will be subject to extensive sensitivity analysis, and the results will be presented using ICERs and CEACs.

16. TRIAL ORGANISATIONAL STRUCTURE

16.1. Sponsor

The Sponsor for this trial is University of Birmingham.

16.2. Coordinating Centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit, based at UoB.

16.3. Trial Management Group

The Trial Management Group will take responsibility for the day-to-day management of the trial, and will include (but is not limited to) the CI, Trial Statistician, Trial Manager, Health Economist, and senior BCTU oversight staff. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

16.4. Trial Steering Committee

A TSC will be created for the ADEPP trial and meet via teleconference, or in person, as required depending on the needs of the trial.

Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the TSC will: provide overall oversight of the trial, including the practical aspects of the trial, as well as ensuring that the trial is run in a way which is both safe for the participants and provides appropriate data to the Sponsor and investigators.

16.5. Data Monitoring Committee

Data analyses will be supplied in confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with a trial specific charter. The DMC will meet at least annually as agreed by the Committee and documented in the Charter. More frequent meetings may be required for a specific reason (e.g. safety phase) and will be recorded in minutes.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety. The trial will stop early if the interim analyses shows differences between treatments that are deemed to be convincing to the clinical community.

16.6. Finance

The research costs of the trial are funded by a National Institute for Health Research (NIHR) Health Technology Assessment (HTA), reference NIHR127700, awarded to Professor Rachel Upthegrove at UoB. The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. Additional costs, service support costs and excess treatment costs associated with the trial, e.g. gaining consent, are estimated in the Statement of Activities. These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network.

17. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: *http://www.wma.net/en/30publications/10policies/b3/index.html*).

The trial will be conducted in accordance with the approved protocol, UK Policy Framework for Health and Social Care Research 2017, the Data Protection Act 2018, and the principles of Good Clinical Practice as defined by the European Good Clinical Practice (GCP) Directive and laid down in UK law by the Medicines for Human Use (Clinical Trials) Regulations (2004) and subsequent amendments thereof.

The trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use (Clinical Trials) regulations. The protocol will be submitted to and approved by the REC prior to circulation and the start of the trial. All correspondence with the MHRA and/or REC will be retained in the Trial Master File/ISF, and an annual progress report (APR) will be submitted to the REC within 30 days of the anniversary of the favourable REC opinion annually until the trial is declared ended. A trial-specific risk assessment and monitoring plan will be developed before submission to the REC and will be reviewed regularly during the trial.

Before any participants are enrolled into the trial, the PI at each site is required to obtain local R&D confirmation of capacity and capability. Sites will not be permitted to enrol participants until written confirmation of R&D confirmation of capacity and capability is received by the BCTU trials team.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local confirmation of capacity and capability. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

18. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018.

Participants will always be identified using their unique trial identification number on the Case Report Form and correspondence between the BCTU. Participants will give their explicit consent for the movement of their consent form, giving permission for BCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process.

The PI must maintain documents not for submission to BCTU (e.g. **Participant Recruitment and Identification Log**) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

BCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party. Representatives of the Trial Office and Sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

19. FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests associated with this trial protocol.

20. INSURANCE AND INDEMNITY

UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to UoB for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at UoB's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the participant, responsibility for the care of the participants remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

UoB is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

21. POST-TRIAL CARE

Unblinding will occur after the primary outcome assessment at 6 months. Following discussion with the clinical team the participant will then continue with their usual care in EIP services.

22. PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer-reviewed journal. The manuscript will be prepared by the CI and authorship will be determined by input.

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of UoB and BCTU. Intellectual property rights will be addressed in the Clinical Trial Site Agreement between Sponsor and site.

23. ACCESS TO FINAL DATA SET

Only the TMG will have access to the full trial dataset in order to ensure that the overall results are not disclosed by an individual trial site prior to the main publication. Following publication of the findings, the final trial dataset will be made available to external researchers upon approval from the TMG and the BCTU data sharing committee in line with standard data sharing practices for clinical trial data sets.

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