antidepressants to prevent relapse in depression

PROTOCOL

Full title of trial	A Phase IV double blind multi-site, individually randomised parallel group controlled trial investigating the use of citalopram, sertraline, fluoxetine and mirtazapine in preventing relapse in patients in primary care who are taking long term maintenance antidepressants but now feel well enough to consider stopping medication.
Short title of trial	ANTLER, ANTidepressants to prevent reLapse in dEpRession
Version and date of protocol	Version 1 28-Jan-2016
Sponsor	University College London (UCL)
Sponsor protocol number	14/0647
Funder	NIHR HTA
Trial registration number	2015-004210-26
EudraCT number	ISRCTN15969819
Active IMP(s)	citalopram, sertraline, fluoxetine, mirtazapine
Placebo IMP(s)	Matched placebo tablets
Phase of trial	Phase IV
Sites	Multisite– London UCL, University of Southampton, University of Bristol, Hull York Medical School
Chief Investigator	Glyn Lewis Professor of Psychiatric Epidemiology Division of Psychiatry University College London 149 Tottenham Court Rd London, W1W 7NF Email: glyn.lewis@ucl.ac.uk, Tel: 0207 6799711
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UCL University of Bristol HYMS The Hull York Medical School University of Southampton NHS National Institute for Health Research

SIGNATURES

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

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

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

Chief Investigator: Professor Glyn Lewis

Sign:

Date:

Sponsor Representative: Priment

Sign:

Date:

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

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

VERSION HISTORY

Version number	Version date	Reason for Change
V 2	22 Feb 2016	Response to REC's comments at 10 Feb 2016

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2 LIST OF ABBREVIATIONS

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

QC	Quality Control
QP	Qualified Person for release of trial drug
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Document Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TRG	Trial Review Group
TSC	Trial Steering Committee

3 TRIAL PERSONNEL

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4 SUMMARY

Title:	ANTidepressants to prevent reLapse in dEpRession
Short title:	ANTLER
Trial medication:	citalopram, sertraline, fluoxetine, mirtazapine
Phase of trial:	IV
Objectives:	Primary outcome will be time to depressive relapse. Secondary outcomes will include depressive and anxiety symptoms, adverse effects, quality of life and the resources and costs used.
Type of trial:	Phase IV, double-blind, randomised, parallel group, multi-site trial in people who are taking long term maintenance antidepressants and now feel well enough to consider stopping medication.
Trial design and methods:	The study is a double blind individually randomised parallel group randomised controlled trial. We will recruit individuals who are currently on the four antidepressant medications licensed below but are currently well enough to consider stopping medication. We will carry out an individually randomised parallel group controlled trial that will compare (1) continuing with the following antidepressant medication (citalopram 20mg, sertraline 100mg, fluoxetine 20mg or mirtazapine 30mg) with (2) replacement of the medication with an identical placebo that will include a double blind tapering period of two month. We will follow up participants at 3, 6, 9 and 12 months.
Trial duration per participant:	52 weeks
Estimated total trial duration:	35 months
Planned trial sites:	Multisite, 4 sites including UCL, Bristol, York and Southampton
Total number of participants planned:	479
Main inclusion/exclusion criteria:	Patients being treated for depression. Eligible participants will have had at least two episodes of depression, be aged 18-74 years, be taking antidepressants for 9 months or more and currently taking: citalopram 20mg, sertraline 100mg, fluoxetine 20mg or mirtazapine 30mg. Be well

	enough to consider stopping their antidepressant medication. Participants will be excluded if they: meet internationally agreed (ICD10) criteria for a depressive illness, score above 12 on the depressive symptom questionnaire, PHQ9, have bipolar disorder, psychotic illness, dementia or a terminal illness, are not able to complete self-administered questionnaires in English, have contraindications for any of the prescribed medication.
Statistical methodology and analysis:	The primary outcome will be the time to a depressive relapse. The analysis and reporting will follow CONSORT and EVEREST guidelines. The primary analysis will follow intention to treat principles and will use a Cox constant proportional hazards model, accounting for baseline depressive symptoms.

5 INTRODUCTION

5.1 BACKGROUND

Depression is a common and disabling health problem that leads to considerable disability for the individual and the community. It is the most common reason for claiming of incapacity benefit in the UK. The effective treatment of depression is therefore an important health priority. The mainstay of treatment for depression is with antidepressant medication or psychological treatment, particularly cognitive behavioural treatment. Antidepressants are almost always prescribed in primary care and are more accessible and more often given for depression than psychological treatment and in the 2007 Adult Psychiatric Morbidity Survey, medication was four times more likely to be taken by people with depression than psychological treatment.(1) There were about 53m prescriptions in 2013 in England.(2) Though antidepressants are now relatively cheap, the cost was still £282m in 2013 and there are also costs associated with regular monitoring by the GP. However, the main economic burden of depression results from its impact on work, education, employment and the families and friends of those affected. McCrone(3) has estimated that the cost of lost employment amounted to £5.8bn in England in 2007.

Antidepressants are used both for treating acute episodes of depression but also for preventing relapse once someone has recovered, so called maintenance treatment. The current evidence base reviewed below provides support for short term maintenance treatment (up to 9 months) but there is little evidence for the effectiveness of maintenance treatment in preventing relapse for depression. The trial population will therefore be those who are taking long term maintenance treatment are now well enough to consider stopping their antidepressant. It should be noted that the intervention that is being studied is therefore to take someone off medication rather than starting medication.

Antidepressant prescriptions are increasing by about 6-8% per annum and there were about 47m prescriptions in 2011 in England and 53m in 2013. In the 2014 report on prescriptions, antidepressants were the BNF category with the largest proportionate increase in prescription for the period between 2003 and 2013.(2) The reasons for the increase in antidepressant prescriptions are not well understood, however Moore(4) has estimated that 90% of prescriptions are for chronic and intermittent users of antidepressants and that prescription to this chronic group has accounted for a substantial amount of the increase. As a result the proportion of the population taking antidepressants is quite high. In a Scottish study in 78 practices, 8.6% of the registered population were prescribed an antidepressant and half of these had been taking them for more than 2 years.(5) It is worth noting that this increase in antidepressant prescription has occurred in all European countries and in the US.(6, 7) Meanwhile, there is no evidence that the rates of depression in the community are falling.(8)

Though antidepressants are well tolerated there are a number of adverse effects, for example, reduced sexual drive and orgasmic impairment in men and women, and weight gain, that are potentially serious and sometimes not brought to the attention of GPs. Patients also often report effects on emotional reactivity and cognition. The costs of the antidepressants, the monitoring by GPs to the NHS and the personal and societal costs of maintenance treatment also have to be taken into account.

5.2 PRECLINICAL DATA

There are no relevant preclinical data on the clinical question as the clinical question is concerned with the removal of antidepressant treatment for relapse of depression. There are no animal models for this clinical situation.

5.3 CLINICAL DATA

We are aware of three published systematic reviews of randomised controlled trials on the effectiveness of maintenance antidepressant treatment (9-11) and the NICE guideline group also carried out a review.(12) These all provide evidence that maintenance treatment substantially reduces the risk of relapse in people with previous depression by between 50% and 70%.

The constituent studies for these reviews have mainly used a design in which people with depression are recruited and treated with an "open label" antidepressant and those who meet criteria for recovery have a further "continuation" period of open treatment. The participants are then randomised to placebo or continuation of the antidepressant. The time point of randomisation is usually determined by the start of the initial open treatment phase. The majority of the evidence is for a period of treatment before randomisation of between 12 and 36 weeks. The amount of evidence for a treatment period of more than 36 weeks is relatively small. In the existing reviews there are only 2 studies that have treated patients for more than 32 weeks. (Cook(13) N=16, Kupfer(14) N=20) These studies still support the effectiveness of maintenance treatment(9) but the evidence base for what we will call long term maintenance treatment is poor.

There are further weaknesses in the evidence base even for shorter periods of maintenance. For example, many studies have been funded by industry in a wide variety of different health systems with medication that is not used in the UK. Some studies have had poor follow up rates, for example in Keller 1998(15) only 59 of the 161 randomised patients completed the 12 month follow-up. They did not follow-up anyone who withdrew from the study medication.

The current NICE guidelines(12) recommend that someone who has recovered from an episode of depression should stay on their antidepressant medication for at least 6 months after remission and this accords with the systematic review evidence mentioned above. However, the guidelines add that the medication should be continued for 2 years after remission in those "at risk of relapse" defined as "two or more episodes .. residual

symptoms .. severe or prolonged episodes". This conclusion is based upon consensus and the NICE report (p.533)(12) and Kaymaz 2008(10) both conclude that there is no evidence that these proposed factors (number of episodes, residual symptoms and severity of previous episodes) affected the difference between antidepressant and placebo maintenance treatment. It should be noted though that the factors proposed by NICE are related to a poorer prognosis overall.(16)

There are no relevant trials in ISCRTN and clinicaltrials.gov except for studies of experimental compounds run by industry. The HTA PREVENT trial (PI Kuyken, Exeter, co-app GL)(17) compares Mindfulness Based Cognitive Therapy with maintenance antidepressants so does not investigate the effectiveness of maintenance antidepressants.

Prof Dee Mangin's (now McMaster but formerly Christchurch, New Zealand) has carried out a similar trial that is about to complete (N=280) and will report shortly. This study used fluoxetine and included patients who had been on antidepressants for one year or more. It was stopped prematurely by the Christchurch earthquake and is underpowered according to our calculations. In addition, the population studied may not be generalizable to UK general practice.

5.4 RATIONALE AND RISKS/BENEFITS

The dramatic rise in antidepressant prescription in the UK is a major cause of concern.(18, 19) The evidence reviewed above indicates that a substantial proportion, perhaps up to 45%, of the individuals on long term prescription are well and taking it to prevent relapse. However, there is currently poor evidence for the effectiveness of long term maintenance antidepressants if someone has been taking them for more than 9 months. This leads to uncertainty for the group of patients who are taking antidepressants as well as for those who are not taking them because of the lack of evidence for their effectiveness.

The research question is:

"What is the clinical and cost-effectiveness in UK primary care of continuing on long term maintenance antidepressants compared to a placebo in preventing relapse of depression in those who have taken antidepressants for more than 9 months and who are now well enough to consider stopping maintenance treatment?"

The proposed study will provide a valid and generalizable estimate of the clinical and cost-effectiveness of long term maintenance treatment with antidepressants in UK primary care. The relevant population is those people who are taking long term maintenance antidepressants and now feel well enough to consider stopping medication.

We will carry out an individually randomised parallel group controlled trial that will compare (1) continuing with the following antidepressant medication (citalopram 20mg, sertraline 100mg, fluoxetine 20mg or mirtazapine 30mg) with (2) replacement of the medication with a placebo after a tapering period. We will follow up participants for 12

months. Our primary outcome will be time to depressive relapse. We will also examine secondary outcomes and perform a cost-effectiveness analysis based upon results of the trial.

There are a large number of antidepressants all of which act on the monoamine systems, especially serotonin (5 hydroytryptamine or 5HT) and noradrenaline. The tricyclic antidepressants are 5HT and/or noradrenaline reuptake inhibitors though they tend also to have other pharmacological actions that increase the side effect burden. The most commonly prescribed antidepressants are now the selective serotonin reuptake inhibitors (SSRIs): citalopram, escitalopram, sertraline, paroxetine and fluoxetine. Citalopram was the commonest prescription in 2013 (32% of antidepressant prescriptions, after excluding amitriptyline which is mostly used for pain and sleep), followed by sertraline (15%) and fluoxetine (14%). Other commonly used antidepressants include venlafaxine which has both serotonin and noradrenaline reuptake inhibitory properties (SNRI). Mirtazapine has a slightly different mode of action and is a described as a noradrenergic and specific serotonergic antidepressant (NaSSA) although the net effect of its action is to increase serotonergic transmission and to some extent noradrenaline. Use of mirtazapine is increasing rapidly and led to 13% of prescriptions in England in 2013.

Given the marked pharmacological similarities between the antidepressants it is usually assumed that they share a common mode of action and any differences in efficacy are likely to be relatively minor.(20) When the different classes of antidepressants have been studied in meta-analysis there has been no evidence to suggest that the tricyclics, SSRIs and SNRIs differ in their effectiveness as a maintenance treatment.(9, 11)

In designing the study we have therefore been primarily guided by the pragmatics of recruitment and carrying out the study. We think it is important to compare the active treatment with a placebo in a condition such as depression with well described placebo effects. Therefore we wanted to minimise the number of antidepressants to make the manufacture and distribution of placebo easier. We have chosen not to use paroxetine as it has a short half-life and is associated with a more marked withdrawal syndrome and might not be tolerated by some individuals when they are withdrawn after randomisation. Escitalopram is not widely used in primary care in the UK and has not been included in many primary care formularies. Venlafaxine tends to be used more by secondary care than primary care doctors, can be poorly tolerated and also has more marked withdrawal effects. Amitriptyline is often used for treatment of pain and insomnia and much less often as an antidepressant so we have also omitted.

We therefore propose to recruit participants who are on maintenance treatment with the SSRIs citalopram 20mg, sertraline 100mg, fluoxetine 20mg and we have also included mirtazapine 30mg given its increasing use. Together these medications comprise about 75% of all antidepressant prescriptions in England and are all licensed for treatment of depression. All these medications are off patent and relatively inexpensive. However, we

think the results will be applicable to all the major classes of antidepressants. ASSESSMENT AND MANAGEMENT OF RISK

The inclusion criteria for the study require participants to have been taking the IMP for at least 9 months. Therefore we are expecting that any safety issues that would emerge would have been dealt with by that stage. The main risk is that we are replacing the IMP with placebo for those participants allocated to placebo. The participants will continue to consult with their general practitioner during the study.

The SSRIs to be used in this trial are licensed for use in this indication and very commonly prescribed. Therefore the potential risk associated with the IMP is considered to be low and no greater than standard medical care. However, due to the placebo comparison arm, the trial is categorised as Type B according the MHRA guidance; the potential risk associated with the design of the study is somewhat higher than standard medical care.

The risks of removal from medication are as follows:

1) Risk of relapse

As indicated there is clinical equipoise concerning the possibility that long term maintenance antidepressants reduce the risk of relapse. As the intervention is to remove antidepressant treatment, there is a possibility that participants will relapse and indeed we would expect this in both arms of the trial.

This risk will be explained to participants and the participants' general practitioner. If the participant is concerned about the possibility of relapse they will be told to immediately seek medical opinion usually from their general practitioner who can then discuss the clinical circumstances with the PI. If in the judgement of the PI the participant should be withdrawn from study medication and treated outside the trial then the PI will make this decision unless this leads to a prolonged delay in which case any medical practitioner would need to decide on this course of action. If a member of the research team is concerned about the possibility of relapse then they will advise the participant to consult their GP and the research team member will also inform the PI who will take any further necessary action.

2) Risk of withdrawal symptoms

It has been known for some time that some people experience withdrawal effects from SSRIs (21) particularly those with a short half-life such as paroxetine. The symptoms experienced include dizziness, headache, shock-like symptoms, irritability and anxiety.

The protocol reduces the risk as there is a 4 week period after randomisation when the antidepressant dose will be halved, followed by another 4 week period when the antidepressant dose will be quartered before the placebo is introduced. We are also not

proposing to recruit people using the antidepressants paroxetine or venlafaxine as these lead to the most marked withdrawal effects.

We will also monitor withdrawal symptoms using an existing questionnaire(22) and supplement our questions on the advice of our PPI representatives. Some patients report quite marked and serious withdrawal effects but at present this evidence is anecdotal and so we think it is important to carefully monitor such symptoms in the study and the study will provide important new information on the existence and severity of any withdrawal symptoms. The comparison with placebo will also distinguish any symptoms that might emerge because of relapse of depressive symptoms.

If serious withdrawal effects occur then the PI and GP will discuss what appropriate action should be taken. At present there is no consensus on the course of action to take if someone reports serious withdrawal symptoms. Reinstating the antidepressant is often not indicated and also not requested by the patient though there are anecdotal accounts of successful withdrawal with very slow reduction in dose.

3) Risk of self-harm

People with depression have an increased risk of self-harm and suicide. We will therefore have a Suicidal Ideation SOP in place and staff will be trained to follow this procedure.

4) Potential risk associated with other medical conditions

It is possible that some potential participants with other medical conditions will be taking antidepressants even though they are subject to a caution. As the person has been taking antidepressants for at least 9 months the decision to prescribe antidepressants in the presence of the caution has already been taken by their own GP. We do not propose to exclude those people. However, we will collect information on relevant medical conditions and the PI will make the final decision about the appropriateness or not of entering the person into the trial.

5) Risk of QT prolongation with citalopram

Citalopram can prolong the QT interval especially in higher doses. In this study only people taking 20mg citalopram will be included so we do not think the QT interval possibility is at high risk. At baseline the PI will also see if there are any other medications that might also prolong the QT interval and take a decision whether the participant should be randomised. We will ask GPs to inform us of any medication changes during the study so that the PI will be aware of any other medication introduced after randomisation that might increase the QT interval. The PI will then make a decision about whether the participant should continue on the IMP. The PI will consider the same caution for other trial medication: sertraline, fluoxetine and mirtazapine.

6) Risk associated with IMP distribution

Risks associated with IMP distribution have been considered. IMP will be dispensed from a central pharmacy via Royal Mail to participant home addresses or GP practices, if more convenient for participants. Recorded delivery will be used to ensure deliveries can be tracked and confirmed as received. Further confirmation of receipt will be obtained from participants. Full accountability details are described in section 10.8. Postage will be at ambient temperature, in line with manufacturer's recommendations. An electronic stock control system will be used to ensure continuity of supply between deliveries. Patient identifiable data will be processed and stored by the dispensing pharmacy in line with the Data Protection Act.

6 OBJECTIVES

To estimate the effectiveness and cost-effectiveness of antidepressant medication in preventing relapse in UK primary care in people who have had two or more episodes of depression (including the current episode) have taken antidepressants for at least 9 months and are now well enough to consider stopping the antidepressant.

We will carry out an individually randomised controlled trial that will compare (1) continuing with antidepressant medication (citalopram 20mg, sertraline 100mg, fluoxetine 20mg or mirtazapine 30mg) with (2) replacement of the medication with a placebo after a tapering period. We will follow up participants for 12 months.

Primary outcome will be time to depressive relapse.

Secondary outcomes will include depressive and anxiety symptoms, adverse effects, withdrawal effects, quality of life and we will also perform a cost-effectiveness analysis based upon results of the trial.

7 TRIAL DESIGN

7.1 OVERALL DESIGN

The study is a double blind individually randomised parallel group randomised controlled trial that is funded by the National Institute of Health Research (NIHR) Health Technology Assessment programme. We will recruit individuals in primary care who are currently on the four antidepressant medications licensed below but are currently well enough to consider stopping medication.

We will carry out an individually randomised parallel group controlled trial that will compare (1) continuing with the following antidepressant medication (citalopram 20mg, sertraline 100mg, fluoxetine 20mg or mirtazapine 30mg) with (2) replacement of the

medication with an identical placebo that will include a double blind tapering period of two month. We will follow up participants at 3, 6, 9 and 12 months.

8 SELECTION OF PARTICIPANTS

The GP will refer patients as per the exclusions and inclusions listed below.

8.1 INCLUSION CRITERIA

The eligible participants will

1) have had at least two episodes of depression
2) be aged 18-74 years (we have excluded older people as different assessments for depression are used in the older age groups)
3) be taking antidepressants for 9 months or more and currently taking: citalopram 20mg, sertraline 100mg, fluoxetine 20mg or mirtazapine 30mg
4) have satisfactory adherence to medication We will use the same criteria as used in the COBALT trial to define adherence using an adapted Morisky 4-item self-report measure of compliance (20) (21) as adapted for the COBALT trial.(23) Given the relatively long half-life of antidepressant medication, individuals who have forgotten to take one or two tablets will not be excluded and this will be established with an extra question “Did you forget to take 2 days of your medication in a row?” Therefore our criteria defined people as adherent if (1) they scored zero on all four questions (2) they scored one and said No to the extra question (3) scored 2 because of forget and careless questions and said No to extra question.
5) are considering stopping their antidepressant medication

8.2 EXCLUSION CRITERIA

Participants will be excluded if they:

1) meet internationally agreed (ICD10) criteria for a depressive illness
2) score 12 and above on the depressive symptom questionnaire, PHQ9
3) have bipolar disorder, psychotic illness, dementia, alcohol or substance dependence or a terminal illness
4) are not able to complete self-administered questionnaires in English
5) have contraindications for any of the prescribed medication
6) pregnancy or intention to get pregnant with the next 12 months
7) use of monoamine oxidase inhibitors
8) allergies to placebo excipients
9) Current enrolment in another Clinical Trial of an Investigational Medicinal Product

9 RECRUITMENT

Primary care in London, Bristol, York and Southampton. We will select practices to reflect a range of settings from rural to urban, wealthy to deprive.

General practice (GP) electronic patient records will be searched to identify potential participants who have been on antidepressant medication for 9 months or more. The GP will (i) mail these individuals and invite them to contact the study team or (ii) discuss the trial at consultation. Those who respond and agree to take part will be sent a short depressive symptom questionnaire (PHQ9) and if they score 10 or below and have been adherent to medication they will be telephoned by the research assistant in order to apply further eligibility criteria. If still potentially eligible they will be invited for a baseline assessment that will establish any remaining eligibility criteria and carry out the Revised Clinical Interview Schedule (CISR) that will be used to exclude those with ICD10 depression. (25) The participant will be invited to give consent for randomisation and final eligibility criteria confirmed before randomisation.

10 STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

10.1 INFORMED CONSENT PROCEDURE

The potential participants will be posted or given in person by their GP or nurse prescriber a patient information sheet (PIS) that gives details of the study. A screening telephone call will elicit any further screening questions and then potential participants will be invited to a baseline assessment; at least 24 hours will be given for consideration of the PIS. Both at the screening telephone call and at this meeting the study will be explained, including the aims, methods, anticipated benefits and potential hazards by a research assistant who will be GCP trained, suitably qualified, experienced and delegated this duty by the CI/PI on the appropriate delegation log. The patients will be given the opportunity to ask questions. Patients will be under no obligation to enter the trial and they will be advised that they can withdraw at any time during the trial without providing a reason. The local PI or delegated physician will be available by phone if there are any queries. Adequate time will be given for consideration by the patient; it is expected that most patients will be willing to consent to the study at the baseline visit. If a patient is unsure then they may be rescheduled for consent and baseline assessments at a later date. A delegated member of staff will then obtain written consent. Consent will not denote enrolment into the trial. A copy of the consent form will be given to the patient, the original will be retained in the trial file and a copy will be sent to the general practitioner. A letter will also be sent to the patient's GP to inform them of their enrolment in the trial. No clinical trial procedures will be conducted prior to taking consent.

If new safety information results in significant changes in the risk/benefit assessment, the participant information sheet and consent form will be reviewed and updated if necessary. All participants, including those already being treated, will be informed of any new information, giving a copy of the revised information sheet and participants will be re-consented as appropriate.

10.2 RANDOMISATION PROCEDURES

Prior to randomisation the eligibility will be confirmed by PI or delegate. Randomisation will be concealed by using a remote computerised system provided by Sealed Envelope and the pharmacy will be directly informed of the randomisation outcome. The randomisation will be minimised by the four study centres, the four medications and severity of depressive symptoms at baseline (two categories).

The pharmacy will be informed of the randomised allocation and post the medication to either the patient's home or GP surgery.

10.3 UNBLINDING

Emergency Unblinding

The study code should only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the patient is receiving before the participant can be treated. Subject always to clinical need, where possible, members of the research team should remain blinded.

The code breaks for the trial are held at dispensing pharmacy and are the responsibility of the same pharmacy.

In the event a code is required to be unblinded a formal request for unblinding will be made by the Investigator/treating health care professional.

If the person requiring the unblinding is a member of the Investigating team then a request to the holder of the code break envelope/list, or their delegate will be made and the unblinded information obtained.

If the person requiring the unblinding is not the CI/PI then that health care professional will contact the pharmacy directly, who will then notify the Investigating team that an unblinding participant has taken place.
On receipt of the treatment allocation details the CI/PI or treating health care professional will deal with the participant's medical emergency as appropriate.

The CI/PI documents the breaking of the code and the reasons for doing so on the CRF/data collection tool, in the site file. The GPs will also be notified.

The CI/Investigating team will notify PRIMENT (acting on behalf of the Sponsor) in writing as soon as possible following the code break detailing the necessity of the code break. The relevant authorities will also be notified.

Unblinding for the submission of SUSAR reports

The following procedure will be used to unblind for the submission of a SUSAR report to the regulatory agencies:

An authorised user from Priment will obtain via pharmacy the treatment allocation for a specified patient. This information will not be forwarded to the trial team and kept in the Sponsor File.

Unblinding at request of patient

At the end of the study patients can ask to have their allocation revealed in order to inform future treatment. This will occur after the last 12 month assessment. The GP will be sent a letter and the patient can then consult with the GP to discuss future treatment options.

Unblinding on withdrawal from study medication

At the request of the patient, the allocation will be revealed if the patient withdraws from the study medication. The allocation will be sent to the GP as above. The study team will not be informed of the allocation.
Further details will be specified in the trial-specific unblinding SOP.

10.4 SCREENING PERIOD

Electronic search of GP database.

The GP databases will be searched for those who meet the eligibility criteria for age, antidepressant use, and where possible (this may vary according to GP practice) data on contraindications for the medication.

Those who respond to the mailed request by returning the reply slip to the study team will be sent a questionnaire that will include the depressive symptom questionnaire (PHQ9) and questions on adherence to medication. There will be a follow up telephone call to ask about any outstanding screening questions. For potential participants the research team will contact them to arrange a baseline assessment. The GP will be sent a questionnaire asking them to report on any medical conditions known to them that are contraindications for antidepressant medication.

10.5 BASELINE VISIT

The baseline visit will include the

- revised clinical interview schedule CISR to assess ICD10 criteria for depression

- Past medical history questions including any physical illness contraindications and past psychiatric treatments
- Sociodemographic and other background information
- depressive symptoms (PHQ9)(26)
- anxiety symptoms(GAD7),
- EQ5D-5L(27) for quality adjusted life years (QALYs),
- Adverse effects of antidepressants (a modified Toronto Side Effects scale we have used previously)(28)
- adherence to study medication (modified Morisky)(24)
- health related quality of life (SF12).
- Withdrawal symptoms – based on (22)
- Emotional processing tasks
- Pregnancy testing

10.6 TREATMENT PROCEDURES

At baseline participants will be taking either citalopram 20mg, sertraline 100mg, fluoxetine 20mg or mirtazapine 30mg. They will be randomised to either (1) remaining on their current medication or (2) having 1 month of the same medication at half the dose (citalopram 10mg, sertraline 50mg, fluoxetine 10mg or mirtazapine 15mg), followed by a quarter of the dose (citalopram 5mg, sertraline 25mg, fluoxetine 5 mg or mirtazapine 7.5mg) for a month and then taking placebo for the remainder of the study.

No one in either group will be allowed to vary their dose of study medication.

10.7 SUBSEQUENT ASSESSMENTS

Follow up assessments will be carried out at 12, 26, 39 and 52 weeks after randomisation.

- Modified shortened revised clinical interview schedule CISR to assess onset of a depressive episode in previous 12 weeks (see primary outcome section for more details)
- depressive symptoms (PHQ9)(26)
- anxiety symptoms(GAD7),
- EQ5D-5L(27) for quality adjusted life years (QALYs),
- Adverse effects of antidepressants (a modified Toronto Side Effects scale we have used previously)(28)
- adherence to study medication (modified Morisky)(24)
- health related quality of life (SF12).

- Withdrawal symptoms – based on (22)
- Question on whether participant on placebo or active medication
- Questions on resource use (6 and 12 months)

After 52 weeks we will obtain further resource use information from the GP notes in those who provide permission. We will examine the test retest reliability of the PHQ9, GAD7, Retrospective CISR, adverse effects, withdrawal symptoms and the question on placebo or active. The participants will be asked to repeat those questionnaires at one of the follow up appointments.

10.8 FLOWCHART OF STUDY ASSESSMENTS

	Screening	Baseline				
	Telephone and GP information	0	12 Weeks	26 Weeks	39 Weeks	52 Weeks
Informed Consent		X				
Medical History (including medication review)	X	X				
Sociodemographic information		X				
Eligibility determination, incl pregnancy test at BL		X				
Depressive Symptom Questionnaire PHQ9	X	X	X	X	X	X
Anxiety Symptoms GAD7		X	X	X	X	X
Revised Clinical Interview Schedule		X				
Retrospective CISR			X	X	X	X
Quality Adjusted Life Years QALYs (EQ-5D-5L)		X	X	X	X	X
Randomisation		X				
Adverse Effects		X	X	X	X	X
Adherence to study medication; questions about other medication incl con review		X	X	X	X	X
Pill Count				X		X
Health related quality of life (SF12)		X	X	X	X	X
Health and social care resource use - questionnaire		X		X		X
GP appointments and medication – patient files						X
Withdrawal Symptoms			X	X	X	X
Global rating question		X	X	X	X	X

Question: if on placebo/active drug			X	X	X	X
Emotional processing tasks		X	X			X
Unblinding on request						X
IMP distribution						

* IMP distribution occurs at week 0, month 1, 2 and bimonthly subsequently until the end of the trial.

10.9 DEFINITION OF END OF TRIAL

The end of the trial is when the last assessment of the last participant in the trial is completed.

The participant ends their participation in the trial when their last assessment is completed.

10.10 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS AND 'STOPPING RULES'

Participants may withdraw from the study at any time. They can either withdraw from taking the study medication while continuing to participate in any remaining assessments or they can also refuse to complete any further assessments. The participant will be asked to give their reasons for withdrawal. Participants can ask for any data that has been collected on them to be destroyed. The reasons for withdrawal if known will be recorded.

The trial may be prematurely discontinued by the Sponsor, Chief Investigator, Regulatory Authority or Funder on the basis of new safety information or for other reasons given by the Data Monitoring Committee / Trial Steering Committee regulatory authority or ethics committee concerned.

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the Trial Steering Committee, who will advise on whether to continue or discontinue the trial and make a recommendation to the Sponsor. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected.

11 NAME AND DESCRIPTION OF ALL DRUGS USED IN THE TRIAL

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/guidance-on-imp_nimp_04-2007.pdf

The following drugs will be used in this trial:

Mirtazapine 30mg, 15mg, 7.5mg: White round biconvex film coated tablet with a diameter of 10mm manufactured on behalf of the sponsor in the EU under GMP compliance. Tablets will be packed in bottles of 31 tablets labelled as per annex 13 that will disguise the identity of the medicine to maintain the blinding of the product.

Citalopram 20mg, 10, 5mg: White round biconvex film coated tablet with a diameter of 10mm manufactured on behalf of the sponsor in the EU under GMP compliance. Tablets will be packed in bottles of 31 tablets labelled as per annex 13 that will disguise the identity of the medicine to maintain the blinding of the product.

Sertraline 100mg, 50mg, 25mg: White round biconvex film coated tablet with a diameter of 10mm manufactured on behalf of the sponsor in the EU under GMP compliance. Tablets will be packed in bottles of 31 tablets labelled as per annex 13 that will disguise the identity of the medicine to maintain the blinding of the product.

Fluoxetine 20mg, 10mg, 5mg: White round biconvex film coated tablet with a diameter of 10mm manufactured on behalf of the sponsor in the EU under GMP compliance. Tablets will be packed in bottles of 31 tablets labelled as per annex 13 that will disguise the identity of the medicine to maintain the blinding of the product.

Placebo: White round biconvex film coated tablet with a diameter of 10mm manufactured on behalf of the sponsor in the EU under GMP compliance. Tablets will be packed in bottles of 31 tablets labelled as per annex 13 that will disguise the identity of the medicine to maintain the blinding of the product.

11.1 TREATMENT OF PARTICIPANTS

Investigational product/treatment

The placebo will have an identical appearance to the IMP such that allocation concealment and blinding of the trial is maintained. The IMP and the placebo will be manufactured by a UK MIA (IMP) licence holder.

Participants will be asked about adherence at all the follow-up points. It will be requested that empty packaging and unused medicines are returned as described in section 12.8.

11.2 CONCOMITANT MEDICATION

The participants will have already been taking the antidepressant medication for at least 9 months before entering the trial. It is possible that some participants might be taking medication, before entry to the study, that is cautioned for use with their antidepressant. If this does occur, the PI will make a clinical judgement about whether that person should be entered into the study. The only strict contraindication for use with the antidepressants in the study is for monoamine oxidase inhibitors so use of this is excluded.

12 INVESTIGATIONAL MEDICINAL PRODUCT

According to the definition of the EU clinical trial directive 2001/20/EC, an investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation, but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

12.1 NAME AND DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

Citalopram, Sertraline, Fluoxetine, Mirtazapine in tablet form

Placebo tablets

12.2 SUMMARY OF FINDINGS FROM NON-CLINICAL STUDIES

May be found in the Summary of Product Characteristics.

12.3 SUMMARY OF FINDINGS FROM CLINICAL STUDIES

Maybe found in the Summary of Product Characteristics.

12.4 SUMMARY OF KNOWN AND POTENTIAL RISKS AND BENEFITS

The adverse effects of citalopram, sertraline, fluoxetine and mirtazapine have been well described and included in the Patient Information Leaflet supplied by the manufacturer and in the British National Formulary, www.medicines.org.uk/emc.

Table: Adverse Reactions

12.4.1 CITALOPRAM

Very Common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1000 to <1/100)	**Rare** (≥1/10000 to <1/1000)	**Very rare** (<1/10000)	**Frequency not Known**
Infections and Infestations					
Neoplasms benign, malignant (including cysts and polyps)					

Blood and lymphatic system disorders					
Immune system disorders					
Endocrine disorders					
Metabolism and Nutrition Disorders					
	Decreased appetite, decreased weight, weight loss (anorexia)				
Psychiatric Disorders					
Sleepiness, difficulty sleeping	Abnormal dreaming, memory loss, amnesia, absence of emotion or enthusiasm Agitation, anxiety, nervousness, confusion Decreased sex drive (libido) Problems in concentration				
Nervous System Disorders					
Headache Increased sweating	Tiredness, yawning Tremor, Dizziness Sensation of tingling, pricking or numbness in skin (paraesthesia)				

Feeling sick (nausea)	Muscle pain (myalgia), joint pain (arthralgia) Itching (pruritus)				
Eye Disorders					
Ear and Labyrinth Disorders					
	Ringing in ears (Tinnitus)				
Cardiac Disorders					
Vascular Disorders					
Respiratory, Thoracic, and Mediastinal Disorders					
	Yawning				
Gastrointestinal Disorders					
	Diarrhoea, vomiting, constipation, indigestion (dyspepsia), stomach pain, wind(flatulence), increased saliva Dry Mouth				
Hepatobiliary Disorders					
Skin and Subcutaneous Tissue Disorders					

Musculoskeletal and Connective Tissue Disorders					
	Muscle pain (myalgia) Joint pain (arthralgia)				
Renal and Urinary Disorders					
*Reproductive System and Breast Disorders***					
	Inability in women to achieve orgasm Menstrual pain Impotence Ejaculation failure				
General Disorders and Administration Site Conditions					
Investigations					
Injury and poisoning					
Surgical and medical procedures					

12.4.2 SERTRALINE

Very Common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1000 to <1/100)	**Rare** (≥1/10000 to <1/1000)	**Very. rare** (<1/10000)	**Frequency not Known**
Infections and Infestations					
Neoplasms benign, malignant (including cysts and polyps)					
Blood and lymphatic system disorders					
Immune system disorders					
Endocrine disorders					
Metabolism and Nutrition Disorders					
Psychiatric Disorders					
	Anorexia Increased appetite Depression Feeling strange Nightmare	Halluncinatio n Feeling too happy Lack of caring		physical symptoms due to stress or emotions, drug dependenc e,	

	Anxiety Agitation Nervous ness decreased sexual interest Teeth grinding Lack of attention	Thinking abnormal Amnesia Weight decreased, weight increased		psychotic disorder, aggression, paranoia, suicidal thoughts, sleep walking, premature ejaculation	
Nervous System Disorders					
	numbness and tingling, shaking, muscle tense, abnormal taste visual disturbance, ringing in ears increased sweating	convulsion, involuntary muscle contractions, abnormal coordination, moving a lot, decreased feeling, speech disorder, dizziness while standing up, migraine, muscular weakness, back pain, muscle twitching Weakness Thirst		Abnormal movements Difficulty moving Increased sensation Sensory disturbance difficulty walking	
Eye Disorders					

		Eye swelling		tear problem spots in front of eyes, double vision, light hurts eye, blood in the eye, enlarged pupils,	
Ear and Labyrinth Disorders					
		Ear pain		Ear infection	
Cardiac Disorders					
	Palpitations chest pain	Fast heartbeat High blood pressure		heart attack, slow heart beat, heart problem poor circulation of arms and legs	
Vascular Disorders					
Respiratory, Thoracic, and Mediastinal Disorders					
	Sore throat	breathing difficulty,		losing up of throat,	

	Yawning	possible wheezing, shortness of breath, nose bleed inflammation of the oesophagus problem, difficulty swallowing, haemorrhoids, increased saliva, tongue disorder, burping,		breathing fast, breathing slow, difficulty talking, hiccups sore mouth, tongue ulceration, tooth disorder, tongue problem, mouth ulceration	
Gastrointestinal Disorders					
	abdominal pain, vomiting, constipation, upset stomach, gas			Intestine problem blood in stool	
Hepatobiliary Disorders					
Skin and Subcutaneous Tissue Disorders					
	Hot flush rash	Flushing purple spots on skin, hair loss, cold		skin problem with blisters, hair rash, hair	

		sweat, dry skin, hives,		texture abnormal, skin odour abnormal	
Musculoskeletal and Connective Tissue Disorders					
	muscle pain	osteoarthritis			
Renal and Urinary Disorders					
		night time urination, unable to urinate, increase in urination, increase in frequency of urination, problem urinating,		decreased urination, urinary incontinence, urinary hesitation	
*Reproductive System and Breast Disorders***					
	sexual dysfunction, erectile dysfunction	vaginal haemorrhage, female sexual dysfunction		excessive vaginal bleeding, dry vaginal area, red painful penis and foreskin, genital discharge, prolonged erection,	

				breast discharge semen abnormal,	
General Disorders and Administration Site Conditions					
		Chest cold, runny nose Chills Fever		cancer, swollen glands, high cholesterol, low blood sugar, coma glaucoma, bone disorder, hernia, drug tolerance decreased	
Investigations					
Injury and poisoning					
Surgical and medical procedures					

12.4.3 FLUOXETINE

Very Common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1000 to <1/100)	**Rare** (≥1/10000 to <1/1000)	**Very. rare** (<1/10000)	**Frequency not Known**
Infections and Infestations					
Neoplasms benign, malignant (including cysts and polyps)					
Blood and lymphatic system disorders					
Immune system disorders					
Endocrine disorders					
Metabolism and Nutrition Disorders					
	Decreased appetite, weight loss				
Psychiatric Disorders					
Insomnia	Sleep problems, unusual dreams, tiredness, sleepiness anxiety, nervousness Decreased sex drive (libido)				Irritability and extreme agitation

	Restlessness, poor concentration Feeling tense				
Nervous System Disorders					
Headache Feeling sick (nausea)	Tiredness, yawning Dizziness Itching (pruritus) Change in taste Uncontrollable shaking movement Excessive sweating				Feelings of weakness drowsiness or confusion
Eye Disorders					
	Blurred vision				
Ear and Labyrinth Disorders					
Cardiac Disorders					
	Rapid and irregular heartbeat sensations				
Vascular Disorders					
Respiratory, Thoracic, and Mediastinal Disorders					
	Yawning				
Gastrointestinal Disorders					

Diarrhoea feeling sick (nausea)	Vomiting, indigestion Dry Mouth				
Hepatobiliary Disorders					
Skin and Subcutaneous Tissue Disorders					
	Flushing Rash, urticarial, itching Excessive sweating				
Musculoskeletal and Connective Tissue Disorders					
	Joint pain (arthralgia)				
Renal and Urinary Disorders					
	Passing urine more frequently				
*Reproductive System and Breast Disorders***					
	Decreased sex drive or sexual problems (including difficulty maintaining an erection for sexual activity) Unexplained vaginal bleeding				Prolonged and painful erection
General Disorders and Administration Site Conditions					

	Feeling shaky or chills				Serotonin syndrome
Investigations					
Injury and poisoning					
Surgical and medical procedures					

12.4.4 MIRTAZAPINE

Very Common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1000 to <1/100)	**Rare** (≥1/10000 to <1/1000)	**Very. rare** (<1/10000)	**Frequency not Known**
Infections and Infestations					
Neoplasms benign, malignant (including cysts and polyps)					
Blood and lymphatic system disorders					
					Granulocytopenia aplastic anemia

					thrombocytopenia eosinophilia hyponatraemia
Immune system disorders					
Endocrine disorders					
					inappropriate anti-diuretic hormone secretion
Metabolism and Nutrition Disorders					
Increase in appetite and weight gain					
Psychiatric Disorders					
Drowsiness or sleepiness	Lethargy, tiredness, vivid dreams, sleeping problems Confusion Feeling anxious	nightmares, feeling agitated, hallucinations feeling aggressive			Sleepwalking thoughts of harming or killing yourself
Nervous System Disorders					

Headache Dry mouth	Dizziness, feeling dizzy or faint when you stand up suddenly Shakiness or tremor	abnormal sensation in the skin e.g. burning, stinging, tickling or tingling (paraesthesia) restless legs, urge to move fainting (syncope) sensations of numbness in the mouth (oral hypoaesthesia) muscle twitching or contractions (myoclonus)			abnormal sensations in the mouth (oral paraesthesia) swelling in the mouth (mouth oedema) slurred speech increased salivation
Eye Disorders					
	Blurred vision				
Ear and Labyrinth Disorders					
Cardiac Disorders					

	Rapid and irregular heartbeat sensations	low blood pressure			
Vascular Disorders					
Respiratory, Thoracic, and Mediastinal Disorders					
	Yawning				
Gastrointestinal Disorders					
Diarrhoea feeling sick (nausea)	Nausea, diarrhoea, vomiting				
Hepatobiliary Disorders					
Skin and Subcutaneous Tissue Disorders					
	Rash or skin eruptions				erythema multiforme
Musculoskeletal and Connective Tissue Disorders					
	Joint pain (arthralgia) or muscles (myalgia) back pain Swelling (typically in ankles or feet) caused by fluid retention (oedema)				
Renal and Urinary Disorders					

	Passing urine more frequently				
*Reproductive System and Breast Disorders***					
	Decreased sex drive or sexual problems (including difficulty maintaining an erection for sexual activity) Unexplained vaginal bleeding				
General Disorders and Administration Site Conditions					
	Feeling shaky or chills		Jaundice		Agranulocytosis Epileptic attack Serotonin syndrome
Investigations					
Injury and poisoning					
Surgical and medical procedures					

12.5 DESCRIPTION AND JUSTIFICATION OF ROUTE OF ADMINISTRATION AND DOSAGE

Daily oral doses: 1 tablet (e.g. citalopram 20mg, sertraline 100mg, fluoxetine 20mg or mirtazapine 30mg) or matching placebo tablet.

12.6 DOSAGES, DOSAGE MODIFICATIONS AND METHOD OF ADMINISTRATION

An active medication arm will take 1 tablet orally (citalopram 20mg, sertraline 100mg, fluoxetine 20mg or mirtazapine 30mg) for 12 months.

Placebo arm: 1 month of the current medication at half the dose (citalopram 10mg, sertraline 50mg, fluoxetine 10mg or mirtazapine 15mg) 1 oral tablet per day, followed by a quarter of the dose (citalopram 5mg, sertraline 25mg, fluoxetine 5 mg or mirtazapine 7.5mg) 1 oral tablet per day for a month and then taking placebo 1 tablet per day for the remainder of the study.

12.7 PREPARATION AND LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCT

The labelling of medication packs will be labelled in accordance with applicable Regulations and MHRA approved. Each Medication Pack will have a Medicine ID number, randomly generated to ensure active and placebo medicine packs are indistinguishable (e.g. avoid all placebo packs being assigned an odd number) and thus maintain allocation concealment. This random number will be generated by the CTU and provided to the manufacturer who will use as a unique identifier for the IMP packages and to the randomisation/ code break service.

12.8 DRUG ACCOUNTABILITY

The manufacturer will labelled the trial medication and store the packages under controlled conditions. Storage will be secure, and there will be a delegation log for access, for which the pharmacy will take responsibility. The same pharmacy will dispense individual patient packs and oversee the packaging and posting of those packs. After randomisation a patient pack containing 1 month supply (31 tablets) of the trial medication will be posted by recorded delivery to the participant's home or GP surgery; after 1 month in the trial a further month worth of medication (31 tablets) will be posted. After 2 months in the trial the medication (62 tablets) will be sent bimonthly by recorded delivery. All deliveries will be logged to ensure drug accountability.

Full IMP accountability records will be maintained in the trial. Dispensing, distribution, receipt, return and destruction records will be maintained at the pharmacy. If the IMP arrives at the general practice it will be kept in a secure locked cabinet until collected by the participant. The receipt and collection of the IMP will be logged by the research team and further details will be included in the IMP management plan for the trial.

Any used medicine that is returned will be passed to the pharmacy for accountability before destruction following authorisation by the Sponsor in line with the relevant SOP.

12.9 SOURCE OF IMPS INCLUDING PLACEBO

All four types and three strengths of the active together with the placebo will be white round biconvex film coated tablets with a diameter of 10mm manufactured on behalf of the sponsor in the EU under GMP compliance. Tablets will be packed in bottles of 31 tablets labelled as per annex 13 that will disguise the identity of the medicine to maintain the blinding of the product.

12.10 DOSE MODIFICATIONS

No dose modifications are permitted.

12.11 ASSESSMENT OF COMPLIANCE

IMP adherence will be assessed by counting the tablets returned by the participant and by asking questions about their adherence. These data will be recorded in the CRF. Non-compliance to the protocol study procedures will be documented by the investigator and reported to the Sponsor as agreed. The participants will be asked to complete all assessments even if they do not take the study medication. Information on adherence will be used in the final analysis plan that will be agreed by the Trial Steering Committee.

12.12 POST-TRIAL IMP ARRANGEMENTS

Following completion of the study the participants will be asked to consult with their general practitioner to discuss any further treatment that might be necessary. Further trial medication will not be supplied.

13 RECORDING AND REPORTING OF ADVERSE EVENTS AND REACTIONS

13.1 DEFINITIONS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product which **is related** to any dose administered to that participant. *This includes medication errors, uses outside of protocol (including misuse and abuse of product)*
Serious adverse event (SAE), serious adverse reaction (SAR) or	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results in death,

unexpected serious adverse reaction	• is life-threatening, • requires hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
Important Medical Event	These events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'.
Unexpected adverse reaction	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: (a) in the case of a product with a marketing authorization, in the summary of product characteristics for that product, (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
SUSAR	Suspected Unexpected Serious Adverse Reaction

13.2 RECORDING ADVERSE EVENTS

All AEs of special interest (as defined in section 10.7) will be recorded by a structured adverse effects assessment only included in the follow up assessments. If a participant consults the general practitioner with a known adverse event it will be recorded in the medical notes only but not communicated to the PI unless specifically requested.

As this trial is a phase IV trial of licensed medications used within its licensed indication with a well-established safety profile, AEs will not be recorded in the CRF apart from those AEs of special interest included in the follow up assessments.

13.3 ASSESSMENTS OF ADVERSE EVENTS

Each adverse event will be assessed for the following criteria:

13.3.1 SEVERITY

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

13.3.2 CAUSALITY

The assessment of relationship of adverse events to the administration of IMP is a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of the adverse event:

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

13.3.3 EXPECTEDNESS

Category	Definition
Expected	An adverse event that is consistent with the information about the IMP listed in the Investigator Brochure (or SmPC if Licensed IMP) **or clearly defined in this protocol.**
Unexpected	An adverse event that is not consistent with the information about the IMP listed in the Investigator Brochure (or SmPC if Licensed IMP)

The Reference Safety Information for IMP in this trial is as follows:

Sertraline: section 4.4 , withdrawal on discontinuation, of Sertraline SmPC (Bristol Labs).
Citalopram: section 4.4 , withdrawal symptoms seen on discontinuation, of Citalopram SmPC (Bristol Labs).

Mirtazipine: section 4.4, special precautions for use, of Mirtazipine SmPC (Actavis)
Fluoxetine: section 4.4, withdrawal symptoms seen on discontinuation of SSRI treatment, of Fluoxetine SmPC (Bristol Labs)

13.3.4 SERIOUSNESS

Seriousness as defined for an SAE in section **13.1.**

Collection, recording and reporting of adverse events (including serious and non-serious events and reactions) to the sponsor will be completed according to Priment SOP.

13.4 PROCEDURES FOR RECORDING AND REPORTING SERIOUS ADVERSE EVENTS

All serious adverse events will be recorded in the sponsor's SAE log. The SAE log will be reported to the sponsor twice per year

For events meeting the criteria for seriousness, the Principal Investigator will complete the sponsor's serious adverse event form and the form will be emailed to primentsafetyreport@ucl.ac.uk, within 24 hours of his / her becoming aware of the event. The Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

Reporting to the sponsor will be completed as per the sponsor's SOP.

13.5 NOTIFICATION OF DEATHS

All deaths, including deaths deemed unrelated to the IMP will be reported to the sponsor within 24 hours of the CI or PI being made aware of the event.

13.6 REPORTING SUSARS

The sponsor will notify the main REC and MHRA of all SUSARs. SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after the sponsor has learned of them. Other SUSARs must be reported to the REC and MHRA within 15 days after the sponsor has learned of them.

Please refer to section 10.3 for unblinding of a SUSAR.

13.7 DEVELOPMENT SAFETY UPDATE REPORTS

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

13.8 ANNUAL PROGRESS REPORTS

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

The chief investigator will prepare the APR.

13.9 PREGNANCY

Should a study participant become pregnant whilst in the trial, the pregnancy, the patient will be followed up until term or termination and a pregnancy notification form completed and sent to the Sponsor. The BNF advice is that the benefits of the IMP should outweigh the risks if it were to be used in pregnancy. At baseline, we will exclude potential patients who have a positive pregnancy test result or are intending to become pregnant within the next 12 months.

13.10 OVERDOSE

The participants have been taking maintenance medication for some time so we are not expecting any overdose. This will become apparent as the study medication will be sent two monthly. If participants have taken more study medication than prescribed then the local PI will be notified and will decide what action needs to be taken.

13.11 REPORTING URGENT SAFETY MEASURES

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

13.12 THE TYPE AND DURATION OF THE FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE EVENTS.

In the event that a participant suffers from a SAE, we will advise the participant to contact their GP immediately and follow up with the participant until a resolution or stabilisation is reached.

Events and reactions will be regarded as not related to the IMP if they occur more than 2 weeks after stopping the IMP unless it is fluoxetine, then it is 5 weeks. The follow-ups will be completed by the PI or a delegate.

Any SUSAR related to the IMP will be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

13.12.1 NOTIFICATION OF SERIOUS BREACHES TO GCP AND/OR THE PROTOCOL

A “serious breach” is a breach which is likely to effect to a significant degree –

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

(b) the scientific value of the trial.

The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of –

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

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor's SOP on the 'Notification of violations, urgent safety measures and serious breaches' will be followed.

14 DATA MANAGEMENT AND QUALITY ASSURANCE

14.1 CONFIDENTIALITY

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

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

14.2 DATA COLLECTION TOOLS AND SOURCE DOCUMENT IDENTIFICATION

Participants will be explained before consent the requirement to attend all follow up assessments. The 3, 6, 9 and 12 months assessments will be face to face appointments. We will write letters, email and telephone the participants in order to maximise the response rate.

CISR – Revised clinical interview schedule. This is a self-administered assessment of psychiatric symptoms including depression. It generates a computer file that will then be incorporated into the main CRF held on a database.

PHQ9, BDI-II, SF12, EQ5D, GAD7 – Are self-administered questionnaire will either be administered in a paper and pencil format or in computerised format. The electronic or paper records will then be transferred to the main CRF held on a database.

Resource use collection:

Collection of resource use data for the economic analysis will be either in the form of a questionnaire given to the participants to fill in at baseline, 6 months and 12 months, (health and social care resource use and employment and welfare details) or will be found from the participants' GP notes (appointments and medication) and transferred by a research assistant into the main CRF, covering the same time period."

Emotional processing tasks.

Emotional memory task: the participant will be asked to write down the words that are remembered. These will be coded as correct or incorrect by the delegated member of staff and that information will be transferred onto the database.

Emotion recognition task: the participant carries out the task on a PC and this generates an electronic file that contains responses and reaction times. The file will be stored and achieve electronically.

Go-Nogo emotional processing task: is as follows and will take approximately 12 minutes and will be administered on a laptop computer. Each trial will consist of three events: a fractal cue, a target detection task and a probabilistic outcome. There will be 4 trial types depending on the nature of the fractal cue presented at the beginning of the trial: press the correct button in the target detection task to gain a reward (go to win); press the correct button in the target detection task to avoid punishment (go to avoid losing); do not press a button in the target detection task to gain a reward (no-go to win); do not press a button in the target detection task to avoid punishment (no-go to avoid losing). The meaning of the fractal images is randomized across participants.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database. Source data will be maintained at each trial site for each patient and will be defined prior to the start of data collection at each site.

All data at site will be handled according to the Data Protection Act 1998. Any patient identifiers will be removed prior to the submission of documents to the Sponsor or coordinating centre

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

14.3 DATA HANDLING AND ANALYSIS

A database will be prepared by CTU and Sealed Envelope that will include facility for data entry. This will be accessed via a secure website to allow data to be entered from all sites.

Data management activities will be described in a trial specific Data Management Plan. The local PI will be responsible for the data quality.

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

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

15 RECORD KEEPING AND ARCHIVING

Archiving will be authorised by the Sponsor following submission of the end of study report. Archiving will be carried out in line with Sponsor SOP.

The Chief Investigator will be responsible for the secure archiving of essential trial documents (for each site, if multi-site trial) and the trial database as per local trust policy. All essential documents will be archived for a minimum of 5 years after completion of trial.

Destruction of essential documents will require authorisation from the Sponsor.

16 STATISTICAL CONSIDERATIONS

Prof Nicholas Freemantle is the trial statistician who will be responsible for all statistical aspects of the trial from design through to analysis and dissemination.

16.1 OUTCOMES

16.1.1 PRIMARY OUTCOMES

The primary outcome will be the time in weeks to the beginning of the first episode of depression after randomisation.

The primary outcome will be assessed using a modified and shortened standardised psychiatric assessment (Clinical Interview Schedule – Revised; CISR)(25) that will ask retrospectively over the previous 12 weeks and will be used at all follow up points. Five of the 14 CISR sections (depression, depressive ideas, concentration, sleep and fatigue) are used for the diagnosis of depression. This shortened CISR with 5 sections will be supplemented with questions asking about symptoms during the previous 3 months. Additional questions will establish the time to the nearest week when the depression section score was >= 2, used to indicate clinical important symptoms. An episode will be defined as those reaching 2 or more on the depression section of the CISR for a period of 2 weeks or more and also met the ICD10 criteria during the most severely affected week during that period. The beginning of the episode (and the time used for the primary outcome) will be the first week that the participant scored 2 or more on the depression section.

16.1.2 SECONDARY OUTCOMES

Depressive symptoms (PhQ9)(26)

Anxiety symptoms (GAD7),

EQ5d-5L(27) for quality adjusted life years (QALYS) this will be used as a continuous variable in the economic analysis

Adverse effects of antidepressants (a modified Toronto side effects scale we have used previously)(28) – the analysis of this will depend upon the frequency and distribution of side effects.

Health related quality of life (SF12) – this will be analysed as a continuous variable

Withdrawal symptoms – based on (22)

A detailed analysis plan will be agreed with the Trial Steering Committee and will describe in more detail how these outcomes will be analysed. The choice of statistical approach will depend upon the nature of the variables.

16.2 SAMPLE SIZE AND RECRUITMENT

16.2.1 SAMPLE SIZE CALCULATION

The Geddes(9) systematic review estimated a reduction in odds of relapse of 70%, Kaymaz(10) 65%, Glue(11) 65% and NICE(12) about 50%. Between 15% and 22% of those on active drug relapsed in 12 months. To detect the difference between 15% (continuation) and 30% (withdrawal) (hazard ratio 0.46), or 20% (continuation) and 35% (withdrawal) (hazard ratio 0.52) will require sample sizes of respectively 333 and 383 for 90% power at the 5% significance level.(37) Allowing for 20% attrition we therefore propose to recruit 479 participants. In the COBALT study 84% completed assessments at 12 months follow up so we will work to achieve this figure or higher.

16.3 STATISTICAL ANALYSIS PLAN

16.3.1 SUMMARY OF BASELINE DATA AND FLOW OF PATIENTS

The analysis and reporting will follow CONSORT and EVEREST guidelines. We will describe proportions for the randomised groups. We will examine the scores on the baseline assessments and the clinical and sociodemographic information as detailed in the baseline assessment. We will prepare a consort flow diagram.

16.3.2 PRIMARY OUTCOME ANALYSIS

We propose to analyse the primary outcome using an exact Cox proportional hazards model (to account for ties), accounting for the depressive symptom score at baseline. We will undertake further supportive analyses including the minimization variables as patient level explanatory variables.

16.3.3 SECONDARY OUTCOME ANALYSIS

The statistical models for each secondary analysis will be chosen depending upon the nature of the outcome variable. A detailed analysis plan for each secondary outcome will be agreed with the Trial Steering Committee prior to database lock.

16.4 ECONOMIC ANALYSIS

We will calculate the mean incremental cost per quality adjusted life year (QALY) gained of antidepressant maintenance compared to placebo over 12 months from an NHS and social care perspective using trial data.

Health care resource use will be collected from GP electronic records and a modified version of the client service receipt inventory (CSRI) and will include information on primary and acute care health service contacts, pharmaceutical prescriptions, mental health community and inpatient service use, social care, employment and welfare payments. Services will be costed using nationally published sources. The cost of antidepressant maintenance will be calculated for the treatment group. For the primary analysis costs will be from the NHS and social care perspective. A secondary analysis from the societal cost perspective will also be conducted.

QALYs will be calculated as the area under the curve using utility scores calculated from the EQ-5D-5L(27), adjusting for baseline differences using regression analysis.

We will conduct one and two-way sensitivity analyses for any assumptions made and sub-group analyses as identified. Missing data will be handled in the same way as the statistical analysis plan, with the primary analysis being an intention to treat analysis and secondary analyses taking into account assumptions about missingness and multiple imputation. Bootstrapping will be used to construct confidence intervals and a cost-effectiveness acceptability curve of the probability that anti-depressant maintenance is cost-effective for a range of values of willingness to pay for a QALY gained.

16.5 SENSITIVITY AND OTHER PLANNED ANALYSES

Our primary analysis will be using all available data following an intention to treat principle to minimize bias, and we will work hard to minimize missing data as we have done in previous trials. We will conduct sensitivity analyses in which various assumptions about the reasons for missing data will be investigated. Multiple imputation will be considered if missing at random assumptions appear to be met in order to examine the likely impact of missing data.

Because of the risk that patients in the control group will stop taking their antidepressant medication, and indeed that patients in the experimental condition may elect to continue taking antidepressants, we will carry out a per protocol analysis. We will also consider a Complier Average Causal Effect (CACE) analysis(26) for the active group that would assume different reasons for non-adherence in the two groups. If there is differential adherence we will also investigate structural mean approaches(27) to take account of this though developments of CACE might also be applicable.(28) We will also consider undertaking an analysis where we condition the effects on the propensity of patients

following the experimental condition. These analyses will also be described in the trial analysis plan when agreed with the Trial Steering Committee.

16.6 RANDOMISATION METHODS

Randomisation will be concealed by using a remote computerised system and the pharmacy will be directly informed of the randomisation outcome. The randomisation will be minimised by the four study centres, the four medications and severity of depressive symptoms at baseline (two categories). The randomisation will be arranged and overseen by Priment. Individual randomisation will allocate to two groups, remaining on the antidepressant or withdrawal from the antidepressant.

16.7 INTERIM ANALYSIS

There are no planned interim analyses except for any requested by the Data Management and Ethics Committee.

16.8 OTHER STATISTICAL CONSIDERATIONS

We will follow the relevant Priment SOPs.

17 NAME OF COMMITTEES INVOLVED IN TRIAL

A trial management group will meet regularly at minuted meetings to review AE logs, recruitment rates and all other aspects of the trial.

There will be a Trial Steering Committee (TSC) whose external members will include two clinicians and a PPI representative. The TSC will advise on the composition of a Data Management Committee (DMC). The DMC will be appointed to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial in accordance with Sponsor SOPs.
Terms of reference, agreed with sponsor, will be in place for each committee.

18 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

19 ETHICS AND REGULATORY REQUIREMENTS

The sponsor will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate

regulatory body (MHRA in UK) and a main research ethics committee, prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

Before the site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee must apply for NHS permission from their Trust Research & Development (R&D) and be granted written permission. It is the responsibility of the Chief Investigator/ Principal Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section 13.11 for reporting urgent safety measures).

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

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

20 MONITORING REQUIREMENT FOR THE TRIAL

A trial-specific monitoring plan will be established, based on the trial risk assessment and agreed by the Sponsor.

The risk assessment and subsequent monitoring plan will be regularly reviewed in case of any changes during the course of the study.

21 FINANCE

The study is funded by the National Institute of Health Research.

22 INSURANCE

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

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

23 PUBLICATION POLICY

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

24 STATEMENT OF COMPLIANCE

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

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