Antidepressants to prevent relapse in depression in older people (ANTLER 75+ Trial) – a double blind randomised controlled trial to evaluate the effectiveness and cost-effectiveness of continuing antidepressants

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Sponsor	University College London (UCL), CCTU
Comprehensive Clinical Trials Unit Trial Adoption Group # Sponsor R&D ID #	CTU/2022/394 149926
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CTA #	20363/0467/001-0001
REC #	24/SC/0247
IRAS #	1009793

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General information

This document was constructed using the Comprehensive Clinical Trials Unit (CCTU) at UCL Protocol template Version 6. It describes the ANTLER 75+ trial, sponsored by UCL and co-ordinated by CCTU.

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

CCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on an adaptation of the Medical Research Council CTU protocol template and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement for protocols of clinical trials [1]. The SPIRIT Statement Explanation and Elaboration document [2] can be referred to, or a member of CCTU Protocol Review Committee can be contacted for further detail about specific items.

Sponsor

University College London (UCL) the trial sponsor and has delegated responsibility for the overall management of the ANTLER 75+ trial to CCTU. Queries relating to sponsorship of this trial should be addressed to the CCTU Director, CCTU at UCL, Institute of Clinical Trials & Methodology, 90 High Holborn 2nd Floor, London, WC1V 6LJ or via the Trial Team at cctu.antler75@ucl.ac.uk.

Funding

This trial is being funded by the National Institute for Health and Care Research, Health Technology Assessment (NIHR HTA), grant number NIHR153131.

Trial Registration

This trial will be registered with the ISRCTN Clinical Trials Register and ClinicalTrials.gov.

Trial Administration

Please direct all queries to cctu.antler75@ucl.ac.uk in the first instance; clinical queries will be passed to the Chief Investigator by the Trial Manager.

Coordinating Unit:
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Structured trial summary

Acronym or short title	ANTLER 75+
Scientific Title	Antidepressants to prevent relapse in depression in older people (ANTLER 75+ Trial) – a double blind randomised controlled trial to evaluate the effectiveness and cost-effectiveness of continuing antidepressants
CCTU Trial Adoption Group #	CTU/2022/394
Sponsor R&D ID #	149926
CTA #	20363/0467/001-0001
REC #	24/SC/0247
IRAS #	1009793
Primary Registry and Trial Identifying Number	ISRCTN26190474
Date of Registration in Primary Registry	22Aug2024
Secondary Identifying Numbers	NIHR HTA grant ref: 153131
Source of Monetary or Material Support	NIHR HTA Researcher-led call Primary Research Grant
Sponsor	University College London (UCL) with sponsor responsibilities delegated to CCTU.
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Countries of Recruitment	England
Health Condition(s) or Problem(s) Studied	Depression in people aged 75 years or older
Intervention(s)	Continuation of antidepressant medication vs tapering and discontinuing antidepressant medication to estimate the effectiveness and cost-effectiveness in preventing depression relapse in people aged 75 and over. Participants will be randomised into 2 groups: **Arm A** (continue with usual antidepressant) and **Arm B** (taper off and discontinue usual antidepressants) **Comparator (Arm A):** Continued treatment with citalopram 20mg, sertraline 50mg or mirtazapine 30mg using identical appearing study IMP. **Intervention (Arm B):** 12 months' discontinuation after tapering in patients receiving treatment with citalopram 20mg, sertraline 50mg or mirtazapine 30mg. Using identical appearing tapering dose of antidepressants and placebos.

	Weeks 1-6 participants will be instructed to take 1 capsule a day from a single bottle: **Arm A:** (continuation of current antidepressant): usual dose **Arm B:** (tapering and discontinuation): half of usual dose **Weeks 7-12** participants will receive 2 bottles of medication and instructed to take one capsule a day from alternate bottles: **Arm A:** usual dose in each bottle **Arm B:** half dose in bottle 1 and placebo in bottle 2 **Weeks 13-52** participants will be instructed to take 1 capsule a day from a single bottle: **Arm A:** usual dose **Arm B:** placebo only
Key Inclusion and Exclusion Criteria	**Inclusion criteria:** 1. Age 75 years or older. 2. Either 2 or more previous episodes of depression treated with antidepressants (any antidepressant for any length of time) OR taking any antidepressant for at least a 2-year period at any time. 3. Currently has been taking either citalopram, sertraline or mirtazapine for at least 9 months, of which the last 3 months should be at the following doses: 20mg citalopram, 50 mg sertraline or 30mg mirtazapine. These 9 months can be included in the 2-year period stated in inclusion 2. 4. Currently not depressed (scores <5 on 15-item Geriatric Depression Scale) and are now well enough to consider stopping the antidepressant. 5. Presence of a Study Partner (a family member, friend or formal caregiver) who sees or speaks to the participant at least once a week and is prepared to support completion of outcome measures that involve recall of the previous 8 weeks. 6. Provides Informed Consent **Exclusion criteria:** 1. Diagnosis of bipolar disorder. 2. Diagnosis of Dementia (although people diagnosed with mild cognitive impairment will be eligible for the trial). 3. Currently prescribed a combination of antidepressants or an antidepressant and a mood stabiliser or an antipsychotic as this

	would indicate individuals with a history of more severe depression who would be at higher risk of relapse of depression. 4. Enrolled in another interventional study. 5. Participated in a CTIMP or a trial of psychological intervention in the preceding 3 months. 6. GP considers the patient would be unsuitable for the trial (for any reason)
Study Type	Phase IV, multicentre, parallel group, double-blind 1:1 individually randomised placebo-controlled clinical trial with an internal pilot.
Study setting	Primary care, with participants recruited from general practices within England and Wales. General Practices will be PIC sites All research activity (consent, screening, randomisation and FU assessments) will occur at Research sites, which will be NHS or University sites. Further sites may be added by way of amendment. All follow-up assessments will be conducted via questionnaires completed at home, or via telephone or videocall should they prefer.
Date of First Enrolment	March 2025
Target Sample Size	430 participants
Trial Duration	51 Months
Primary Outcome(s)	**Primary Outcome:** The first relapse of depression in time-to-event analysis during 52 weeks of follow-up. Relapse will be assessed with an adapted Clinical Interview Schedule – Revised Version[3] to assess symptoms over the previous 8 weeks.
Key Secondary Outcomes	**Secondary Outcomes:** 1. Caseness for depression, defined as a score of five or more on the 15-item Geriatric Depression Scale[4,5] 2. Symptoms of anxiety with the Generalized Anxiety Disorder Assessment 7-item version [6], 3. Physical symptoms of side-effects of antidepressants with the Toronto Side-Effect Scale[7] 4. Antidepressant withdrawal effects of antidepressants with the Discontinuation-Emergent Signs and Symptoms Checklist[8], 5. Quality of life scores for physical and mental health categories on the modified 12-item Short-Form Survey[9], 6. Cognitive functioning with the Montreal Cognitive Assessment[10],

	7. The Pictorial Fit-Frail Scale to quantify participants' levels of fitness-frailty, polypharmacy and multimorbidity[11], 8. Health and social care resource use with the Client Service Receipt Inventory[12], 9. Health-related quality of life with EQ-5D-5L to allow economic evaluation[13].
Nested studies	Nested Qualitative Study

Roles and responsibilities

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

Protocol contributors

Name	Affiliation	Role
Professor Robert Howard	UCL	Chief Investigator
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Nick Freemantle	UCL CCTU	Director of Comprehensive Clinical Trials Unit
Carolyn Chew-Graham	Keele University	Qualitative study Lead
Rebecca Gould	UCL	Professor of Psychological Therapies

Role of trial sponsor and funders

Name	Affiliation	Role
UCL Comprehensive Clinical Trials Unit (UCL CCTU)	UCL	UCL as the trial sponsor has delegated all sponsor duties to UCL CCTU. CCTU will be involved in trial design; collection, management, analysis, and interpretation of data; writing of the report
National Institute for Health and Care Research, Health Technology Assessment (NIHR HTA)	NIHR	Sole funder of the trial

Trial Team

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Dr Mark Grocutt	GP Partner, South Birmingham	Independent Clinician
Professor Karen Bloor	University of York	Independent Health Economist
Ms Lucy Bradshaw	University of Nottingham	Independent Statistician
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Independent Data Monitoring Committee (IDMC)

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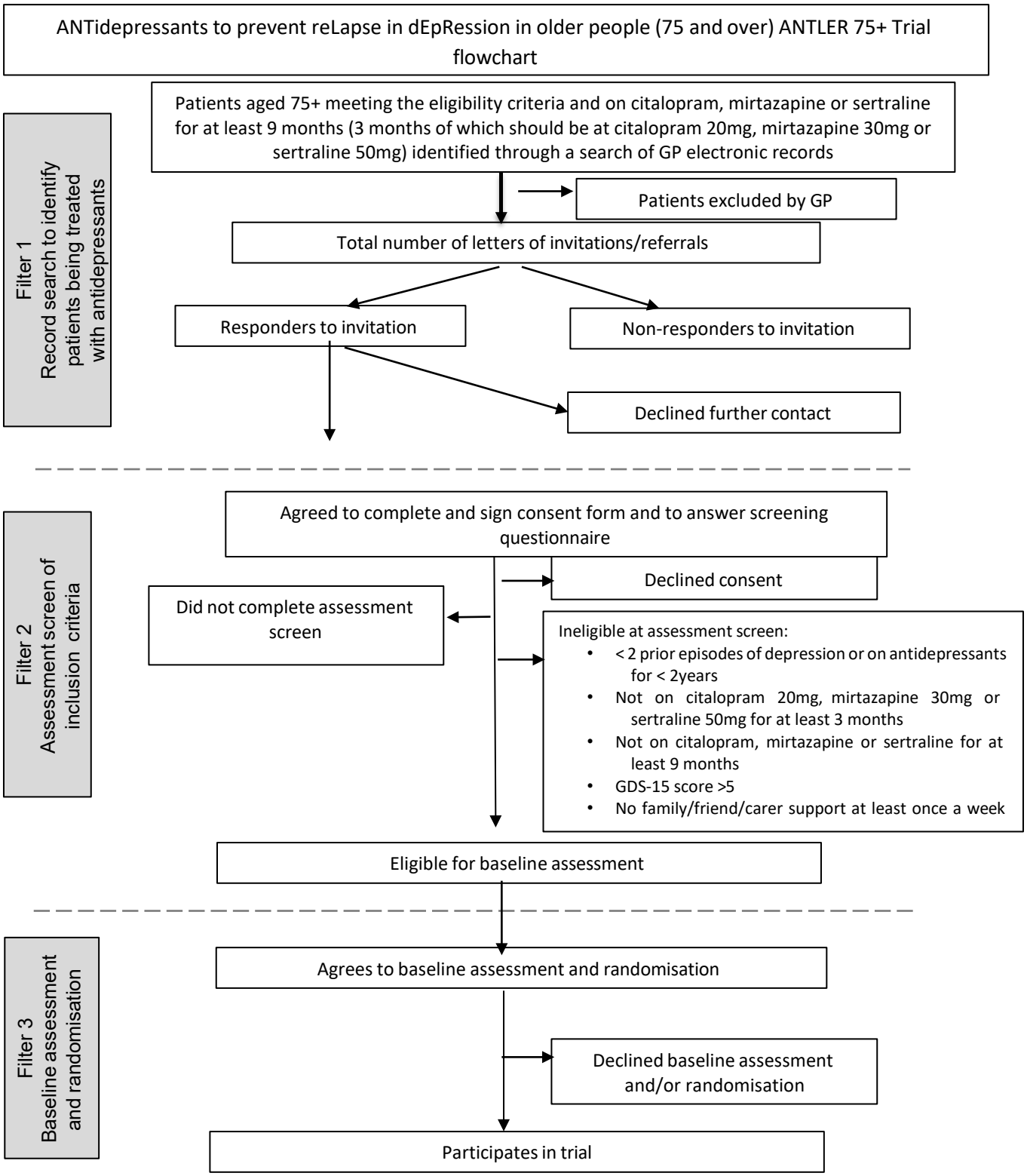
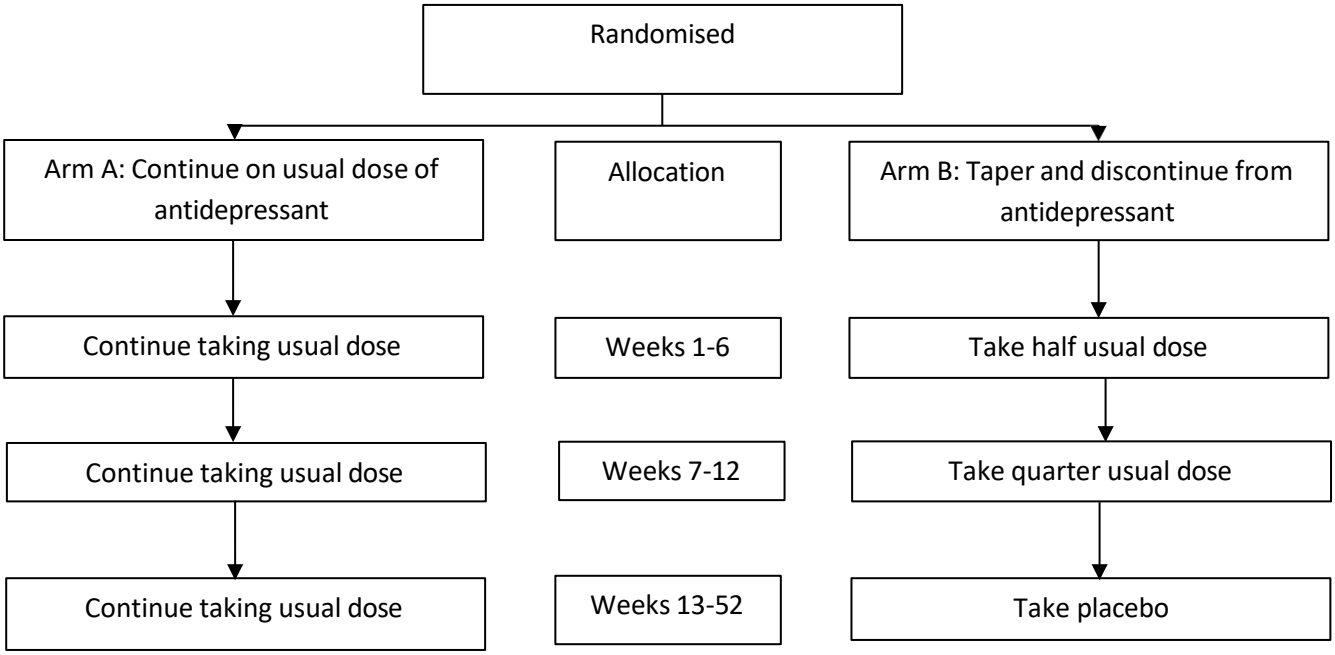
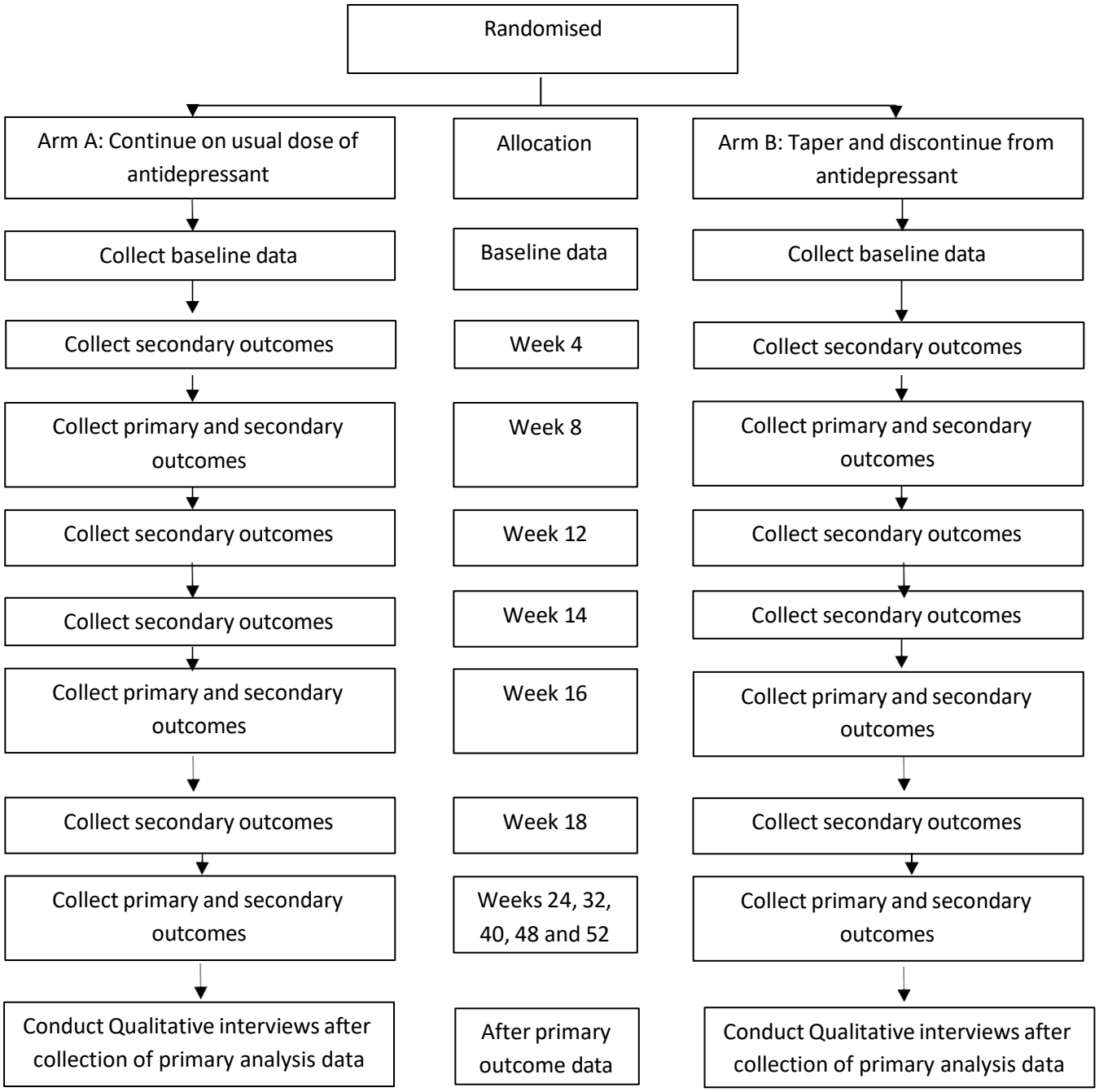
Dr Sarah Alderson	University of Leeds	Chair (Professor of Primary Care and GP)
Mr Dominic Stringer	King's College London	Independent Statistician
Professor Paramjit Gill	University of Warwick	Independent Clinician

Trial Diagrams







Abbreviations

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CBT	Cognitive Behavioural Therapy
CCTU	Comprehensive Clinical Trials Unit at UCL
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CPRD	Clinical Practice Records Datalink
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product
DoP	Division of Psychiatry
DSUR	Development Safety Update Report
EC	Ethics Committee
EDC	Electronic Data Capture
EU	European Union
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GP	General Practitioner
HE	Health Economist
HEAP	Health Economics Analysis Plan
HRA	Health Research Authority
IAPT	Improving Access to Psychological Therapies (now called NHS Talking Therapies)
IB	Investigator Brochure
ICER	Incremental Cost-effectiveness Ratios
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to Treat
MBCT	Mindfulness-Based Cognitive Therapy
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NAE	Notifiable Adverse Event
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NIMP	Non-Investigational Medicinal product
OID	Organisation Information Document
PAG	Patient Advisory Group
PI	Principal Investigator
PIN	Participant Identification Number
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PSF	Pharmacy Site File
QA	Quality Assurance
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
QP	Qualified Person
R&D	Research and Development
REC	Research Ethics Committee
RDN	Research Delivery Network
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor

SOP	Standard Operating Procedure
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCA	Tricyclic Antidepressant
TMF	Trial Master File
TMG	Trial Management Group
ToR	Terms of Reference
TSC	Trial Steering Committee
UCL	University College London
VSE	Value Set tariff for England
WTP	Willingness to Pay
WoCBP	Women of Childbearing Potential

Glossary

Term	Definition
Citalopram	Antidepressant medication to treat symptoms of depression
Mirtazapine	Antidepressant medication to treat symptoms of depression
Sertraline	Antidepressant medication to treat symptoms of depression
Depression	Low mood or loss of pleasure or interest in activities for long periods of time
Serotonin noradrenaline reuptake inhibitors	A class of drugs that are commonly used to people with treat anxiety and/or depression
Selective serotonin reuptake inhibitors	A class of drugs that are typically used to treat people with anxiety and/or depression
Randomisation Groups	The two randomisation groups are: Arm A: Participants are randomised to continue on their usual dose of antidepressant Arm B: Participants are randomised to taper off and then discontinue their usual dose of antidepressant

1 Background

1.1 Rationale

There is little evidence to guide antidepressant prescribing in older people once they have recovered from depression but continue to take maintenance antidepressants to prevent relapse. Antidepressants are commonly prescribed in older people but can have significant side-effects and contribute to polypharmacy. The risks and benefits of continued prescription, in particular effects on preventing depression relapse, are not established. This trial has been designed to answer the question**:** Should older (≥75 years old) adults continue to take antidepressants for a further 12 months after recovery from depression?

Depression is the most burdensome mental health disorder in older people. 15% of people aged >65 years have case-level (that which a psychiatrist would consider in need of treatment) depression[14]. The recent Lancet Commission on depression[15] highlighted a peak of depression in later life associated with significant public health burden and a different pattern of symptoms from younger adults. In addition to causes of depression that apply at all ages, neuropsychological impairments such as executive dysfunction[16] and physical illnesses such as cardiovascular disease, diabetes and stroke increase risk[17]. Depressive symptoms also worsen outcomes in physical health conditions[18]. Older people are under-represented within psychological therapy services such as IAPT (improving access to psychological therapies) but are more vulnerable to the adverse effects of antidepressants, particularly cognitive side-effects and effects on cardiac rhythm and increased risk of falls[19]. Despite this, antidepressants are prescribed for longer periods in older people, so most of the overall increase in antidepressant prescription has come from increased duration of treatment[20].

There is little evidence to guide antidepressant prescribing in older people once symptoms of depression have improved, although it is known that relapse of depression is common and that 50% of patients will be depressed at 2-year follow-up[21]. The latest National Institute for Health and Care Excellence (NICE) Depression Guideline emphasises the lack of evidence on treatments for chronic depression in older people and the importance of awareness of withdrawal symptoms if treatment is stopped abruptly. A 2016 Cochrane Review, *Continuation and maintenance treatments for depression in older people* authored by PW[22], identified 3 trials with 247 participants in total comparing depression recurrence at 12 months in older (>60 or 65 years) people in remission from depression and randomised to receive antidepressant or placebo. Two of the trials had involved a tricyclic and the third a selective serotonin reuptake inhibitor (SSRI) antidepressant. The relative risk of relapse with antidepressant continuation compared to placebo was 0.67 (95% CI 0.55-0.82). However, the review authors rated the evidence from all three trials as low-quality owing to their imprecision, lack of clarity about allocation and blinding in two of the trials and unavailability of study protocols for any of them. The review concluded: *The long-term benefits and harm of continuing antidepressant medication in the prevention of recurrence of depression in older people are not clear and no firm treatment recommendations can be made on the basis of this review. Continuing antidepressant medication for 12 months appears to be helpful with no increased harms; however, this was based on only three small studies, relatively few participants, use of a range of antidepressant classes and clinically heterogeneous populations. Comparisons at other time points did not reach statistical significance. Further, larger trials are required to clarify any benefits of antidepressant and psychological treatments. These trials should include more people aged over 75 and people with other problems typical of people treated in routine clinical*

services, such as long-term physical illness and mild memory problems. No relevant further trials in older people have been identified since the 2016 Cochrane Review was published.

The recent HTA ANTLER[23] trial showed that patients aged 18-74, treated with an antidepressant in primary care, with a history of at least two depressive episodes and/or receiving treatment for at least two years and randomised to continue their antidepressant or taper and discontinue with matching placebo, experienced a relapse of depression symptoms in 39% of the maintenance and 56% of the placebo group (HR 2.06 95% CI 1.56-2.70)[23]. It might be reasonable to question, after the conduct of ANTLER, whether a trial involving participants aged ≥75 years is necessary to guide the decisions of patients and their prescribing doctors. Participants in ANTLER-75+ would be expected to have systematically different outcomes from younger adults and this needs direct investigation for the following reasons. (1) *Limitations of extrapolating ANTLER data to over-74s:* The maximum age of ANTLER participants was 74 and our analyses of the effects of increasing age on the benefits of treatment continuation in the trial showed reduction in relapse was less in those aged 65-74 years (HR 1.61 95% CI 0.93-2.79), though the interaction with age was non-significant (0.69 95% CI 0.37-1.27). This is an indication of continuing uncertainty about the effectiveness of long-term maintenance antidepressants in those ≥75 years. (2) *In the ≥75s, age-associated and ageing-disease related factors have impact on depression outcomes and treatment response that are significantly different from younger people:* Physical illness burden[24,25] is associated with a worse outcome in depression and most ≥75s with depression have at least one co-morbid physical illness diagnosis. (3) *Cerebrovascular changes common in ≥75s both predispose to depression and reduce treatment effects:* Whilst most older adults have some evidence of vascular brain lesions on neuroimaging, such lesions are much more frequent (OR 2.15 (1.5-3.1)) and severe (Cohen's d 0.6 (0.3-0.9)) in older people with depression and especially relevant to >75s with depression[26] and are associated with poor outcomes: worse response to antidepressants[27], increased relapse rates[28,29], and persistent cognitive impairment[30], which is itself associated with higher relapse rates[31]. (4) *50% of over-75s take >5 regular medicines and are at greater risk of antidepressant side-effects and drug-drug interactions*. The pressure on GPs and patients to deprescribe and any cost-benefit analysis for continuing antidepressants is different than with younger patients.

Recent NICE Guideline, *Depression in adults: treatment and management NG222 29 June 2022*[32], contains specific advice on stopping antidepressant medication. Patients should be advised that it is usually necessary to reduce and stop treatment slowly, in stages over time and that most people can stop antidepressants successfully (1.4.13). Patients should be advised that they may experience withdrawal symptoms if they stop treatment abruptly or miss doses (1.4.14), that it should be explained that there is a range of possible withdrawal symptoms and length of experience of difficulties (1.4.15) and that patients may need support to manage their fears and concerns about withdrawal (1.4.16). In 1.4.17, the guidance suggests *slowly reduce the dose to zero in a stepwise fashion, at each step prescribing a proportion of the previous dose (for example 50% of the previous dose).* The guidance advises that prescribers recognise that withdrawal may take weeks or months to be completed successfully and that paroxetine and venlafaxine are the drugs most likely to be associated with withdrawal phenomena: *Monitor and review people taking antidepressant medication while their dose is being reduced, both for withdrawal symptoms and the return of symptoms of depression. Base the frequency of monitoring on the person's clinical and support needs* (1.4.18).

The NICE Guideline Committee concluded: *there was good evidence that SSRIs, SNRIs and TCAs, group CBT and MBCT were effective for relapse prevention and were, on average, cost-effective treatments for people at high risk of relapse, with data for treatment periods of up to 2 years.*

https://www.nice.org.uk/guidance/ng222/chapter/Recommendations#preventing-relapse).

However, the evidence review that underpinned their relapse prevention recommendations, for the comparisons of SSRIs v. pill placebo, contains: *Relapse: very low quality evidence from 4-7 RCTs (n=825-1653) shows a clinically important and statistically significant benefit of an SSRI relative to pill placebo at 16-34, 44-48 and 52-87 weeks post-randomisation (https://www.nice.org.uk/guidance/ng222/evidence/c-preventing-relapse-pdf-11121004416).* NICE guidance on prevention of relapse after successful treatment of depression contains the following: *Discuss with people the potential risks of continuing with antidepressants long term and how these balance against the risks of depression relapse. These include possible side-effects, such as an increased bleeding risk or long-term effects on sexual function and difficulty stopping antidepressants* (1.8.3). If patients decide to continue with antidepressants for the prevention of relapse of depression, their prescription should be reviewed at least every 6 months (1.8.11).

The Guideline Committee also made a specific recommendation for research, which is relevant to this proposal. *What is the incidence and severity of withdrawal symptoms for antidepressant medication?*

1.1.1 Explanation for choice of comparators

We are comparing citalopram, mirtazapine and sertraline with identical placebo. All tablets will be over-encapsulated to maintain the blind.

- Mirtazapine 30mg
- Mirtazapine 15mg
- Placebo to match mirtazapine
- Citalopram 20mg
- Citalopram 10mg
- Placebo to match citalopram
- Sertraline 50mg
- Sertraline 25mg
- Placebo to match sertraline

Strengths are blinded to one another of the same medicine; the 2 different strengths of each medicine and their respective placebos will look identical.

This is so we can investigate the effectiveness and cost-effectiveness of continuing or tapering and stopping antidepressant medication.

1.2 Objectives

The aim of this trial is to estimate the effectiveness and cost-effectiveness of continuing antidepressant medication for one year, compared to discontinuation, in preventing depression relapse in UK primary care in people aged 75 and older who have had two or more episodes of depression or have been taking antidepressants for at least 2 years, have taken

citalopram, mirtazapine or sertraline for at least nine months and are now well enough to consider stopping the antidepressant. We will compare maintenance antidepressants with discontinuation following a taper period.

The objectives are:

1. To estimate the difference in time to depressive episode between randomised groups.
2. To estimate the difference in depression and anxiety symptoms between randomised groups.
3. To estimate the difference in adverse effects of antidepressants by randomised groups.
4. To determine the difference in withdrawal symptoms between randomised groups.
5. To estimate the difference in health-related quality of life between randomised groups.
6. To compare the relative cost-effectiveness of the two arms of the trial.
7. To understand older adults' decision-making about antidepressants, their experiences of reducing and stopping antidepressants and withdrawal symptoms.
8. To understand the perspectives of general practitioners about the diagnosis and management of depression in older adults, prescribing, monitoring and deprescribing antidepressants.

1.3 Trial Design

ANTLER 75+ is a double-blind individually randomised parallel group-controlled trial of continuing versus tapering and discontinuing antidepressants in 430 people aged 75 years and over who have had two or more episodes of depression or taken antidepressants for at least two years at any time, have taken antidepressants for at least nine months and are now well enough to consider stopping their antidepressant. There is a 12-month follow-up period.

At the end of the 12 months, there will be a nested qualitative study – including interviews with trial participants and general practitioners.

1.4 Benefit Risk Assessment

Citalopram, Mirtazapine and Sertraline are all licenced for use in people with depression. Their adverse effects are well described as they are commonly used clinically. Participants in this trial will have already been taking one of these antidepressant drugs for at least 9 months prior to entering the trial. Therefore, we are expecting any safety issues that would emerge would have been dealt with at that stage. Adverse effects associated with taking the IMP can be seen in Table 1 (Summary of risks, frequencies and mitigations of the IMP). This information has been taken from the Summary of Product Characteristics (SmPC) for each antidepressant. Participants randomised to Arm A (continue with their current anti-depressant drug and dose) will continue to be monitored as per their usual care and so any potential risk associated with the IMP is considered to be low and no greater than standard medical care.

The trial is categorised as Type A according to MHRA guidance; the potential risk associated with the design of the study is no higher than that of standard medical care. Participants in Arm B will be tapered off their drug over a 12-week period, in line with NICE Guidelines, prior to stopping completely.

The risks of tapering and stopping medication are as follows:

1) Risk of relapse of depression

There is a possibility that participants will relapse in both arms of the trial. This risk will be explained to participants. Participants will be reviewed regularly by trial researchers throughout the trial via regular phone calls and completion of questionnaires. If the participant has developed a concern that they might be experiencing a relapse, or the researchers or PI are concerned, they will be told to seek medical advice from their GP or usual clinician.

2) Risk of self-harm

People with depression have an increased risk of self-harm and suicide. We will therefore have a Suicide Ideation Management Plan in place and staff will be trained to follow this procedure. There will be a separate risk protocol for use in the qualitative study undertaken by the team at Keele at the end of the study.

3) Risk of withdrawal symptoms

Risk of withdrawal symptoms are reduced due to the gradual tapering off from the antidepressant. In weeks 1-6, participants in Arm B will receive half their normal dose of antidepressant. This will be halved again in weeks 7-12, before stopping at week 12 and replaced fully with placebo until the end of the trial at week 52.

Withdrawal symptoms will be monitored using the Discontinuation-Emergent Signs and Symptoms (DESS) Checklist[8].

Withdrawal symptoms from citalopram, mirtazapine and sertraline are listed below, although these are generally related to sudden stopping. Tapering off slowly, in line with NICE guidelines, as is the case in this trial, should reduce the risk of these occurring.

Withdrawal symptoms (as per SmPC), seen on discontinuation of citalopram, include dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability and visual disturbances. Generally, these events are mild to moderate, non-serious and are self-limiting, however in some patients they may be severe and/or prolonged.

Although mirtazapine is not addictive, abrupt termination of treatment may sometimes result in withdrawal symptoms. The majority of withdrawal reactions (as per SmPC) are mild and self-limiting. These include dizziness, agitation, anxiety, headache and nausea.

Withdrawal symptoms for patients taking sertraline (as per SmPC), are more common, if discontinuation is abrupt. Withdrawal symptoms include dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity.

If serious withdrawal symptoms occur, then the PI and GP will discuss what appropriate action should be taken.

Other risks include:

4) Risk associated with IMP distribution

IMPs will be dispensed from a central pharmacy via Royal Mail to the participants' home addresses. Recorded delivery will be used to ensure deliveries can be tracked and confirmed as received. IMP will be sent out well in advance of participants running out of IMP to ensure there is no period when they are without medication. Patient identifiable data will be processed and stored by the pharmacy in line with the Data Protection Act.

Research sites will contact participants to ensure that their IMP has arrived. If not, the central pharmacy will be contacted and further IMP will be dispensed, if appropriate.

A Medication Participant Information Sheet will be enclosed with each IMP delivery detailing how and when to take the IMP. A checklist will be enclosed for the participants to tick off each time they take the IMP to ensure they do not miss a dose or take a capsule from the wrong bottle. This is particularly important for weeks 7-12, where the IMP will be supplied in 2 bottles and the participant must alternate between the bottles each day. So, on day 1, the participant will take one capsule from Bottle 1, on day 2, the participant will take one capsule from Bottle 2, on day 3, the participant will take one capsule from Bottle 1 and so on. The bottles will be clearly labelled with different coloured labels on the 2 bottles.

The follow-up schedule of this trial means that participants will be monitored regularly, and researchers will confirm at each assessment that the participant has received and been taking their trial medication as instructed. Researchers can also ask the participant to confirm how many capsules are left in the bottle.

A trial information/ contact card will also be provided to participants with numbers to call in an emergency, and we will have an emergency unblinding system so that we can alert people to the content of the study medication should an emergency arise.

Further details can be found in the IMP Management Plan.

Table 1. Summary of the risks, frequencies, and mitigations of the IMPs

Name of IMP(s)	Potential risk	Risk Frequency	Risk Management
Citalopram	1. Thrombocytopenia 2. Hypersensitivity, anaphylactic reaction 3. Hyperprolactinaemia, inappropriate ADH secretion 4. Hypokalaemia 5. Panic attack, bruxism, restlessness, suicidal ideation, suicidal behaviour 6. Convulsions, serotonin syndrome, extrapyramidal disorder, akathisia, movement disorder 7. Visual disturbance 8. Electrocardiogram QT-prolongation, ventricular arrhythmia including torsade de pointes 9. Orthostatic hypotension 10. Epistaxis 11. Gastrointestinal haemorrhage (including rectal haemorrhage) 12. Abnormal Liver function tests 13. Ecchymosis, angioedemas 14. Female: Metrorrhagia, postpartum haemorrhage; reduced libido 15. Male: priapism, galactorrhoea, reduced libido	Not known	The participant has been on this IMP for at least 9 months and any safety concerns are likely to have emerged by this stage. Participants will remain under the care of their GP throughout the trial and will be advised to continue seeing their GP for ongoing health problems.
Citalopram	1. Sleep disorders 2. Somnolence, insomnia, headache 3. Dry mouth, nausea 4. Sweating increased 5. Asthena	Very Common (≥1/10)	The participant has been on this IMP for at least 9 months and any safety concerns are likely to have emerged by this stage. Participants will remain under the care of their GP throughout the trial and will be advised to continue seeing their GP for ongoing health problems.

Name of IMP(s)	Potential risk	Risk Frequency	Risk Management
Citalopram	1. Appetite decreased, weight decreased 2. Agitation, libido decreased, anxiety, nervousness, confusional state, abnormal orgasm (female), abnormal dreams 3. Tremor, paraesthesia, dizziness, disturbance in attention, migraine, amnesia 4. Tinnitus 5. Palpitations 6. Yawning, rhinitis 7. Diarrhoea, vomiting, constipation, dyspepsia, abdominal pain, flatulence, salivary hypersecretion 8. Pruritus 9. Myalgia, arthralgia 10. Impotence, ejaculation disorder, ejaculation failure 11. Fatigue	Common (≥1/100 to <1/10)	The participant has been on this IMP for at least 9 months and any safety concerns are likely to have emerged by this stage. Participants will remain under the care of their GP throughout the trial and will be advised to continue seeing their GP for ongoing health problems.
Citalopram	1. Increased appetite, weight increased 2. Aggression, depersonalisation, hallucination, mania, increased libido euphoria 3. Syncope 4. Mydriasis 5. Bradycardia, tachycardia 6. Urticaria, alopecia, rash, purpura, photosensitivity reaction 7. Urinary retention 8. Female: menorrhagia 9. Oedema	Uncommon (≥1/1,000 to <1/100)	The participant has been on this IMP for at least 9 months and any safety concerns are likely to have emerged by this stage. Participants will remain under the care of their GP throughout the trial and will be advised to continue seeing their GP for ongoing health problems.
Citalopram	1. Hyponatremia 2. Convulsive grand mal, dyskinesia, taste disturbance	Rare	The participant has been on this IMP for at least 9 months and any safety concerns are likely to have emerged by this stage. Participants will remain

	3. Haemorrhage 4. Coughing 5. Hepatitis 6. Pyrexia, malaise		under the care of their GP throughout the trial and will be advised to continue seeing their GP for ongoing health problems.

Name of IMP(s)	**Potential risk**	**Risk Frequency**	**Risk Management**
Mirtazapine	1. Bone marrow depression (granulocytopenia, agranulocytosis, aplastic anaemia thrombocytopenia), Eosinophilia 2. Inappropriate antidiuretic hormone secretion, hyperprolactinemia (and related symptoms e.g. galactorrhoea and gynecomastia) 3. Hyponatraemia 4. Suicidal ideation, suicidal behaviour, somnambulism 5. Convulsions (insults), serotonin syndrome, oral paraesthesia, dysarthria 6. Mouth oedema, increased salivation 7. Stevens-Johnson syndrome, dermatitis bullous, erythema multiforme, toxic epidermal necrolysis 8. Drug reaction with eosinophilia and systemic symptoms (Dress) 9. Rhabdomyolysis 10. Urinary retention 11. Priapism 12. Generalised oedema, localised oedema 13. Increased Creatinine Kinase	Not known	The participant has been on this IMP for at least 9 months and any safety concerns are likely to have emerged by this stage. Participants will remain under the care of their GP throughout the trial and will be advised to continue seeing their GP for ongoing health problems.

Mirtazapine	1. Increase in appetite, weight increase 2. Somnolence, sedation, headache 3. Dry mouth	Very Common (≥1/10)	The participant has been on this IMP for at least 9 months and any safety concerns are likely to have emerged by this stage. Participants will remain under the care of their GP throughout the trial and will be advised to continue seeing their GP for ongoing health problems.

Name of IMP(s)	**Potential risk**	**Risk Frequency**	**Risk Management**
Mirtazapine	1. Abnormal dreams, confusion, anxiety, insomnia 2. Lethargy, dizziness, tremor, amnesia 3. Orthostatic hypotension 4. Constipation, nausea, diarrhoea, vomiting 5. Exanthema 6. Arthralgia, myalgia, back pain 7. Oedema peripheral, fatigue	Common (≥1/100 to <1/10)	The participant has been on this IMP for at least 9 months and any safety concerns are likely to have emerged by this stage. Participants will remain under the care of their GP throughout the trial and will be advised to continue seeing their GP for ongoing health problems.
Mirtazapine	1. Nightmares, mania, agitation, hallucinations, psychomotor restlessness (inc. akathisia, hyperkinesia) 2. Paraesthesia, restless legs, syncope 3. Hypotension 4. Oral hypoesthesia	Uncommon (≥1/1,000 to <1/100)	The participant has been on this IMP for at least 9 months and any safety concerns are likely to have emerged by this stage. Participants will remain under the care of their GP throughout the trial and will be advised to continue seeing their GP for ongoing health problems.
Mirtazapine	1. Aggression 2. Myoclonus 3. Pancreatitis 4. Elevation in serum transaminase	Rare (≥1/10,000 to <1/1,000)	The participant has been on this IMP for at least 9 months and any safety concerns are likely to have emerged by this stage. Participants will remain under the care of their GP throughout the trial and will be advised to continue seeing their GP for ongoing health problems.

Sertraline	1. Maculopathy 2. Colitis microscopic 3. Trismus 4. Postpartum haemorrhage	Not known	The participant has been on this IMP for at least 9 months and any safety concerns are likely to have emerged by this stage. Participants will remain under the care of their GP throughout the trial and will be advised to continue seeing their GP for ongoing health problems.

Name of IMP(s)	**Potential risk**	**Risk Frequency**	**Risk Management**
Sertraline	1. Insomnia 2. Dizziness, headache, somnolence 3. Nausea, diarrhoea, dry mouth 4. Ejaculation failure 5. Fatigue	Very Common (≥1/10)	The participant has been on this IMP for at least 9 months and any safety concerns are likely to have emerged by this stage. Participants will remain under the care of their GP throughout the trial and will be advised to continue seeing their GP for ongoing health problems.
Sertraline	1. Upper respiratory tract infection, pharyngitis, rhinitis 2. Decreased appetite, increased appetite 3. Anxiety, depression, agitation, libido decreased, nervousness, depersonalisation, nightmare, bruxism 4. Tremor, movement disorders (including extrapyramidal symptoms such as hyperkinesia, hypertonia, dystonia, teeth grinding or gait abnormalities), paraesthesia, hypertonia, disturbance in attention, dysgeusia 5. Visual disturbance 6. Tinnitus 7. Palpitation 8. Hot flush 9. Yawning	Common (≥1/100 to <1/10)	The participant has been on this IMP for at least 9 months and any safety concerns are likely to have emerged by this stage. Participants will remain under the care of their GP throughout the trial and will be advised to continue seeing their GP for ongoing health problems.

	10. Dyspepsia, constipation, abdominal pain, vomiting, flatulence 11. Hyperhidrosis, rash 12. Back pain, myalgia 13. Menstruation irregular, erectile dysfunction 14. Malaise, chest pain, asthenia, pyrexia 15. Weight increase 16. Injury		
Name of IMP(s)	**Potential risk**	**Risk Frequency**	**Risk Management**
Sertraline	1. Gastroenteritis, otitis media 2. Neoplasm 3. Hypersensitivity, seasonal allergy 4. Hypothyroidism 5. Suicidal ideation/behaviour, psychotic disorder, thinking abnormal apathy, hallucination, aggression, euphoric mood, paranoia 6. Amnesia, hypoaesthesia, muscle contractions involuntary, syncope, hyperkinesia, migraine, convulsion, dizziness postural, coordination abnormal, speech disorder 7. Mydriasis 8. Ear pain 9. Tachycardia, cardiac disorder 10. Abnormal bleeding (such as gastrointestinal bleeding), hypertension, flushing, haematuria 11. Dyspnoea, epistaxis, bronchospasm 12. Melaena, tooth disorder, oesophagitis, glossitis, haemorrhoids, salivary hypersecretion, dysphagia, eructation, tongue disorder 13. Periorbital oedema, urticaria, alopecia, pruritus, purpura, dermatitis, dry skin, face oedema, cold sweat	Uncommon (≥1/1,000 to <1/100)	The participant has been on this IMP for at least 9 months and any safety concerns are likely to have emerged by this stage. Participants will remain under the care of their GP throughout the trial and will be advised to continue seeing their GP for ongoing health problems.

	14. Osteoarthritis, muscle twitching, muscle cramps, muscular weakness 15. Pollakiuria, micturition disorder, urinary retention, urinary incontinence, polyuria, nocturia 16. Sexual dysfunction, menorrhagia, vaginal haemorrhage, female sexual dysfunction 17. Oedema peripheral, chills, gait disturbance, thirst 18. Alanine aminotransferase increased, aspartate aminotransferase increased, 19. weight decrease		
Name of IMP(s)	**Potential risk**	**Risk Frequency**	**Risk Management**
Sertraline	1. Diverticulitis 2. Lymphadenopathy, thrombocytopenia, leukopenia 3. Anaphylactoid reaction 4. Hyperprolactinaemia, inappropriate antidiuretic hormone secretion 5. Hypercholesterolemia, diabetes mellitus, hypoglycaemia, hyperglycaemia, hyponatraemia 6. conversion disorder, paroniria, drug dependence, sleep walking, premature ejaculation 7. coma, akathisia, dyskinesia, hyperaesthesia, cerebrovascular spasm (including reversible cerebral vasoconstriction syndrome and Call-Fleming syndrome), psychomotor restlessness, sensory disturbance, choreoathetosis, also reported were signs and symptoms associated with serotonin syndrome or neuroleptic malignant syndrome: in some cases associated with concomitant use of serotonergic drugs that included agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia	Rare (≥1/10,000 to <1/1,000)	The participant has been on this IMP for at least 9 months and any safety concerns are likely to have emerged by this stage. Participants will remain under the care of their GP throughout the trial and will be advised to continue seeing their GP for ongoing health problems.

	8. scotoma, glaucoma, diplopia, photophobia, hyphaemia, pupils unequal, vision abnormal, lacrimal disorder 9. myocardial infarction, Torsade de Pointes, bradycardia, QTc prolongation 10. peripheral ischaemia 11. hyperventilation, laryngospasm, dysphonia, stridor, hypoventilation, hiccups hyperventilation, laryngospasm, dysphonia, stridor, hypoventilation, hiccups 12. Mouth ulceration, pancreatitis, haematochezia, tongue ulceration, stomatitis 13. interstitial lung disease,		
Name of IMP(s)	**Potential risk**	**Risk Frequency**	**Risk Management**
Sertraline	14. hepatic function abnormal, serious liver events (including hepatitis, jaundice and hepatic failure) 15. rare reports of severe cutaneous adverse reactions (SCAR): e.g. Steven-Johnson syndrome and epidermal necrolysis, skin reaction, photosensitivity, angioedema, hair texture abnormal, skin odour abnormal, dermatitis bullous, rash follicular 16. Rhabdomyolysis, bone disorder 17. Urinary hesitation, oliguria 18. Galactorrhoea, atrophic vulvovaginitis, genital discharge, balanoposthitis, gynaecomastia, priapism 19. Hernia, drug tolerance decreased 20. Blood cholesterol increased, abnormal clinical laboratory results, semen abnormal, altered platelet function 21. Vasodilation procedure	Rare (continued)	

2 Selection of Sites/Investigators

2.1 Site Selection

The trial sponsor (UCL) has overall responsibility for site and investigator selection and has delegated this role to CCTU.

2.1.1 Study Setting

The trial will be based in UK Primary Care in England, with participants being selected from general practices across England and Wales.

General practices will be invited to participate via their NIHR Research Delivery Network (RRDN). GP Practices which are interested in participating will be asked to sign a PIC mNCA and will be responsible for carrying out eligibility screens (using pre-defined search terms and/or local practice methods). Practices will then check these lists to ensure it is appropriate to send mailouts to each participant. Following this, they will upload the list of potentially eligible participants to DocMail who will send invitation packs out to patients. Patients interested in the trial will contact their local research site via reply slip, telephone call or email. If patients who receive the information pack wish to tell the local research site they do not want to participate or be contacted, they can also do this. GPs will also be able to directly refer to the study after a consultation with a potential participant and can give the invitation letter, PIS and ICF at routine appointments

Research sites within these regions will perform all research activity from consent onwardsResearch sites will be a mix of NHS institutions and Universities.

Whilst in the trial, research sites will carry out all trial related prescribing and follow-up visits, however participants and GPs will be informed that the participant will remain under the care of their GP and primary care team throughout the study for their usual healthcare needs.

- Universities and NHS organisations will be “Research sites”
- General Practices will be PIC sites
- RRDNs will help co-ordinate this research alongside GP practices.

Trial documentation and IMP will be sent to the participants’ home address. All follow-up assessments will be via questionnaires sent out to the participants to complete at home or conducted over the telephone or via video link for example Zoom or MS Teams with the local research site team.

2.1.2 Site/Investigator Eligibility Criteria

Recruitment will be completed from general practices in England and Wales.

To participate in the ANTLER 75+ trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the Sponsor and ANTLER 75+ Trial Management Group (TMG) and that are defined below.

Eligibility criteria:

1. A named clinician is willing and appropriate to take Principal Investigator responsibility,

2. Suitably trained staff are available to recruit participants, collect and enter data. If this is not the case locally, there is an option for a central Research Team, based at UCL DoP to carry out these tasks on behalf of other "sites".

2.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The Principal Investigator(s) must be willing to sign a Principal Investigator Declaration Schedule 6 of the Clinical Trial Site Agreement, to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications (provide an up-to-date CV), familiarity with the appropriate use of any investigational products and agreement to comply with the principles of GCP. The PI must agree to permit monitoring and audit as necessary at the site, and to maintain documented evidence of staff who have been delegated significant trial related duties.

The trial is registered with the NIHR Associate PI scheme and Associate PIs may participant in line with this scheme.

2.1.2.2 Resourcing at sites

- The investigator should have available an adequate number of qualified staff and suitable facilities for the anticipated duration of the trial in order to conduct the trial properly and safely.
- The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational medicinal product(s) / Intervention, and their trial-related duties and functions.
- The site should have sufficient data management resources to allow prompt data return to the CCTU (refer to the Site Management Plans).
- The trial is adopted onto the NIHR portfolio so is eligible for NIHR Research Team support at sites to undertake follow-up visits / coordinate the trial for site related tasks for participants in their area.
- A trial funded researcher will be employed at the lead site (UCL- Division of Psychiatry- DoP) to undertake trial related tasks for UCL but also for other trial sites should they lacks capacity.
- The CI/ PI for UCL may also act as PI for another site if there is no PI available.
- All researchers working on the trial will be adequately trained on this protocol and complete training and delegation logs appropriately.

2.2 Site approval and activation

Site training will be performed prior to activation and will include all processes for the trial including but not limited to protocol training, data management procedures, procedures for prescribing investigational medicinal products, adverse event reporting procedures, and expectations for monitoring. A log of Site Initiation Visit (SIV) attendees will be kept in the Investigator Site File (ISF) as a record of participants present. The SIV may occur in person or via videoconference.

For each site, there will be general practices who will identify eligible patients and upload patient lists onto the DocMail system, from which the invitation letters, Participant Information Sheet (PIS) and Informed Consent Form (ICF) will be sent out. This may also be done by a RRDN department if appropriate (e.g North Central London Research Network (NoCLoR). A PIC mNCAwill be signed with participating GP practices.

The Trial Manager or delegate will notify the PI in writing of the plans for site activation. Sites will not be permitted to recruit any patients (via GP practices) until a letter for activation has been issued. On receipt of the signed Clinical Trial Site Agreement (mNCA) (including the signed PI Declaration), completed delegation of responsibilities log and staff contact details, the Trial Manager or delegate will complete the green light process and issue written confirmation of site activation to the site PI.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and, by the regulatory authority(ies) (as appropriate), and which was given favourable opinion by the Ethics Committee (EC). The PI or delegate must document and explain any deviation from the approved protocol and communicate this to the trial team at CCTU.

A list of activated sites may be obtained from the Trial Manager.

2.3 Regional Research Delivery Networks (RRDNs)

RRDNs will help the trial team locate and activate GP practices. In some cases (for example NOCLOR) RRDNs will help GP practices with searches and mailouts. 3 Selection of Participants

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

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

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

3.1 Participant Inclusion Criteria

(1) Aged 75 years or older;
(2) Either 2 or more previous episodes of depression treated with antidepressants (any antidepressant for any length of time)
or
taking any antidepressant for at least a 2 year period at any time.
(3) Currently has been taking either citalopram, sertraline or mirtazapine for at least 9 months, of which the last 3 months should be at the following doses: 20mg citalopram, 50 mg sertraline or 30mg mirtazapine. These 9 months can be included in the 2-year period stated in inclusion 2.
(4) Currently not depressed (scores <5 on Geriatric Depression Scale-15) and are now well enough to consider stopping the antidepressant.
(5) Presence of Study Partner (a family member, friend or formal caregiver) who sees the participant at least once per week face-to-face or by video or speaks by telephone and

is prepared to support completion of outcome measures that involve recall of the previous eight weeks.
(6) Provides Informed Consent

3.2 Participant Exclusion Criteria

(1) Diagnosis of Bipolar Disorder;
(2) Diagnosis of Dementia (although people with mild cognitive impairment will be eligible for the trial);
(3) Currently prescribed a combination of antidepressants or an antidepressant and a mood stabiliser or an antipsychotic as this would indicate individuals with a history of more severe depression who would be at higher risk of relapse of depression;
(4) Participation in another interventional study.
(5) Participated in a CTIMP or a trial of psychological intervention in the preceding 3 months.
(6) GP considers the patient would be unsuitable for the trial (for any reason)

3.2.1 Women of Childbearing Potential & Male Participants

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.

Participants who are aged 75 years or older only, will be entered into this trial. No WOCBP will therefore participate. Therefore, **pregnancy tests are not required and no pregnancy monitoring will be required.**

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy. In clinical practice, fertile male patients with partners who are WOCBP are not required to use contraception to prevent pregnancy whilst taking antidepressants used in this trial. Therefore, male participants will not be required to use contraception to prevent pregnancy in female partners whilst participating in the trial.

3.3 Recruitment

Participants will be recruited via general practices, with the help of the lead sites and RRDN. Electronic patient records will be searched to identify participants that fit the eligibility criteria. A pre-defined search list will be provided for this purpose. Input from the Trial Management Group (TMG) will be sought to confirm this list or when any amendments are made to this search criteria. A list of potential eligible patients from each practice will be reviewed by a GP or by /RRDN staff to ensure they are eligible and have no other health or social issues which could affect their participation. Only participants confirmed by the GP or delegate as being suitable will be sent an invitation pack. It is the GPs responsibility to remove anyone unsuitable from the list.

Any patient that has signed the National opt-out register (which allows patients to opt out of their confidential patient information being used for research) will not be invited to participate.

General practices or RRDN staff will send an invitation letter to eligible participants inviting them to contact the study team at their local research site (or UCL DoP if the site does not have capacity) if they are interested. Participants will be advised to spend time reading the Participant Information Sheet (PIS) and discussing with family or friends before deciding if they are interested in participating.

Participants interested will be able to return a reply slip to site researchers (or UCL DoP researchers if sites do not have capacity) using a pre-addressed and pre-paid envelope. They will also have the option of telephoning the research team, emailing the research team, or entering their details via an online form.

If feasible, a staff member from the general practice or RRDN staff will telephone the participant approximately 1 week after they should have received the invitation letter, to see if they are interested in participating (if they have not already replied). This is explained in the invitation letter.

Up to 3 attempts (with a gap of at least 1 week between each call) will be made to contact participants. If there is no response after then, the practiceRRDN staff will assume they are not interested in participating. Participants can also complete a reply slip or contact their local research site, stating that they do not wish to participate/ to be contacted.

GPs will also be able to directly refer to the study after a consultation with a potential participant and can give the invitation letter, PIS and ICF at routine appointments.

Posters and/or leaflets and copies of the PIS will be provided to general practices which can be used to highlight the trial to any patients that are attending the practice. Details of how to register their interest will be written on the poster and information leaflet. If feasible, we will also register the trial on the NIHR Be Part of Research platform, which alerts people to trials which they might be eligible via their NHS app.

Those that respond to the invitation will be consented and screened over the telephone by site researchers (or UCL DoP researchers if a site does not have capacity) using the Geriatric Depression Scale-15 (GDS-15) and asking various questions on adherence to medication and social support. This is to ensure the participant meets the inclusion criteria of having a GDS score of <5, are adhering to their current antidepressant medication schedule and has a friend or family member or carer that they see or speak to at least once a week. Participants that meet all eligibility criteria will then be invited to consent for randomisation.

Participants may prefer to have a friend or family member help them in answering the questions or speaking to the researchers on their behalf. If this is the case, they will be advised to let the researcher know and this can be recorded on the trial database. Verification checks will be put in place to ensure the friend or relative is with the participant at the time and answers correctly for them.

Following consent, during screening, potential participants will be asked to confirm the name and dose of the antidepressant they are currently taking by reading out the name and dose on their box of prescribed medication/ prescription. Despite this information being in the GP search, this step is to confirm exactly which one of the 3 antidepressants the patient is taking and that it is at the correct dose. If brand names are used/ stated by the participant, researchers must check and confirm with a PI or delegate which of the 3 antidepressants the brand name refers to. This check can also be done by the site calling the potential participants GP. Confirmation of this check/ discussion should be documented. Participants should not be randomised until this confirmation is obtained.

The original ANTLER trial[23] completed recruitment from 150 general practices. Practices will have fewer potential participants aged at least 75 years and taking one of the three target

antidepressants for at least 9 months (our Clinical Practice Records Datalink (CPRD) search yielded 96,435 individuals) than in the 18-74 years group targeted for ANTLER (416,456 individuals). However, in ANTLER, older participants were considerably more likely to consider study participation if approached and we anticipate that this potentially greater interest in involvement in the research will mean that we can complete recruitment from 300 practices, so require on average 1.5 participants per practice.

In order to recruit 430 participants in 21 months, we will need to recruit on average just over 20 participants per month.

In accordance with the funders (NIHR) request, we will conduct an internal pilot of 9 months' duration to test this assumption and the robustness of our procedures. This pilot will occur across all sites, with the aim to recruit 180 participants (42% of the total required). If necessary, we will modify the number of practices we require based on the outcome of this pilot. Table 2 shows the internal pilot progression criteria.

Table 2. Internal 9 Month Pilot Progression criteria

Progression criteria	Red	Amber	Green
Number of recruiting practices open	0-150	151-299	300
Total recruitment (%)	0-90/180 (0-50%)	91-179/180 (51-99%)	180/180 (100%)

This will be reviewed at the end of the pilot and results presented to the Trial Steering Committee and Data Monitoring Committee to determine the next steps.

3.4 Co-enrolment Guidance

Participants cannot participate in the ANTLER 75+ trial if they are currently enrolled in any other Clinical Trial of an Investigational Medicinal Product (CTIMP) or are participating in a trial of psychological intervention. They must also not be enrolled if they have participated in a CTIMP or a trial of psychological intervention in the preceding 3 months.

3.5 Screening Procedures and Informed Consent

Potential participants will be provided with a Participant Information Sheet (PIS) and given sufficient time to read it fully (a minimum of 24 hours). If the potential participant is interested in the trial, they can register interest using information provided on the invitation letter sent alongside the PIS. A member of the site research team (or research team at UCL DoP if a site does not have capacity) will then contact the potential participant to discuss the trial. Following a discussion with a medically qualified investigator or suitably trained and authorised delegate, any questions from potential participants will be satisfactorily answered and signed informed consent will be sought. Once consent has been obtained, the participant will be screened to ensure they are eligible for the trial.

As the participant will not be seen in clinic during the consent process or any of part of the trial (unless they wish to attend in person), the study team at sites will aim to confirm their identity during the screening assessment. If possible, the researcher will conduct a video call to confirm by checking some form of ID. If this is not possible, then the researcher will ask the participant to confirm over the telephone their name, date of birth and the name of their GP

practice. Participants will be asked to confirm their name and date of birth at all follow-up assessments as an additional check.

If a patient has capacity and is willing to provide verbal consent, but is physically unable to sign the consent form, a witness independent of the trial team (such as a relative or friend of the participant) will be identified and asked to sign the witness signature field in the consent form, to attest to the patient's verbal consent to participate.

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

Eligibility screening will take place over the phone where the researcher will complete the Geriatric Depression Scale-15 (GDS) questionnaire and ask questions on medication use and social support, to ensure the potential participant meets the inclusion criteria detailed in this protocol.

3.5.1 Process of informed consent

Written informed consent to enter and be randomised into the trial must be obtained from participants, after explanation of the aims, methods, benefits, and potential hazards of the trial and **BEFORE** any trial-specific procedures are performed. The only procedures that may be performed in advance of informed consent being obtained are those that would be performed on all patients as usual standard of care.

It must be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment. It will also be made clear that the participant cannot chose which Arm of the trial they are allocated to and cannot ask to change Arms once they have been randomised.

Consent can be completed by the following methods:

- Paper – the participant can complete and sign the paper consent form and return it to the local study team (or the study team at UCL DoP if a site does not have capacity). This can be done via scanning and sending via email or by posting the consent form back.
- eConsent – the participant can sign the consent form electronically.
- Video call – the researchers will be able to take consent verbally via a video call. This should be done rarely and in exceptional circumstances deemed as such by the PI at site. Reasoning should be clearly stated in participant notes and the CCTU should be informed. Consent should be taken for videos to be saved. This should not be done if appropriate data storage requirements are not in place.

Verbal consent via a video call will be allowed in this research in limited cases where the participant cannot complete the consent form any other way. The participants will be sent a copy of the consent form in advance so that they can read it prior to the researchers

contacting them by video call. This has been discussed fully with the Patient and Public Involvement Group (PPI) group who believe this would be beneficial to the trial in aiding participants to take part. ID checks of the participants may be carried out to verify identity.

The researchers will read the consent form to the patient during the video call, reading all the clauses out one by one to ensure that they understand what they are agreeing to. A copy of the completed consent form (which the site team should complete) will then be posted to the participant for their records. The video call should be recorded. Video consent should not be performed unless it has been confirmed by the site, and the CCTU, that appropriate IG/ GDPR requirements are in place to store recordings of these videos.

Video consent should be clearly documented, in detail, in participant notes.

If a participant chooses to use eConsent, the researchers will request their email address for the form to be sent (this is included on the consent form). Researchers will be provided with training on how to use the eConsent and supplied with a user guide. Upon completion of eConsent, a copy of the consent form will automatically be emailed to the researchers (for secure storage) and the UCL CCTU (which will be deleted upon receipt). Participants will also get a copy.

If a participant is using the paper consent but is physically unable to sign the consent form (due to a particular illness or condition such as Parkinson's disease), a witness independent of the trial team will be identified and asked to sign the witness signature field in the consent form, to attest to the patient’s verbal consent to participate.

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

Participants may be asked to name a delegated family member or friend to help them with the trial requirements including the consent process. The research team will document the need for this family member or friend.

Signed consent forms must be kept by the investigator and a copy given to the participant or family. Following consent a copy of the consent form will be sent to the general practitioner informing them of the trial and the participant's involvement in it. This information should be entered into the patients’ medical records.

Consent forms will be checked at monitoring visits, throughout the trial.

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, given a copy of the revised information sheet and reconsented as appropriate.

Following randomisation, a randomisation notification letter will be sent to each participant’s general practice, notifying them of their patient’s enrolment in ANTLER 75+. GPs will be advised to contact the research team if they have any concerns about their patient participating. The letter will also explain the follow-up procedures and that they will be informed

if trial assessment indicates that the patient has relapsed with their depression or is experiencing concerning withdrawal symptoms or any suicidal thoughts.

Copies of consent forms and randomisation notification letters will be sent by research teams at trial sites.

4 Trial treatments / Intervention

4.1 Introduction

We are examining the antidepressants that are most commonly prescribed to those aged 75 years and over in the NHS. We searched CPRD for people aged >74, with a depression diagnosis and antidepressant prescription for >2 years, and found citalopram prescribed to 55%, mirtazapine 32% and sertraline 21% (some patients had been prescribed more than one antidepressant in this period). Most of the commonly prescribed antidepressants increase serotonin transmission or both serotonin and noradrenaline transmission. Even though we are not including other antidepressants, we will be able to generalise our data to almost all the currently prescribed medications for depression in those over aged 75 years and over.

Participants will be randomised with a 1:1 ratio to continue their current antidepressant (**Arm A**) or to taper and discontinue (by taking a placebo) (**Arm B**).

Participants in **Arm A** will continue their original dose of their antidepressant throughout the trial (Weeks 1-52).

Participants in the taper and discontinue arm **(Arm B)** will halve their dose of antidepressant in the first 6 weeks of the trial.

In weeks 7-12 they halve this again, by taking a placebo tablet every other day.

In weeks 13-52, participants will take just placebo.

Table 3 below explains how this will be managed, illustrating continuation (**Arm A**) and tapering and discontinuation treatment doses (**Arm B**) for each antidepressant.

Table 3. Randomisation Arms

Baseline	**Citalopram 20 mg**		**Mirtazapine 30mg**		**Sertraline 50mg**	
Arm	**Arm A - Maintenance**	**Arm B - Tapering**	**Arm A - Maintenance**	**Arm B - Tapering**	**Arm A - Maintenance**	**Arm B - Tapering**
DE* 1 Weeks 1-6	Pts receive 1 container	Pts receive 1 container	Pts receive 1 container	Pts receive 1 container	Pts receive 1 container	Pts receive 1 container

1 dispensing event	containing 42 capsules: 20 mg	containing 42 capsules: 10mg	containing 42 capsules: 30mg	containing 42 capsules: 15mg	containing 42 capsules: 50mg	containing 42 capsules: 25mg
DE 2 Weeks 7-12 1 dispensing event	Pts receive a PATIENT PACK with 2 active containers (20mg each) labelled bottle 1 and bottle 2, alternating days from bottle 1 and bottle 2	Pts receive a PATIENT PACK with 1 active container and 1 placebo container (10mg and placebo) labelled bottle 1 and bottle 2, alternating days from bottle 1 and bottle 2	Pts receive a PATIENT PACK with 2 active containers (30mg each) labelled bottle 1 and bottle 2, alternating days from bottle 1 and bottle 2	Pts receive a PATIENT PACK with 1 active container and 1 placebo container (15mg and placebo) labelled bottle 1 and bottle 2, alternating days from bottle 1 and bottle 2	Pts receive a PATIENT PACK with 2 active containers (50mg each) labelled bottle 1 and bottle 2, alternating days from bottle 1 and bottle 2	Pts receive a PATIENT PACK with 1 active container and 1 placebo container (25mg and placebo) labelled bottle 1 and bottle 2, alternating days from bottle 1 and bottle 2
DE 3 &4 Weeks 13-52 **(2 separate dispensing events)**	Pts receive 5 containers containing 60 capsules: 20mg	Pts receive 5 containers containing 60 capsules: 0mg (placebo)	Pts receive 5 containers containing 60 capsules: 30mg	Pts receive 5 containers containing 60 capsules: 0mg (placebo)	Pts receive 5 containers containing 60 capsules: 50mg	Pts receive 5 containers containing 60 capsules: 0mg (placebo)

- DE= dispensing event. There are 4 dispensing events in the trial (extra dispensing events can take place if needed, for example, IMP lost in post)

4.2 Arm A: Continuation Arm

4.2.1 Product

- Citalopram 20mg
- Mirtazapine 30mg

- Sertraline 50mg

All medication will be over-encapsulated.

4.2.2 Regulatory Status

Citalopram, Mirtazapine and Sertraline are all licenced drugs and indicated for depression.

4.2.3 Dispensing & Storage

The Pharmacy Trials Unit at Bristol Royal Infirmary (BPTU) will act as the central pharmacy and will be responsible for dispensing and storage of trial drugs (which will be stored at ambient temperatures). Trial IMP will be sent directly to the participant's home address. More information regarding the distribution to participants can be found in the IMP Management Plan.

There will be 4 dispensing events in total as detailed in Table 3. Extra dispensing episodes can take place if necessary (for example, IMP lost in post)

4.2.4 Dose Modifications, Interruptions and Discontinuations

Dose modifications are not permitted.

A letter will be sent to the GP for unblinding if requested by the GP.

Participants will be informed not to stop their trial medication suddenly. If they wish to stop they will be advised to contact their GP, or site PI as soon as possible to discuss this.

GPs can discuss any issues pertaining to interruptions and discontinuations with a trial PI at a research site if required to aid decision-making. Brief interruptions, for example missed dose(es) due to participant forgetting to take their medication, may be permitted. All interruptions should be reported to the site team and the PI should advise accordingly based on clinical judgement. Interruptions reported should be recorded by the site team.

Once participants have discontinued study medication, they must be unblinded and they will not be able to re-commence

Participants who discontinue the trial medication will be invited to all follow-up assessments for data collection purposes.

If a participant is having issues and their clinical team have implemented appropriate measures to improve their wellbeing (not including addition of a further antidepressant or any other item that deems them ineligible), then the participant may not need to discontinue trial medication and unblinding may not be necessary. It is possible that some participants may still be receiving follow-up from secondary mental health care services in which case a letter for unblinding will also be sent to this team if requested.

See also Section 4.7 for treatment discontinuation.

See section 1.4 for a summary of the risks, frequencies, and mitigations of the Investigational Medicinal Products (IMP(s)).

4.3 Arm B: Tapering and withdrawal arm

4.3.1 Products

As this is a double-blind trial, participants in Arm B will be given the same instructions as those in Arm A however placebo will be incorporated.

- Citalopram 10mg and matching placebo
- Mirtazapine 15 mg and matching placebo
- Sertraline 25mg and matching placebo

All medication will be over encapsulated.

4.3.2 Regulatory Status

Citalopram, Mirtazapine and Sertraline are all licenced drugs and indicated for depression.

4.3.3 Dispensing & Storage

See section 4.2.3

4.3.4 Dose Modifications, Interruptions and Discontinuations

See section 4.2.4 for details. As this is a double blinded trial, the information in section 4.2.4 is applicable to participants on Arm B.

4.4 Concomitant Care

The participants will continue with their usual care with their GP/ consultant while they are in the study but should not be given another antidepressant whilst in the study.

If a participant starts to take another antidepressant outside of the trial, the research team should be made aware and the participant will be withdrawn.

This is explained in the Participant Information Letter.

4.5 Overdose of Trial Medication

If someone takes an overdose of the trial medication, they should attend accident and emergency department as soon as possible. The clinician at the A&E can then decide if emergency unblinding is needed and will take any further action as required.

This is explained in the Participant Information Letter. Participants will also carry a participant contact card with necessary emergency contact information for unblinding included.

Please refer to section 4.6.1 for unblinding information.

4.6 Unblinding

The central pharmacy is responsible for unblinding throughout the trial.

At least a week before the participant is due to complete the trial, site teams will send GPs a letter informing them that the participants time on the trial is coming to an end. At this point, site teams will also send an unblinding request letter to central pharmacy. Central pharmacy will enter the allocation arm and email this to the GP practice so that further treatment can be discussed with the participants.

Participants will be reminded to plan a GP appointment which they should attend at the end of the study. The reminder will be given at least a month prior to completion to ensure an appointment can be made. Informing the GP of the unblinded trial allocation, as above, at least a week prior to the end of the study ensures they are aware of this in time for the appointment and can take the most appropriate course of action regarding the participants ongoing treatment outside of the trial. The research team will remain blind to this information.

Unblinding can also occur for those participants for whom it is deemed medically necessary or to aid treatment decisions. The GP and the participant will be unblinded, but the CCTU research team will remain blind to this information.

4.6.1 Emergency Unblinding

Unblinding may occur for any participant experiencing a medical emergency (including overdose of IMP) for which the clinical management would be facilitated by the unblinding of the patient's treatment allocation. All participants will be given a card with contact details for the trial team including emergency contact details for the central pharmacy for unblinding 24 hours a day, 7 days per week. Their delegated family or friend should also have access to this card.

In the event of unblinding becoming necessary, the central pharmacy will provide unblinding 24-hours, 7 days a week. The Principal Investigator (PI) or delegate cannot overrule any decision made by a referring clinician. It is anticipated that in most instances, appropriate clinical management can proceed with the assumption that the patient has been treated with active IMP without needing to unblind the participant.

Detailed information regarding unblinding is provided in the Randomisation and Unblinding Plan.

4.6.2 Unblinding for the Submission of SUSAR reports

All SAEs that are related to the trial medication or the tapering and discontinuing arm (i.e., SARs) and are suspected to be unexpected i.e., SUSARs, need to be submitted to the regulatory agencies within pre-specified timelines. When SAEs reports are received at the CCTU, if the event is recorded as being a SUSAR then the following procedure will be used to unblind the SUSAR to determine which arm the participant is allocated to and to onward report accordingly. :

- A member of the CCTU trial SUSAR Reporting Team (who are trained and independent of the main Trial Team) will unblind the participant's trial treatment allocation via the central pharmacy. It must be made clear on SUSAR reports whether the participant was in the maintenance arm (Arm A) or tapering and discontinuing (Arm B) as the event may be due to withdrawal.

- The CCTU trial SUSAR Reporting Team member will report the SUSAR to the UCL Joint Research Office (JRO) who will be responsible for reporting this via ICSR Submissions portal to the MHRA and REC as required.

- This information will not be forwarded to the trial team at the CCTU or at the sites. It will be kept in a separate file by the CCTU SUSAR reporting team.

- The GP/ treating clinician will be informed that the participant has had a SUSAR and of their unblinded allocation. All efforts will be made to keep the site PI blinded unless it is deemed clinically necessary to share this information.

4.7 Protocol Treatment Discontinuation

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

1. Unacceptable treatment toxicity or adverse event;
2. Inter-current illness that prevents further treatment;
3. Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of trial treatment;
4. Inadequate compliance with the protocol treatment in the judgement of the treating clinician;
5. Withdrawal of consent for treatment by the participant;
6. Deviation from the dosing regime, as deemed significant by Clinical team.

If at any point in the trial, the PI is concerned about the clinical condition of a participant and decide they should be treated by their GP, theparticipant will bereferred back to their GP to ensure that they receive appropriate treatment outside the trial. The decision to withdraw will require a clinical judgement about the appropriateness of doing so. If withdrawal from trial medication is required, the treating clinician/ GP should undertake this according to NICE guidelines following unblinding. Participants will continue to be followed up for data collection purposes if appropriate.

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

It should be clear to the patient and recorded in the patient notes what aspect(s) of the trial the participant is discontinuing their participation. These could include:

- Early cessation of **further treatment**
- Early cessation **from further trial follow-up**

Withdrawal CRFs will be completed by the research team.

All participants must be advised to taper the study medication in line with clinician and NICE guidance and reduce the dose gradually if they want to stop the medication. They must not stop suddenly.

Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Patients should remain in the trial for the purpose of follow-up and data analysis (unless the patient withdraws their consent from all stages of the trial). If a patient ceases follow-up early, refer to Section 5.4.

Data from patients who stop follow-up early will be kept and included in analysis.

4.8 Accountability & Unused Trial Medication

The central pharmacist will be delegated oversight of IMP supplies. Full IMP Accountability records will be maintained at the central pharmacy. The CCTU will request copies of accountability logs and confirmation of destruction/disposal of any expired/unused IMP.

Any unused medication (due to withdrawal or trial completion) should be disposed of via the following methods:

- Returned by participant to a local or central pharmacy for disposal;
- Pre-paid envelopes may also be considered to allow participants to return trial medication directly to the central pharmacy (where necessary);
- Returned to research site and disposed of by research team according to local processes.
- The central pharmacy will destroy any unused IMP at the end of the trial.

Further details may be found in the ANTLER 75+ IMP Management Plan.

4.9 Compliance and Adherence

Adherence to the study medication will be assessed at each follow up point (see section 5.2).

Participants will be provided with specific Medication Instruction Participant Information Sheets which are posted along with their medication- for weeks 1-6, weeks 7-12, weeks 13-52 (medication for weeks 13-52 will be sent out in 2 dispensing events with a medication information sheet included each time). These will have detailed instructions regarding exactly how to take their medication. A “Medication Checklist” will be included to help participants track their treatment regimes.

The research team will confirm with the participant that they have received the trial medication for all 4 dispensing visits. These checks will be documented on the CRFs..

Participants' delegated family or friend can also refer to these instructions if necessary to aid treatment adherence/ compliance.

A participant flow chart will be provided at the end of the Participant Information Sheet for participants to have as a useful reminder of what is required regarding the follow-up schedule.

5 Assessments & Follow-Up

5.1 Outcomes

Participants will be asked to complete questionnaires at set time points (see section 5.2) in order to collect outcome data. Questionnaires can be completed by the participant at home or data will be collected by telephone by site researchers (or UCL DoP researchers if a site does not have capacity) or by video call, for example MS Teams or Zoom. This is to ensure that participants have a choice about the most convenient method for them. Family/ friend representatives can be present on these calls. Researchers will attempt follow-up calls at a time that best suits the participant and their delegated family member or friend should they require assistance.

Researchers will make every effort to ensure questionnaires are completed on the visit due dates. However, if the participant is unable to complete it then, due to illness or vacation, then it should be completed at the first available opportunity. If a follow up visit is delayed, then

researchers should ensure the following visit is not completed early to avoid creating large gaps between visits.

Participants may be contacted between the set visits if site research team need to collect any follow up information following adverse events.

5.1.1 Primary Outcome(s)

The primary outcome measure is the time to first relapse of depression during the 52-week follow-up, as determined in a time-to-event analysis. As in the original ANTLER study, this will be determined using the retrospective Clinician Interview Schedule-Revised (rCIS-R).

The original CIS-R is a structured interview that asks about depressive symptoms during the last week and determines whether the symptoms indicate a diagnosis that meets the ICD-10 Criteria for depressive episodes. The CIS-R also includes a method for scoring the severity of depression on a scale from 0-21, with higher scores indicating more severe depression, as determined by the sum of the five sections of the CIS-R (depression, depressive ideas, fatigue, concentration and sleep problems).

The primary outcome is defined as a new episode of depression as determined by the components of a retrospective CIS-R (the rCIS-R). The rCIS-R uses questions from the original CIS-R and inquires specifically about the patient's experiences during the past 8 weeks. Our case definition of relapse of depression will be meeting criteria for ICD-10 depression as assessed by the rCIS-R. This involves an affirmative answer to either of two mandatory rCIS-R questions. First, *have you had a spell of feeling sad, miserable or depressed?* And second, *have you been unable to enjoy or take an interest in things as much as you usually do?* To meet the outcome of a depressive episode, patients also have to report that one of the preceding responses has lasted for two weeks or more and describe the occurrence of at least one of the following symptoms: depressive thoughts, fatigue, loss of concentration or sleep disturbance. The test-retest reliability of the rCIS-R on 396 ANTLER participants showed kappa 0.84 (95% CI 0.71-0.97) for presence of relapse and 0.84 (95% CI 0.74-1.00) for agreement on the number of weeks when relapse of depression started. In ANTLER, the rCIS-R was administered every 12 weeks. Because some ANTLER 75+ participants will have memory difficulties, we have shortened the interval between rCIS-R assessments to 8 weeks. In addition, and to maximise participant safety, we will also include an assessment at week 4. Assessments will therefore take place at baseline, 4, 8, 16, 24, 32, 40, 48 and 52 weeks.

5.1.2 Secondary Outcomes

(1) **Binary variable, depression present or absent**, with the 15-item Geriatric Depression Scale (GDS-15)[4,5]. This is a validated scale for the assessment and diagnosis of depression in older people, based on the responses to 15 questions. Scores range from 0-15, with higher scores indicating worsened depressive symptoms and a score of five or more indicating case-level depression. This will be measured at screening, 4, 8, 16, 24, 32, 40, 48 and 52 weeks.

(2) **Symptoms of anxiety** with the Generalized Anxiety Disorder Assessment 7-item version (GAD-7)_[6] which scores how frequently seven symptoms of anxiety have been experienced in the preceding 14 days (not at all = 0, on several days = 1, on more than half of days = 2

and nearly every day = 3). The scale is scored from 0-21 and a score of 8 or more represents case-level anxiety (Plummer 2016). Measured at baseline, 8, 16, 24, 32, 40, 48 and 52 weeks.

(3) **Physical symptoms of side-effects of antidepressants** with the Toronto Side Effect Scale (TSES)[7]. This asks about a range of potential symptoms (29 in women and 32 in men), experienced in the preceding fortnight and the frequency (scored 1-5) and severity (scored 1-5) of each. An intensity score for each symptom is derived by multiplying the frequency by the severity score. Measured at baseline, 8, 16, 32 and 48 weeks.

(4) **Antidepressant withdrawal effects** with a modified 15-item version of the Discontinuation-Emergent Signs and Symptoms (DESS) Checklist[8]. The DESS was developed to evaluate the discontinuation syndrome after the interruption or reduction of an antidepressant and is a 43-item symptom list. Patients rate whether over the last seven days they have experienced changes in any of the symptoms with one of five responses (new symptom, old symptom but worse, old symptom but improved, old symptom but unchanged, or symptom not present). We adapted this in the light of our PPI for ANTLER, shortening the scale to 15 items, including a question about “brain zaps” (i.e. buzzing, shivering or electric shock-like sensations in the brain), that are characteristically described by patients withdrawing from antidepressants but were not included in the original DESS, and a question about experience of any other unexpected or new symptoms. Because of the importance of antidepressant withdrawal symptoms and the lack of placebo-controlled data on their occurrence in older people, we will administer the adapted DESS during and following the 12-week tapering period at baseline and weeks 4, 8, 12, 14, 16 and 18, 24 and 52. Anecdotally, these symptoms are reported to be most common and troublesome in the weeks following tapering to stop antidepressant and this is why we will collect data every 2 weeks for 2 months after the point of tapering to stop at week 12.

(5) **Quality of life scores for physical and mental health** categories on the modified 12-item Short-Form Survey (SF-12)[9], on which participants self-assess how they are impacted by health conditions within eight domains. Measured at baseline, 24 and 52 weeks.

(6) **Cognitive functioning** with the Montreal Cognitive Assessment (MOCA)[10]. The MOCA is a 30-point screening test for cognitive impairment, validated for use in mild cognitive impairment. Scored from 0-30, with higher scores indicating better cognitive function, a score of 26 or greater is considered to be normal. Measured at baseline, 24 and 52 weeks.

(7) **Levels of fitness-frailty, polypharmacy and multimorbidity** with the Pictorial Fit-Frail Scale (PFFS)[12]. The PFFS uses visual images to assess level of fitness-frailty in 14 different domains. Within each domain, 3-6 levels of ability are represented, and the participant or assessor selects the image that best represents the usual state of the person being assessed. Images make the scale accessible across literacy levels, languages and cultures. Scores can be transformed into frailty index scores and the scale also scores number of regular prescribed medications. Measured at baseline, 24 and 52 weeks.

(8) **Resource use for health and social care** with a modified version of the Client Service Receipt Inventory[12]. Measured at baseline, 24 and 52 weeks.

(9) **Health related quality of life** with the EQ-5D-5L (a five item, five level questionnaire, scored 1 (no problem) to 5 (extreme problem) to allow economic evaluation. Measured at baseline, 24 and 52 weeks) to allow economic evaluation[13].

5.2 Participant Timeline

Table 4. Participant Timeline

Visit Number	**Consent**	**Screening**	**Baseline**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Follow-up qualitative interview**
Week		-28 to -1 day***	**0**	**4**	**8**	**12**	**14**	**16**	**18**	**24**	**32**	**40**	**48**	**52**	**56**	**Post primary outcome visit**
Protocol visit window†				**+/- 14 days**	**+/- 14 days**	**+7/ – 14 days**	**+/- 7 days**	**+/- 7 days**	**+21/- 7 days**	**+28 / - 21 days**	**+/- 28 days**	**+/- 28 days**	**+14/- 28 days**	**+/- 14 days**	**+/- 14 days**	
Consent*	**X**															
Eligibility screen		**X**														
Randomisation/Treatment group allocation			**X**													
Medication adherence check				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Clinical Interview Schedule-Revised (CIS-R)			**X**	**X**	**X**			**X**		**X**	**X**	**X**	**X**	**X**		
Adverse events/physical symptoms check (and reporting if required) and any changes in concomitant medication recorded			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Geriatric Depression Scale (GDS-15)		**X**			**X**			**X**		**X**	**X**	**X**	**X**	**X**		
Generalised Anxiety Disorder Assessment (GAD-7)			**X**		**X**			**X**		**X**	**X**	**X**	**X**	**X**		

Toronto Side Effect Scale (TSES)			X		X			X			X		X			
Discontinuation-Emergent Signs and Symptoms (DESS) Checklist			X	X	X	X	X	X	X	X				X		
Quality of Life scores for physical and mental health categories (SF-12)			X							X				X		
Cognitive Functioning with the Montreal Cognitive Assessment (MOCA) – Blind version for telephone interviews			X							X				X		
Levels of fitness-frailty, polypharmacy and multimorbidity with the Pictorial Fit-Frail Scale (PFFS)**			X							X				X		
EQ-5D-5L			X							X				X		
Client Service receipt Inventory (CSRI)			X							X				X		
Final follow-up phone call to capture any AEs that may have occurred since the trial ended															X	
Follow-up interview																X

* Informed consent must be obtained prior to formal trial screening with site team

** The PFFS questionnaire use visual images to assess the participant's cognitive state. This questionnaire will be posted out to the participant one week prior to the assessment. During the phone call the researcher will ask the participant each of the questions and the participant will use the questionnaire as a guide to provide the answer

*** If the baseline visit occurs more than 28 days after the screening visit, the screening visit must be repeated to ensure the participant is still eligible

† Visits should be completed as close to the due date as possible. If one visit is completed earlier than the due date, every effort will be made to ensure that the following visit is completed on time (and not late)

5.3 Participant Transfers

If a participant moves from the area to another GP practice, then they may still be able to participate in the trial if the GP practice sits within one of the trial sites. In this case, site researchers will contact the new GP to explain the participants involvement in the trial and the new site will take over responsibility. Reconsent will be taken at the new site and the participants data will be safely and securely transferred to the new site (on the trial database). GP letters will be sent to new GP if relevant.

5.4 Early Stopping of Follow-up

If a participant chooses to discontinue their trial treatment, they should be asked to continue trial follow up, providing they are willing, and encouraged to not leave the trial completely; if they do not wish to remain on trial follow-up, however, their decision must be respected, and the patient will be withdrawn from the trial completely. Participants stopping early may have a negative impact on trial data integrity and the ability to reach the stated endpoints.

Participants will be advised not to stop their trial treatment suddenly and to seek clinical advice.

Any participant choosing to discontinue their trial treatment will be advised to discuss their ongoing treatment with their GP. The GP will be sent a letter informing them of their patients' decision and will be unblinded to the trial treatment. The participant will be unblinded when they see their GP to discuss their ongoing treatment.

Data already collected during the patient's participation in the trial will be kept for analysis.

(See also Section 4.7 Protocol discontinuation)

5.5 Loss to Follow-up

The researchers will make every effort to follow-up participants by different means (e.g., phone, email, text) to minimise any loss to follow up. We will provide detailed guidance for research staff about the best way to approach participants and to minimise loss to follow up. If necessary, we will contact the nominated family member or friend to check on the welfare of the participant. Consent will be sought for this. If one appointment is missed, the researcher will still try to contact the participant or their nominated relative for the next subsequent time point. IMP will continue to be sent to the participant if they miss an appointment to reduce the risk of sudden withdrawal.

5.6 Completion of Protocol Follow-Up

The end of trial is defined as the date when all outstanding data queries have been resolved following the last participant's last follow-up data collection.

5.6.1 Post Trial Care

At the 48-week assessment, the participant will be advised to make an appointment with the GP in week 52 to discuss the appropriate treatment going forward. The GP will also be informed via letter from the research site, that the participant is nearing trial completion and

will finish the trial IMP in one month and that the participant has been advised to make an appointment with them to discuss ongoing treatment.

The researchers will confirm this has been done at the 52-week assessment. The GP will be sent a letter prior to the appointment which details unblinded treatment allocation so that they can have an informed discussion with the participant and provide the appropriate care moving forward.

It will then be for the GP and the individual participant to decide whether to continue with their original antidepressant dose or discontinue treatment. If they decide to discontinue, it is recommended that they follow the current NICE guidance[32] regarding discontinuation..

GP/ participant letters for the various scenarios discussed in this protocol have been approved.

Approved text from these letters may be sent to GPs or participants by email, should they state that this is their preference.

6 Safety reporting

The principles of GCP require that both investigators and Sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section of the protocol. **Section 6.1** lists definitions, **Section 6.3** gives details of the investigator responsibilities and information on CCTU responsibilities.

6.1 Definitions

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

Table 5: Definitions

Adverse Event (AE)		Any untoward medical occurrence or effect in a participant treated on a trial protocol, which does not necessarily have a causal relationship with a trial treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a trial treatment, whether or not related to that trial treatment.
Adverse Reaction (AR)		All untoward and unintended responses to a trial treatment related to any dose administered. A causal relationship between a trial treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)		An AE or AR that at any dose: • Results in death • Is life threatening* • Requires in person hospitalisation or prolongs existing hospitalisation** • Results in persistent or significant disability/ incapacity • Is a congenital anomaly or birth defect • Is otherwise medically significant***
Suspected Unexpected Serious Adverse Reaction (SUSAR)		A serious adverse reaction, the nature, specificity or severity of which **is not consistent** with the known potentially expected events associated with the applicable trial treatment as detailed in the Reference Safety Information. The event is evaluated as having at least a reasonable possibility for a causal relationship to a trial treatment **and** is unexpected for that trial treatment.

* The term “life threatening” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE.
*** For example, important medical events that may not be immediately life threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed above (e.g. suicidal behaviours). Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations.

6.1.1 Medicinal Products

An investigational medicinal product is defined as the tested investigational medicinal product and the comparators used in the study (see section 4 of this protocol).

Adverse reactions include any untoward or unintended response to drugs. Reactions to an IMP or comparator should be reported appropriately.

6.1.2 Adverse Events

Adverse events include:

- an exacerbation (i.e., increase in the frequency or intensity) of a pre-existing illness, episodic event or symptom (initially recorded at the screening/baseline visit), that is detected after trial drug administration/intervention
- occurrence of a new illness, episodic event or symptom, that is detected after trial drug administration/intervention

Adverse events do NOT include:

- Medical or surgical procedures: the condition that leads to the procedure is the adverse event;
- Pre-existing disease or a condition present before treatment that does not worsen;
- Hospitalisation where no untoward or unintended response has occurred e.g., elective cosmetic surgery;

6.2 Notifiable Adverse Events

6.2.1 Pregnancy

Not applicable for this trial.

6.3 Investigator responsibilities

AEs will be collected via the questionnaires completed at each follow-up assessment or via the participants’ GP informing site teams. If the participant is not able to inform the researchers themselves (i.e. if they have been admitted to hospital), we will ask that a friend or relative contacts us on their behalf if possible.

SAEs and SARs should be notified to CCTU immediately when the investigator becomes aware and no later than 24 hours after becoming aware of the event.

6.3.1 Investigator Assessment

6.3.1.1 Seriousness

When an AE or AR occurs, the investigator responsible for the care of the participant at site must first assess whether or not the event is serious using the definition given in Table 5. If the event is classified as 'serious' then an SAE form must be completed and CCTU (or delegated body) notified immediately (within 24 hours).

6.3.1.2 Severity or Grading of Adverse Events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the toxicity gradings in the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (2017).

Grades for AEs and ARs according to the CTCAE are:

Grade 1: Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.

Grade 3: Severe or medically significant but not life threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**.

Grade 4: Life threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE or AR.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

Where no specific grading criteria exist for an event, the event should be graded according to the CTCAE general guidelines outlined above.

6.3.1.3 Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 6. **There are two categories: unrelated, or related.** If the causality assessment is unrelated, the event is classified as an SAE. If the causality is assessed as related, then the event is classified as an SAR.

Table 6: Assigning Type of SAE Through Causality

Relationship	Description	Event type
Related	A causal relationship between an IMP/investigational treatment and an adverse event is at least a **reasonable possibility**, i.e., the relationship cannot be ruled out	AR
Not related	There is **no reasonable possibility** of a causal relationship between an IMP/investigational treatment and an adverse event	Unrelated AE

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

6.3.1.4 Expectedness

If there is at least a possible involvement of the trial treatment (or comparator), making this an SAR, expectedness will be assessed by the Sponsor Independent Safety Review Team (ISRT) at CCTU. Expectedness assessments will be required for suspected SARs (causality "related"), and not for all SAEs (for example if causality "unrelated") as the assessment is required to determine expedited reporting of SUSARs. If information of expectedness is provided by the investigator this should be taken into consideration by the sponsor. An unexpected adverse reaction is one not reported in the current and approved version of Reference Safety Information (IB, or SPmCs) for the trial, or one that is more frequently reported or more severe than previously reported.

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SAEs (unrelated) will be reviewed by a trained clinical reviewer.

If a clinical reviewer disagrees on causality, making an SAE a potential SAR, the event may be sent to the ISRT for expectedness assessment.

6.3.1.5 Reference Safety Information (RSI)

The Reference Safety Information (RSI) for Citalopram, Mirtazapine and Sertraline for the ANTLER 75+ trial can be found in section 4.8 of the respective current approved versions of the SmPCs. The RSI for the placebo for the ANTLER 75+ trial is in the approved Investigational Medicinal Product Dossier (IMPD). If a SAR is assessed as being unexpected it becomes a SUSAR (suspected, unexpected, serious adverse reaction) and MHRA reporting guidelines apply (see Notifications sections of the protocol).

6.3.2 Notifications

6.3.2.1 Notifications by the Investigator to CCTU

CCTU must be notified of all SAE/Rs immediately after site staff become aware of the event (in no circumstances should this notification take longer than 24 hours).

Investigators should notify CCTU of any SAEs and other Notifiable Adverse Events (NAEs) occurring from the time of randomisation **until 30 days after the 52 week follow up visit, including SARs and SUSARs. Participants will be reminded to contact the Research Team to inform them of any AEs post 52 weeks for 30 days.** From this point forward the site will not actively monitor SAEs or NAEs but will notify the CCTU of any SARs and SUSARs if they become aware of them until trial closure.

Any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system (https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/).

For SAE/Rs, an SAE form must be completed by the site staff named on the delegation with this responsibility assigned by the PI. The form should be reviewed and signed off by the

investigator (listed on the delegation log) who is responsible for the participant's care with attention paid to the grading and causality of the event.

The SAE form should be completed directly in the OpenClinica database, if possible. If not possible, then a paper CRF should be completed and sent via encrypted email to the Sponsor to notify them of this event. Encrypted emails should be sent to cctu.antler75@ucl.ac.uk. **All SAEs should be reported to the Sponsor within 24 hours of the site becoming aware of the event (via OpenClinica or email).**

In the absence of the responsible investigator at site, an SAE form should be completed and signed by a trained and delegated member of the site trial team. The trial team at the CCTU will review the SAE form for completeness, provide an SAE identifier,and feedback to the site team if further information is required. The responsible investigator/ site team member should check the SAE form at the earliest opportunity and make any changes necessary. The SAE form should then be updated on the database and signed off. A copy of the fully complete SAE form may be sent to the Sponsor by encrypted email if database entry is not possible. Systems should be in place at the site to enable the investigator to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SAE are: one suspect IMP, an identifiable coded subject (i.e. the participant identification number), an event or outcome that can be identified as serious, an identifiable reporting source (i.e. contact details of person reporting), and a trial identifier (for example, trial specific SAE CRF, protocol, IRAS number, or REC reference). The primary event term (per CTCAE v5.0) should ideally be present along with sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be completed as soon as it becomes available.

SAE REPORTING
Within 24 hours of investigator at site becoming aware of an SAE:
SAE form must be completed in the database and confirmation that an SAE form has been entered sent by email to the ANTLER-75+ trial team at cctu.antler75@ucl.ac.uk

Follow-up: Participants must be followed up until clinical recovery is complete, laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or trial follow-up if necessary. Follow-up (or event resolution) SAE forms should be completed as further information becomes available. Additional information and/or copies of test results etc may be provided separately. The participant must be identified by trial number and initials only. The participant's name should not be used on any correspondence and should be blacked out and replaced with trial identifiers on any test results.

If there are ongoing SAEs at the study end this should be discussed with TMG.

Staff should follow their institution's procedure for local notification requirements.

6.3.2.2 CCTU responsibilities

Upon receipt of an SAE form, if classified as unrelated, making this an SAE, the Trial Team at the Sponsors office should inform the delegated Clinical reviewer immediately but ideally within 1 working day. A clinical reviewer (Chief Investigator (CI), or a medically qualified delegate) will review all SAE reports received in OC or on paper if OC is not available. The causality assessment given by the local investigator at the hospital cannot be overruled; in the case of disagreement, both opinions will be provided in any subsequent reports, for example to the CCTU ISRT (if an SAE is deemed possibly related by a clinical reviewer, it will be sent to the ISRT)

The Clinical reviewer should return Clinical review as soon as possible- ideally within 1 working day. This can be done via encrypted email (if on paper) or via Openclinica but all information must be in OpenClinica at the end of the SAE and fully signed off.

Upon receipt of an SAE that has been classified as related, making it an SAR, the trial team will forward this event to the to the Independent Safety Review Team at CCTU who will assess expectedness in line with the Reference Safety Information (RSI).

CCTU is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA) and the ECs as appropriate.

Fatal and life threatening SUSARs must be reported to the competent authorities within 7 days of CCTU becoming aware of the event; other SUSARs must be reported within 15 days.

The trial team will notify the UCL Joint Research Office (JRO) Safety Team within 24 hours following the classification of the SUSAR and send through the SAE reports. The UCL JRO Safety Team will report the SUSAR on the MHRA Individual Case Safety Reports (ICSR) submissions online portal on behalf of the trial team.

CCTU will keep investigators informed of any safety issues that arise during the course of the trial.

A Development Safety Update Report (DSUR) will be submitted to the MHRA within 60 days of the international birth date of the trial and annually until the trial is declared ended.

More information can be found in the ANTLER-75+ Safety Management Plan.

6.3.2.3 Urgent Safety Measures

The CCTU or investigator may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety.

In the UK if any urgent safety measures are taken the CCTU shall immediately (no later than 3 days from the date the measures are taken), give written notice to the MHRA and the REC of the measures taken and the circumstances giving rise to those measures, according to the relevant CCTU SOP.

7 Quality Assurance & Control

7.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the ANTLER 75+ trial are based on the standard CCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; benefit risk of the trial (see section 1.4); and other considerations.

According to the MHRA Risk Assessment, this trial is defined as risk Category A (i.e., no higher than that of standard medical care).

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

The ANTLER 75+ Risk Assessment has been reviewed by the CCTU's Quality Management Group (QMG).

7.2 Central Monitoring at CCTU

CCTU staff will review data and other information provided by investigators to identify trends, outliers, anomalies, protocol deviations and inconsistencies. The frequency and type of central monitoring will be detailed in ANTLER 75+ Quality Management and Monitoring Plan (QMMP).

7.3 Monitoring

The frequency, type and intensity of routine on-site monitoring and the requirements for triggered on-site monitoring will be detailed in the ANTLER 75+ QMMP, including any provision for remote or self-monitoring. The QMMP will detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority UCL CCTU must be notified as soon as possible.

7.3.1 Direct access to Participant Records

Participating investigators must agree to allow trial-related monitoring, including audits, Research Ethics Committee review and regulatory inspections, by providing access to source data and other documents as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

Health economic data will be collected from participants, and general practice records if required, and the site team will have consent to access these. Health economic data may also be accessed remotely, in which case the RRDN may be asked to support with data extraction and collection.

7.3.2 Confidentiality

CCTU will follow the principles of the UK DPA.

Participant's data will be collected and kept securely. Personal, identifiable data will include name, address, email addresses, phone numbers and NHS number. This is required so that the researchers can contact the participant, send them trial information and phone them up to complete all the assessments, and to enable the central pharmacy to receive prescriptions to send out the IMP. This data will be stored in a separate administrative database (RedCap) in the Data Safe Haven, which will only be accessible to the site teams that require access to it.

Confidentiality of participant's personal data is ensured by not collecting participant names and other personally identifiable information on CRFs and receiving only pseudonymised data. Pseudonymised data will be stored in the OpenClinica database (separate to the administrative database). At trial enrolment, participants will be allocated a Participant Identification Number (PIN), which will be used on all trial related paperwork sent to UCL CCTU and in the trial database. Any documents (e.g. screening and enrolment logs) linking PIN to participant's personally identifiable information will be kept securely at site; only redacted copies will be sent to Sponsor if requested.

Copies of participant's trial data will be kept at the participating site in a secure location with restricted access. Unless working at a site, CCTU staff will only have access to the data collected on the trial CRFs (i.e. they will not have access to any other personal data) and applicable source data, moreover only staff working on the trial will have access to these data. Data stored electronically are held on secure servers, that have restricted access.

The informed consent form will carry the participant's name and an appropriate signature (applies to both paper and e-consent forms); these will be retained at the trial site. The consent forms will only be accessed by delegated UCL staff working on the study for purposes of monitoring the consent procedure at the site. e-consent forms may be automatically sent to trial team staff at the sponsors office but if this happens, they will be deleted immediately.

7.4 Source Data

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data are contained in source documents and are defined by EU guidelines as all information in original records that are used for the reconstruction and evaluation of the clinical trial. Source documents are the first place where the source data are recorded.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). Each data element should only have one source.

For this trial, the CRFs/eCRFs will be the main source documents for the data elements listed below because the majority of the data will be collected directly from the participant over the telephone/ video call. If an SAE is reported, the researchers will contact the participant's GP practice for additional information if required. These data elements will be recorded directly on the CRFs/eCRFs and therefore the CRFs/eCRFs will be regarded as source data. Site researchers (or researcher based at UCL DoP, if a site does not have capacity) will enter the data on behalf of the participant. Data collected will include:

- *Patient questionnaires/ assessments*
- *Treatment compliance data*
- *Trial Management Data*
- *Medical Data from GP records*

7.5 Data Collection and Transfer Methods

Data collected will need to be directly entered by the researchers at site onto the Sponsor's central database (eCRFs).

Training on data collection, secure data transfer and storage for site staff listed on the delegation of responsibilities log will be provided at the site initiation meeting(s), extra database training meetings per site and whenever someone new is added to the delegation log.

7.6 Data Management

Data will be collected at the time-points indicated in the Participant Timeline (Section 5.2). Data will be entered under their PIN onto the central database. The database software provides a number of features to help maintain data quality, including maintaining an audit trail, allowing custom validations on data, allowing users to raise data query requests, and search facilities to identify validation failure and missing data.

Data collection, data entry, queries raised by a member of the ANTLER 75+ trial team and database lock(s) will be conducted in line with the CCTU SOPs and trial-specific Data Management Plan.

The database will be password protected and only accessible to members of the ANTLER 75+ trial teams at CCTU, delegated site staff at UCL DoP, and other named research sites and external regulators if requested. Database users will only be granted permissions to use the database functionality appropriate to their role in the clinical trial.

Identification logs, screening logs and enrolment logs will be completed and held securely with access limited to trial staff that require the information. The administrative database within the DSH, hosted at UCL, will collect participant identifiable data in order to generate letters and tracking of participants. We will also store the name and contact number for the participants nominated family member or friend in the DSH (this information will be deleted within a month of the participant finishing on the trial). Only authorised site staff will have access to this.

All data will be handled in accordance with the Data Protection Act 2018, the UK Data Protection Regulation (GDPR) (and subsequent updates and amendments).

7.7 Data Storage

Trial data will be stored in databases created specifically for the ANTLER 75+ trial. An admin database for patient identifiable data will be hosted by RedCap and stored within the UCL Data Safe Haven with access limited to site and UCL DoP researchers. All other pseudonymised data will be saved in a trial database hosted by OpenClinica, and stored on secure, GDPR-compliant, cloud-based servers held within UK and EU: https://www.openclinica.com/privacy-policy/

The randomisation service is hosted by Sealed Envelope LTD. The data are stored on a secure, GDPR-compliant, cloud-based servers held within the EU: https://www.sealedenvelope.com/security/

7.8 Data Archiving

Once all primary and secondary analysis has been completed the trial data will be archived. Once the trial data has been archived the trial database will be decommissioned and will no longer be available. Any subsequent/ further analysis will be performed using the archived data.Data should be archived for at least 5 years.

7.9 Quality Issues

Quality Issues are issues that can have an impact on patient safety, rights, and well-being; data integrity and/or scientific rigor; and compliance with regulatory requirements; these can classified as protocol deviations, potential serious breaches, near misses etc.

A protocol deviation is any departure from procedures documented in this protocol, this includes deviations that cannot be predicted. If a protocol deviation is identified the Trials team should be contacted and CCTU's protocol deviation reporting process will be followed. This includes issues being escalated to the Quality Management Group.

A 'serious breach' is a deviation from procedures documented in this protocol, GCP or other clinical trial regulations that is likely to affect to a significant degree:

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

If a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee and/or Regulatory authority (MHRA) within 7 days.

8 Statistical Considerations

8.1 Sample Size

In ANTLER, relapse occurred in 92 of 238 patients (39%) in the maintenance group and 135 of 240 (56%) in the discontinuation group by 52 weeks. The Hazard Ratio for rate of relapse in the discontinuation compared with the maintenance group was 2.06 (95% CI 1.56 to 2.70) and 1.61 (95% CI 0.93-2.79) in our analysis of ANTLER participants aged 65-74 years. In the review by Wilkinson and Izmeth (2016), relapse occurred in 73% of patients in the discontinuation group and 48% in the maintenance group at 52 weeks (HR 1.5). By 52 weeks, attrition was 18% in ANTLER and 22% in the studies reviewed by Wilkinson and Izmeth (2016). Sample size calculations based on Hazard Ratios ranging from 1.5 to 2.0 were calculated, assuming 90% power (1-β) and 5% two sided α and allowing for 20% additional participants for loss to follow-up and other methodologic challenges. Estimates were based upon log rank test of time to event data. A HR of 1.6, based on our analysis of the older group

in ANTLER and which would still represent a worthwhile benefit for continuing treatment, based on a maintenance group control event rate of 49%, would need a total sample size of 430.

While we have good reason to believe that the maintenance rate will be in the order of 49%, an obvious concern for the scientific robustness of the trial is a lower-than-expected control event rate. Should the maintenance event rate be 45%, then 371 evaluable subjects will be required and should it be 40%, then 412 will be required. In both cases this is fewer than the 430 who will be randomised. The Trial Steering Committee will monitor the overall event rate and ensure it is in line with the study assumptions as the trial progresses.

8.2 Assignment of Intervention

8.2.1 Randomisation Procedures

Following the screening visit and signing off that they are eligible according to the screening criteria the PI or delegate will enter the participant trial ID, participant age and name of antidepressant they are currently taking, confirm they are eligible into the Sealed Envelope secure online randomisation system The PI or delegate will then radomise the participant within Sealed Envelope.

Delegated staff will be provided with a secure login to the SealedEnvelope.com website according to their role in the trial. The randomisation result will be sent directly to the central pharmacy. The trial team will not know the allocation but will be informed that the randomisation has occurred.

Randomisation will be considered completed after allocation has been generated from the randomisation system or equivalent.

8.2.2 Randomisation Method

We will use a web-based computerised system to randomise with a 1:1 ratio per each of the 3 trial drugs, using a minimisation procedure to achieve balance between minimisation groups as these factors may be predictors of outcome and we wish to ensure balanced groups of these factors for the final analysis.

8.2.3 Sequence generation

The minimisation procedure will use a 70:30 ‘biased coin’ procedure to asymptote towards balance while including a random element in each allocation. It will be provided by Sealed Envelope (https://www.sealedenvelope.com/) under the supervision of UCL Comprehensive Clinical Trials unit, CCTU (https://www.ucl.ac.uk/comprehensive-clinical-trials-unit/).

8.2.4 Allocation concealment mechanism

Randomisation will be concealed by using a remote computerised system and the pharmacy will be directly informed of the randomisation outcome. The active and placebo drug will be identical in appearance and researchers, clinicians and patients will be blind to allocation. A participant will be considered randomised at the point that they take their first IMP, and participants returning their unopened IMP will not be considered to have been randomised and thus will not be listed as not having completed the study.

8.2.5 Allocation Implementation

Once informed that an eligible patient has been identified and has consented to enter the trial, the random allocation of the patient to medication will be done by Sealed Envelope (https://www.sealedenvelope.com/). Analyses will be carried out to ensure that the randomisation procedure was successful in producing equal groups for each of the minimisation criteria. The procedure is unpredictable as the minimisation allocation will employ a 70:30 “biased coin” to asymptote towards equality which ensures an element of randomness in each allocation.

8.2.6 Blinding

This will be a double-blind designed trial. Investigators, research teams at sites, participants, the research team at UCL CCTU and the analysing trial statistician will be masked to treatment allocation. The only exception being the delegated unblinded trial statistician at UCL CCTU, central pharmacy and unblinded monitor (Trial Manager from the CCTU, independent of the trial team) who will monitor the pharmacy and SUSAR reporting team (independent of the trial team) at CCTU.

Blinding will be maintained by over-encapsulation and by using matching medicinal preparation for each of the three trial drugs and their matched placebo (i.e. the 2 different strengths of each medicine and their respective placebos will look identical). The blinded treatment identity will be maintained in the online Sealed Envelope randomisation service except in the case of medical emergency (see 4.6.1 Emergency unblinding) and routine unblinding (see 4.6.Unblinding).

Neither the participant, UCL researchers, PI or GP will know whether the participant is taking active or placebo medication. Unblinding will not be possible without requesting this from the central pharmacy.

8.3 Statistical Considerations

8.3.1 Estimand Framework

Estimand Parameter	Definition and method of analysis
Population	**Inclusion criteria:** Patients who are at least 75 years of age, are not depressed (scores <5 on Geriatric Depression Scale-15) are being treated with citalopram, sertraline or mirtazapine for at least 9 months and who have an Identified Study Partner (e.g. a family member or friend) who sees or speaks to the participant at least once per week. **Exclusion criteria:** Patients with a diagnosis of bipolar disorder or dementia (although people with mild cognitive impairment will be eligible for the trial) or those who have been prescribed a combination of antidepressants or are enrolled in another interventional study or have participated in a CTIMP in the preceding 3 months.
Treatment conditions	A double blind, placebo-controlled study of 12 months' discontinuation after tapering in patients receiving treatment with citalopram 20mg, sertraline 50mg or mirtazapine 30mg (using placebo) versus continued treatment with continued dose of the same three choices of pre-randomisation medication.
Endpoint	The time to the first relapse of depression during 52 weeks of follow-up (relapse will be assessed with an adapted Clinical Interview Schedule – Revised Version (Lewis 1992) to assess symptoms over the previous 8 weeks).
Summary Measure	Hazard ratio of having a relapse for up to a year after first day of taking study medication.
Intercurrent events i. Death before outcome ii. Withdrawal from randomised medication (stays in trial) iii. Withdrawal from randomised medication (leaves trial)	 While alive policy Treatment Policy While in trial policy

8.3.2 Statistical Analysis Plan

Analyses will follow a pre-specified Statistical Analysis Plan, and which will be held within the Statistics Master File (SMF). It will contain the following sections:

I. Introduction
II. Study Methods
III. Statistical Principles

IV. Trial Population
V. Analysis of Primary and Secondary Outcomes (including statistical models and method of dealing with missingness)

8.3.3 Interim Analyses

This study has an internal pilot with analyses to be conducted at 9 months to assess if the full RCT should proceed. The primary criteria of acceptability are:

i. Trial recruitment, and
ii. Number of recruiting practices open.

Pilot data will be presented in grouped tables with frequency and percentages for the 2 criteria so that it can be determined if the study fulfils the criteria for progression.

The IDMC and its delegates will have unrestricted access to unblinded data and this be provided by the unblinded statistician.

TSC reports will be provided as requested. The contents of the report will be determined by the TSC.

There are no planned interim analyses for the duration of the study, assuming that permission is granted to proceed to a full RCT, unless requested by the IDMC or TSC.

8.3.4 Statistical Methods – Outcomes

We will describe randomised groups at baseline. Summary statistics for continuous variables will be mean, median, SD, lower quartile, upper quartile and reported appropriately according to distribution. Summary statistics for binary and categorical variables will be n (%).

The Primary Analysis will utilise the log rank test (which is robust to potential departures from constant proportional hazards) and contrast the survival functions for those in the discontinuation or continuation groups. In the absence of observed departure from constant proportional hazards we will report the hazard ratio and 95% confidence intervals from a Cox model. We will explore the potential impact of including minimisation factors as explanatory variables in the Cox model in supportive models. In the context of departure from constant proportional hazards (assessed using Kolmogorov-Type Supremum Tests) a logistic model will be substituted considering relapse at any time during the 52 weeks as binary endpoint.

Analogous methods will be used for other survival outcomes. For other non-survival continuous or categorical outcomes, generalised mixed models will be used, including minimisation values as fixed effects, and baseline outcome values, with appropriate link functions and error structures. Missing data will be minimised, and we will utilise threshold analyses to examine the impact by imputing poor outcome at loss to follow-up or censorship by group.

We will not make adjustments for repeated testing in analyses of secondary outcomes but will discuss the possibility that type 1 errors would have increased in the discussion.

Secondary analyses will choose the appropriate analogous generalised mixed model, for the outcome and account for the baseline measurement of the outcome.

We will also investigate baseline variables associated with missing outcome data for the primary outcome. We will carry out mediation analyses to examine the influence of missingness. All principal analyses will be complete case, intention to treat (defined as all patients randomised who have taken at least one dose of the medication to which they were assigned and analysed according to their randomised group regardless of treatment received). Although we will minimise missing data by trial conduct (building on the considerable experience and success of the team on previous studies) we will investigate the potential impact of missing data on the primary objective through threshold analyses which will impute a poor outcome for missing patients assigned to the active arm while assuming an average outcome for missing control patients. We will exclude all randomised participants who had taken no study medication and for whom there is evidence of the return to a suitable study centre of untampered medication packaging.

8.3.5 Additional Analyses - Subgroup

Subgroup analyses will be described for the primary outcome. We will calculate interactions between randomised groups and each subgroup variable (below). Other variables in these models will be the same as those included in the main analyses of the primary and secondary outcomes. The subgroups investigated will be: category of antidepressant medication at baseline, and dichotomised Geriatric Depression Scale score.

8.3.6 Additional Analyses – Adjusted

Additional secondary analyses will adjust for the minimisation variables in addition to the treatment allocation.

8.3.7 Analysis Population and Missing Data

Outcomes will be analysed by means of Log Rank Test and/or Cox Models as well as Generalised Mixed Models without imputation of missing data. Measurements within individuals will be linked using a random intercept term where appropriate. An Intention-To-Treat (ITT) analysis will be carried out by randomisation group irrespective of medication compliance using the population for analysis as defined above. The analysis population will consist of all those participants who were randomised and who fulfil the additional restriction of having taken at least one dose of their study medication. Mechanisms of missingness will be explored. Participants who have been randomised but who did not take any study medication (and for whom there is evidence of return to a suitable study centre of untampered medication packaging) will also be excluded from the final ITT analysis.

9 Economic Evaluations

We will calculate the mean incremental cost per quality-adjusted life year (QALY) gained of antidepressant maintenance therapy compared with discontinuation over 52 weeks from an NHS and Personal Social Services (PSS) perspective using trial data and, additionally, a wider cost perspective including out-of-pocket and private healthcare information.

The primary economic outcome measure will be QALYs, calculated as the area under the curve using utility scores obtained from the participant responses to EQ-5D-5L quality of life instrument at baseline, 24 and 52 weeks, using the crosswalk algorithm which maps the EQ-5D-5L to the EQ-5D-3L. Supporting analyses will include QALYs calculated from responses to the EQ-5D-5L quality of life instrument using the value set tariff for England (VSE)[33].

Healthcare resource use will be collected using a modified version of the Client Service Receipt Inventory (CSRI)[34] at baseline, 24 and 52 weeks and will include information on primary and acute healthcare service contacts, pharmaceutical prescriptions, community and inpatient service use and social care. Services will be costed using the most recent nationally published sources[35,36], BNF). The cost of antidepressant maintenance will be calculated for the treatment arm.

Missing data will be explored to determine its patterns, extent, and association with any participant characteristics. Depending on the level and pattern of missing information, we will consider performing multiple imputation[37] or other types of imputation as appropriate to predict missing costs and outcomes. Analyses will be conducted in STATA v18[38].

Mean participant-level costs and QALYs over the trial period will be calculated. Seemingly unrelated regression (SUR)[39] will be used to account for correlation between costs and outcomes, with adjustment for baseline costs and utilities, and the site, medication, and baseline Geriatric Depression Scale score as minimisation factors. A bias-corrected and accelerated bootstrap method will be used to calculate 95% confidence intervals (Cis).

Analyses will take an intention-to-treat approach, with findings presented in terms of mean costs and effects for both groups, as incremental cost-effectiveness ratios (ICERs) at 52 weeks. A non-parametric bootstrap re-sampling method will be used to produce confidence intervals around the cost and QALY differences and the ICER. The joint uncertainty surrounding the costs and effects will be represented graphically on a cost-effectiveness plane. Cost-effectiveness acceptability curves (CEACs)[40,41], showing the percentage of cases that the intervention is cost-effective, over a range of values of willingness-to-pay (WTP) for a QALY gained, will be constructed using the bootstrap data from a range of values of WTP for a QALY gained for each different costing perspective and for the different methods of calculating QALYs. The probability that the intervention is cost-effective compared to TAU at a WTP for a QALY gained of £20,000 and £30,000 will be reported.

Sensitivity analyses of key variables will be conducted to ascertain the impact of assumptions on estimates of cost-effectiveness.

9.1 Health Economic Analysis Plan

A Health Economic Analysis Plan (HEAP) will be developed with reference to the statistical analysis plan (SAP), and it will provide a comprehensive and detailed description of the methods and presentation of economic data analysis for the trial. It will contain following sections:

1) Introduction
2) Economic analysis background
3) Economic measurements
4) Overall economic evaluation (including statistical models and method of dealing with missingness)

10. Nested Qualitative study

10.1 Aim

1) To explore the experiences of older adults in under-served and under-researched groups, in the ANTLER 75+ trial of reducing and stopping antidepressants and the nature, incidence and duration of withdrawal symptoms.
2) To explore General Practitioners' perspectives on monitoring antidepressants in older adults.

10.2 Methods

This is a nested qualitative study within the main ANTLER 75+ trial.

At the time of consent to the main trial, participants will be asked if they are willing to take part in one semi-structured interview lasting less than 60 minutes after the primary outcome measure has been assessed.
At the end of the trial, participants in both arms of the trial who have or have not relapsed, and consented to be approached, will be contacted by the qualitative researcher and invited to participate in an interview (which may be conducted by telephone, video call or face-to -face depending on participant preference and qualitative researcher availability. Participants be asked to complete an additional consent form at this time.

Researchers at the final 52-week assessment will also ask participants who did not consent at the start of the trial, if they would be willing to participate in this qualitative study again as they may have changed their minds.

We will purposively sample older adults according to participant gender, age range (75-84 and 85+), ethnicity and index of socioeconomic deprivation. We will purposively sample within areas of the West Midlands, Greater Manchester, London, Nottingham, and Newcastle where people have been historically under-represented in mental health trials.

Approximately 25 interviews with older adults are likely to be needed to achieve information power[42]. Older adults will be offered a reimbursement with a £25 shopping voucher as a ‘thank you’ for their time.

We will convene a separate Patient Advisory Group (PAG) for the qualitative study, with a focus on recruitment to the PAG of older adults from under-served populations (including socio-economically deprived areas, and people from Black Caribbean, Asian and African groups). Members of the PAG will be reimbursed for their time and expertise according to NIHR INVOLVE guidelines.

The topic guide will be developed with the two co-applicants with lived experience of depression and the patient advisory group (PAG), and will explore experiences of depression, particularly in the context of socio-economic and cultural factors, experiences of being diagnosed with depression, and decision-making about management including being prescribed antidepressants. The topic guide will also explore participants' perspectives on being in the ANTLER 75+ trial, experience of the study partner, thoughts about reduction and withdrawal of antidepressants, including withdrawal symptoms experienced, and acceptability of the reducing regime. For those people who relapsed, we will explore their experiences of relapse. In addition, their perspectives on monitoring antidepressants by their GP will be discussed. The topic guide will be modified iteratively as data generation and analysis progresses.

Antidepressants are predominantly prescribed to older adults and monitored by general practitioners (GPs). We will conduct about 15 interviews (telephone or video call) with GPs located in areas of socio-economic deprivation and with a high density of minoritised ethnic groups (identified using Public Health England's SHAPE atlas tool)[43].

Recruitment will be purposive, from practices participating in the ANTLER 75+ trial, but also using snowballing techniques[44], social media, invitations to practices with a high density of minoritised ethnic groups and in 'Deep End' practices, to ensure a range of GPs serving under-served communities are interviewed.
Practices participating in the ANTLER 75+ trial will be sent the PIS and invitation letter, asking for details to be circulated to GPs in the practice (salaried doctors and GP principles); GPs interested in being interviewed will be asked to contact the qualitative researcher. We will advertise the study amongst ANTLER 75+ investigator GP networks and social media using a flyer. Interested GPs will be asked to contact the researcher. In addition, we will ask GPs who participate in an interview to share details of the study with their colleagues. When a GP has contacted the research team, the interview will be arranged at a mutually convenient time.

The topic guide will explore decision-making around making the diagnosis of depression in older adults from under-served populations, prescribing and de-prescribing antidepressants in older adults, monitoring systems within practices and how discussion of reduction or withdrawal of antidepressants might be implemented in practice. The topic guide will be modified iteratively as data generation and analysis progresses. GPs will be reimbursed according to BMA rates (currently £88.80 per hour).

All interviews will be recorded using an encrypted digital voice recorder. The recording will be anonymised before being transcribed verbatim, the transcript forming the data for analysis. We will use a transcription company (The Transcription Company; www.thetranscription.co.uk) which has a contract with Keele University.

Each dataset will be analysed thematically, using constant comparison[45,46], separately and then a framework approach[47] across the data-sets.
We will sensitise the topic guides to underpin the framework analysis using the shared-decision-making[48] literature to understand the barriers and facilitators to implementation of de-prescribing antidepressants in older adults in under-served communities.
Analysis will be conducted by the employed qualitative researcher and Chew-Graham, with input from the PAG, lived experience co-applicants and broader research team.

10.3 Qualitative Data Storage and Management

Personal data will only be accessible to the Keele University research team during the data collection phase of the study. A study database containing participant information will be stored on Keele University's secure network in a password-protected folder in the OneDrive storage area of the project. Personal data will be kept for up to six months after the end of the study and will be stored in a different file to the transcripts. The recording equipment used to record the interviews will be erased after each interview has been uploaded to the secure folder on the University server.

The anonymised interview recording anonymised transcripts, and the consent form with identifiable personal information, will be stored in separate locked and protected folders on Keele University secure servers in line with GDPR requirements and the Keele Data Security Policy.

Research data will be pseudo-anonymised prior to analysis through the use of a unique study code; only members of the study team based at Keele University will have access to the OneDrive folder to identify data, as Keele University is the data controller for this qualitative study. Pseudo-anonymised transcripts will be shared with research team members from external institutes via, for example, Sharepoint. Electronic copies of anonymised transcripts will be stored for **ten** years on a secure university network to be accessible for future research (where participant consent has been obtained) prior to being destroyed. For archiving at the end of the study, all data will be maintained in such a form that they cannot be linked with identifiable participants and will be anonymised in the reports.

Keele University is the 'data controller' and is responsible for looking after the information and using it properly as detailed in the University Privacy Notice. This information is given in the Participant Information Leaflets https://www.keele.ac.uk/privacynotices/privacynotice-researchparticipants/

Data should only be held where there is a legitimate need to do so. Once the stage of the study which involves using this data is complete (inviting participants to take part in research, asking for their express consent, and conducting the interviews) are complete the personal data must be securely destroyed (Keele Data Privacy Policy, 2018). All data will be destroyed (deleted electronically) 10 years after the end of the research study as per Keele University Records Retention Schedule (2021)
https://www.keele.ac.uk/policyzone/data/recordsretentionschedule/

Any paper documentation containing any personal details will be uploaded to the secure folder and paper copies cross-shredded and destroyed through the Keele University approved confidential waste system.

10.4 Qualitative Data Sharing Agreements

Digital recordings of the majority of the interviews will be transferred via a secure online system (**www.sendthisfile.com**) to The Transcription Company for transcription. A data sharing and confidentiality agreement are currently in place between Keele University and The Transcription Company to control data use in line with GDPR. Some digital records of interviews may be transcribed by the ANTLER 75+ researcher.

11 Regulatory & Ethical Issues

11.1 Compliance

11.1.1 Regulatory Compliance

This trial will adhere to the conditions and principles of GCP as outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), as amended.

In conducting the trial, the Sponsor, UCL CCTU and sites shall comply with the protocol and with all relevant guidance, laws and statutes, as amended, applicable to the performance of clinical trials and research including, but not limited to:

- UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority
- Declaration of Helsinki 1996
- Data Protection Act 2018 (DPA number: Z6364106),
- General Data Protection Regulation (EU)2016/679 (GDPR)
- Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) (IMP trials only)
- EU Clinical Trials Regulation No. 536/ 2014 (if applicable, for sites in EU/EEA)
- The Human Medicines (Amendment etc.) (EU Exit) Regulations 2019 (SI 2019/775)
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11.1.2 Site Compliance

Agreements that include detailed roles and responsibilities will be in place between participating sites and CCTU.

Participating sites will inform CCTU as soon as they are aware of a possible serious breach of compliance, so that CCTU can fulfil its requirement to report the breach if necessary (see section 7.9).

11.1.3 Data Collection & Retention

Clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for a minimum of 5 years after the end of the trial. During this period, all data should be accessible, with suitable notice, to the competent authorities, the Sponsor, and other relevant parties in accordance with the applicable regulations. The data may be subject to an audit by the competent authorities. Medical files of trial participants should be retained in accordance with the maximum period of time permitted by the hospital, institution or private practice.

11.2 Ethical Approvals

11.2.1 Ethical Considerations

We will obtain informed consent for all the procedures in the study. We will explain that people can withdraw from the study at any time. We have procedures to ensure that the participant is

withdrawn from study medication if clinically indicated and will work closely with the participants' GP to ensure the safety of the participants. Any participant who is withdrawn from the trial early will be unblinded to their GP to ensure they receive the appropriate treatment.

Participants will remain under the care of their GP throughout the trial.

We will not be reimbursing for time and expenses when taking part in the study.

The participant's GP will be informed of their allocation at the end of the trial so that they can discuss future treatment options. Participants will be advised 4 weeks in advance to make an appointment with their GP as soon as the trial has ended so that they have continuation of treatment. GPs will be sent a letter at the same time, informing them that the trial will be ending soon and that we have advised the participant to make an appointment with them. They will then be sent the end of trial unblinding letter at least one week prior to the end of the trial to ensure they have the information available at the appointment.

Participants in this trial may experience a return of their depression or thoughts of self-harm and suicide. Participants will be advised to see their GP if they think their depression is returning. An ANTLER 75+ Suicide Ideation Management Plan is in place to make sure that if suicidal or self-harm thoughts are expressed to the research teams at sites, their GP will be informed and appropriate action can be taken. If participants become distressed, researchers will be able to offer support during the appointment and direct them to supportive services. Participants must provide informed consent that if a potential risk is identified, contact may be made with other agencies to ensure the safety of the participant and/or others with or without their permission.

Clinicians at site and GPs will have each other's contact details to discuss any matters pertaining to participants throughout the trial, if necessary,

11.2.2 Ethics Committee Approval

Following main REC approval and Health Research Authority (in England and Wales) approvals and before initiation of the trial at each site, the local information pack will be sent by UCL CCTU. The local information pack will contain the protocol, all informed consent forms, and information materials to be given to the prospective participant, the Clinial Trial Site Agreement, the Organisation Information Document (OID), and the validated Schedule of Events Cost Attribution Template (SoECAT). R&D offices at NHS sites will be asked to confirm capacity and capability. Any further substantial amendments will be submitted and approved by the main REC and HRA.

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

11.3 Competent Authority Approvals

This protocol will be reviewed by/submitted to the MHRA in the UK where the trial will be conducted.

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by The Medicines for Human Use (Clinical Trials) Regulations 2004/1031. Therefore, a Clinical Trial Authorisation (CTA) is required in the UK.

The progress of the trial and safety issues will be reported to the competent authority, regulatory agency or equivalent in accordance with relevant national and local requirements and practices in a timely manner.

Safety reports, including expedited reporting and SUSARS will be submitted to the competent authority in accordance with each authority's requirements in a timely manner.

11.4 Other Approvals

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

11.5 Trial Closure

Trial closure is defined as the date when all data have been received, cleaned and all data queries resolved at all sites and the database locked for final analysis.

The MHRA and the REC/HRA will be notified within 90 days of trial completion. Within one year of the end of the trial, the CCTU will submit a final trial report with the results of the trial, including any publications/abstracts of the trial, to the HRA and the MHRA. In case the trial is ended prematurely, the CCTU will notify the HRA and the MHRA within 15 days, including the reasons for the premature termination.

12 Indemnity

UCL holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. Should the participant be admitted to hospital whilst enrolled on the trial, UCL 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 hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

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 UCL 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 UCL's insurers, via the Sponsor's office.

13 Finance

ANTLER 75+ is fully funded by an HTA, NIHR grant number 153131. It is not expected that any further external funding will be sought.

14 Oversight & Trial Committees

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary.

There is a number of committees involved with the oversight of the trial. These committees are detailed below, and the relationship between them expressed in the figure. The Terms of Reference and full composition of each committee can be obtained from cctu.antler75@ucl.ac.uk,

14.1 Trial Management Group

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and CCTU staff and PPI contributors. The TMG will be responsible for the design, coordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG Terms of Reference.

14.2 Trial Steering Committee

The Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. The membership, frequency of meetings, activity and authority will be covered in the TSC Terms of Reference. Two PPI members are part of the TSC.

14.3 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is the only oversight body that has access to the confidential, accumulating data for the trial. The IDMC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity and authority will be covered in the IDMC Terms of Reference. The IDMC will advise the TSC through its Chair.

14.4 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. UCL is the trial sponsor and has delegated the duties as sponsor to CCTU via a signed letter of delegation.

15 Patient & Public Involvement

Patient and Public Involvement (PPI) in research is defined by INVOLVE (an advisory group established by the NIHR) as research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them. INVOLVE intends 'public' to include patients, potential patients, carers and other users of health and social care services, as well as people from organisations that represent people who use services. In some cases, this may include involvement of a trial's participants in guidance or oversight of a trial. Our Lived Experience co-applicants will arrange a Lived Experience Group to provide input when required during the study.

15.1 Potential Impact of PPI

PPI is particularly important in this older cohort (aged 75 years and over) to ensure that all study documentation and methodology is applicable, workable and acceptable to this age group. Members of the PPI will be able to advise us on the best way to recruit participants and the best way to collect the data. The PPI group have been heavily involved in the design of this trial and the preparation of patient facing documentation and this will continue throughout the trial.

15.2 Identifying PPI Contributors

Two lead PPI members have been identified and are an active part of the Trial Management Group. These members are both aged over 75 and have experienced depression in the past. Additional PPI members will be identified through existing channels, and their help will be utilised through the Lived Experience Group Meetings chaired by the existing PPI members. We will ensure that the group is diverse and reflects the views of the wider community. Reimbursement for time and travel costs is available.

15.3 Protocol Design & Trial Set Up

The lead PPI members are members of the Trial Management Group and Trial Steering Committee and have been involved in all aspects of the trial design and set up phase. They will review all participants facing material including the Participant Information Sheet, Informed Consent Form, Medication Participant Information Sheet, and Invitation letter. In person PPI meetings have been budgeted for in the Grant.

15.4 PPI in the Ongoing Running of the Trial

As the existing PPI members are part of the TMG, they will be involved in all meetings throughout the running of the trial and will be able to contribute to decision making. The lead PPI members will be able to feed back to the wider PPI group if required. Any amendments to trial documentation will be reviewed by the PPI group pre submission for approval. The PPI members are very engaged with the CCTU trial team and the CI and have regular meetings which are minuted. Their contribution is very valuable and regular meetings will continue throughout the trial.

15.5 Interpreting & Evaluation Impact of PPI

PPI input will be included in the main publication.

If funding allows, the impact of PPI using a recognised method (e.g. the Public Involvement Impact Assessment Framework, PiiAF), will be described in future publications.

16 Publication & Dissemination of Results

16.1 Publication Policy

16.1.1 Trial Results

The results of the trial will be disseminated regardless of the direction of effect. The publication of the results will comply with the UCL CCTU Publication Policies.

A lay summary of the results will also be produced to be disseminated to those participants who took part. A check with the General Practice will be made to ensure the participants are still alive, prior to sending the results out. We will only send results to those confirmed as being alive.

A summary of results will be submitted to the REC via the HRA (https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/final-report-form/) and published through an open-access mechanism in a peer-reviewed journal within 12 months of the trial closure.

For CTIMPs, a summary of results will be published within one year of the end of study, in the registry where the clinical trial is registered.

More guidance can be found on the HRA website https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/#finalreport

16.1.2 Authorship

Authorship will be according to internationally agreed criteria for publishing in peer reviewed scientific journals. We will draw up a publication policy for the study agreed with co-investigators.

16.1.3 Reproducible Research

We will publish a protocol paper in a peer reviewed journal so that the relevant information will be publicly available.

Applications for access to the extended follow up dataset at the end of ANTLER 75+ should be submitted formally in writing to UCL CCTU and will be considered and approved in writing after formal consideration by the ANTLER 75+ oversight committees and the CI.

17 Data and/or Sample Sharing

Data will be available for sharing after publication of the trial results. Researchers wishing to access ANTLER 75+ data should contact the Trial Management Group in the first instance, clearly outlining the purposes. We would expect any scientists to collaborate with the research team and any requests will need to be approved by the TSC and Sponsor.

18 Ancillary Studies

There are no ancillary studies proposed. If any future ancillary studies are proposed, we will seek approval from TMG, TSC and funder and apply for all the necessary ethics and approvals for the proposed study.

19 Protocol Amendments

Table 7. Summary of Protocol Amendments

Protocol version	Protocol date	Summary of changes
1.0	26Jun2024	Initial submission
2.0	01Aug2024	Changes requested by REC and MHRA following initial submission; SECTION 3 - An additional sentence has been added in page 19 stating that only participants reviewed as suitable for the trial by the GP will be invited to participate. A sentence on page 23 has been amended to state that GPs will also have the option to contact us at time of randomisation if they have any concerns EXCLUSION CRITERIA - A 6th exclusion criteria has been added: GP considers the patient would be unsuitable for the trial (for any reason) SECTION 3.2 – the sentence stating that a GP can lower a patients current dose of antidepressant in order for them to become eligible has been removed SECTION 5 - rCIS_R questionnaire has been added to the week 4 assessment; AE recording has been added to the week 56 schedule SECTION 16: this now includes a sentence to state that we will check with the General Practice that a participant is still alive prior to sending them the results of the trial IDMC Committee Members – this table has been updated to provide professional details of the Chair
3.0	22Aug2024	The REC, CTA and Trial Registration Numbers have been updated Section 1.4 Risk Associated with IMP Distribition:A sentence has been added to state IMP will be sent out well in advance to ensure there is no period when they are without medication (page 7) Section 3.3 Recruitment: A sentence has been added on page to state that anyone who has signed the National Opt-Out Register will not be invited to participate (page 19) Section 5.1 Outcomes: A sentence has been added to state that every effort should be made to ensure visits are completed on time and that extended gaps between visits should be avoided (page 30)

		Section 5.1.2 Secondary Outcomes: The Geriatric Depression Scale has been changed to be measured at screening, instead of baseline (page 31 and 33); The word modified has been added to the SF-12 questionnaire we are using and the reference for this has been corrected Section 5.2 Participant Timeline: the window for all visits to be completed has been extended (page 33); a note has been added to state that the baseline visit must be completed within 28 days of the screening visit; a note has been added that visits should be completed as close to the due date as possible. If one visit is completed early then the every effort should be made to the complete the following visit on time and not late. Section 5.5 Loss to Follow-Up: Additional wording has been added to state that we will contact the participants family member or friend if we are unable to contact them (to check their welfare) and that we will continue to send IMP even if they miss a follow-up assessment to reduce the risk of sudden withdrawal (page 36) Section 7.6 Data Management; additional wording has been added to state the name and contact number of the participants nominated friend or relative will be stored securely in the Data Safe Haven (page 46) Sections 8.3.4 Statistical Methods and 8.3.7 Analysis Population and Missing Data: additional wording has been added in to define intention to treat as all participants who have taken at least 1 dose of the IMP. Anyone who has not (evidenced by the unopened IMP being returned to a site or pharmacy) will be excluded from the intention to treat analysis (page 52)
4.0	28 Oct 2024	REC reference number corrected from 4/SC/0247 to 24/SC/0247 on the front page and page iii Section 7.6 Data Management: additional wording has been added to state that we will delete the contact details of the participants nominated friend or relative within one month of participant finishing on the trial (page 46)
5.0	16 Jan 2025	Page v Study Setting – names of regions have been removed and now says patients will be recruited from GP sites across England and Wales. It has also been clarified that GP practices are PIC sites (for recruitment only), and all research activity will occur at NHS organisations or Universities. Date of first enrolment has been changed to March 2025

		Trial Diagram Consent signing has been moved from Filter 3 (Baseline assessment) to Filter 2 (Screening assessment) (page ix) Section 2.1 Site Selection The wording has been updated to state that participants will be selected from GP practices across England and Wales and that research sites within these regions will perform all research activity (research sites being a mix of NHS organisations and Universities) Section 3.5 Screening Procedures and Informed Consent The wording has been amended in the first paragraph to say that once a participant's questions have been satisfactorily answered, then signed informed consent will be sought prior to the participant being screened. The sentence on eligibility screening has been moved down to paragraph 5 (page 21) Section 3.5.1 Process of informed Consent Wording which stated that screening could be obtained before informed consent has been removed. (page 22) Consent via video call has been updated to state that this should only be done in exceptional circumstances, and the reason must be fully documented. This video call will be recorded and stored securely providing appropriate IG requirements are in place Section 5.1.2 Secondary Outcomes The DESS questionnaire being used is a 15-item questionnaire, this has been corrected from a 17-item questionnaire (page 31) Section 5.2 Participant Timeline Consent has been added A correction has been made to the Pictorial Fit-Frail Scale and we will not ask the participant to return the completed form, instead they will use it as a guide to tell the researcher their answer. (page 34) Section 6.1 Definitions Table 5 Definitions has been updated Section 6.3.1.3 Causality Table 6 Assigning Type of SAE Through Causality has been updated to Related or Unrelated (rather

		than Related, Some evidence, Little evidence, No evidence, Unrelated) Section 6.3.1.4 Expectedness Expectedness will now be assessed by the Sponsor Independent Safety Review Team at CCTU Section 6.3.2.1 Notifications by the Investigator to the CCTU The minimum criteria for reporting an SAE has been updated Section 6.3.2.2 CCTU Responsibilities If the SAE is classified as a SUSAR, then the trial team will notify the UCL JRO safety office who will now report the SUSAR onto the MHRA ICSR submissions online portal
V6.0	09 Apr 2025	Minor administrative changes throughout the document and clarification of processes to ensure procedures conducted correctly. In particular the following sections have minor changes: Table 1 – Summary of risks of the IMPs has been updated Section 2.1.1 – Study Setting as ben amended to clarify the role of RRDNs and the us of DocMail to send out invitation packs; Keele University is no longer acting as a coordinating centre. Section 2.1.2.1 – The trial is registered with the NIHR Associate PI scheme and Associate PIs may participate in line with this scheme Section 2.1.2.2 – The trial is adopted onto the NIHR portfolio and is eligible for NIHR support at sites; The CI or PI at a site may act as PI for another site where required Section 2.3 – Keele is no longer acting as a coordinating centre. This section has been renamed Regional Research Delivery Networks (RRDNs) and their role explained Section 3.3 – Participants will be asked to read the name of their antidepressant to the researcher to confirm which antidepressant they are taking at the start of the trial. This confirmation may also be done by contacting their GP practice for this information. Participants should not be randomised until this check has been completed. Section 4.6 – Clarification has been added to the unblinding section. Section 5.1 – a sentence has been added to say that participants may be contacted between study visits to

		collect information following adverse events. The DESS will now also be collected at weeks 24 and 52 (this has also been changed in Table 4 – Participant Timeline) Section 5.3 – Clarification has been added to participants transfers if a GP moves practice. Section 6 (Safety Reporting) – clarification has been added to this section.

20 References

1. Chan AW, Tetzlaff JM, Altman DG et Al. SPIRIT 2013 Statement: Defining Protocol Items for Clinical Trials. *Ann Intern Med* 2013; 158:200-207.
2. Chan AW, Tetzlaff, Gotzsche et Al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013; 346: e7586.
3. Lewis G, Pelosi AJ, Araya R, Dunn G. Measuring psychiatric disorder in the community: A standardized assessment for use by lay interviewers. Psychological Medicine 1992;22:465-86.
4. D'Ath P, Katona P, Mullan E, Evans S, Katona C. Screening, detection and management of depression in elderly primary care attenders. 1: The acceptability and performance of the GDS15 and the development of short versions. Family Practice 1994;11:260-266.
5. Almeida OP, Almeida SA. Short versions of the Geriatric Depression Scale: A study of their validity in the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. International Journal of Geriatric Psychiatry 1999;14:858-865.
6. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalised anxiety disorder: The GAD7. Archives Internal Medicine 2006;166:1092-7.
7. Vanderkoog JD, Kennedy SH, Bagby RM. Antidepressant side effects in depression patients treated in a naturalistic setting. Canadian Journal of Psychiatry 2002;47:174-85.
8. Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomised clinical trial. Biological Psychiatry 1998;44:77-87.
9. Brazier, J.E. and Roberts, J. (2004) 'The estimation of a preference-based measure of health from the SF-12.', *Medical care*, 42(9), pp. 851–9. Available at: https://doi.org/10.1097/01.mlr.0000135827.18610.0d
10. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005 Apr;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x. Erratum in: J Am Geriatr Soc. 2019 Sep;67(9):1991. PMID: 15817019.
11. Theou O, Andrew M, Ahip SS, Squires E, McGarrigle L, Blodgett JM, Goldstein J, Hominick K, Godin J, Hougan G, Armstrong JJ, Wallace L, Sazlina SG, Moorhouse P, Fay S, Visvanathan R, Rockwood K. The Pictorial Fit-Frail Scale: Developing a Visual Scale to Assess Frailty. Can Geriatr J. 2019 Jun 30;22(2):64-74. doi: 10.5770/cgj.22.357. PMID: 31258829; PMCID: PMC6542581.
12. Chung CCY, Fung JLF, Lui ACY, Chan MCY, Ng YNC, Wong WHS, Lee SL, Knapp M, Chung BHY. Client Service Receipt Inventory as a standardised tool for measurement of socio-economic costs in the rare genetic disease population (CSRI-Ra). Sci Rep. 2021 Dec 13;11(1):23837. doi: 10.1038/s41598-021-03379-5. PMID: 34903789; PMCID: PMC8668911.Hernández-Alava M, Pudney S. Eq5Dmap: A Command for Mapping between EQ-5D-3L and EQ-5D-5L. The Stata Journal. 2018; 18 :395-415 2012;15(5):708–15.
13. Evans O, Singleton N, Meltzer H, Stewart R, Prince M. The mental health of older people. The mental health of older people. London: HMSO, 2003.
14. Herrman H, Patel V, Kieling C, et al. Time for united action on depression: a *Lancet*-World Psychiatric Association Commission. The Lancet 2022; doi.org/10.1016/S0140-6732(21)02141-3.

15. Gansler DA, Suvak M, Arean P, Alexopoulos GS. Role of executive dysfunction and dysexecutive behaviour in late-life depression and disability. American Journal of Geriatric Psychiatry 2015;23(10):1038-45.
16. Valkanova V, Ebmeier KP. Vascular risk factors and depression in later life: a systematic review and meta-analysis. Biological Psychiatry 2013;73:406-13.
17. Lenze EJ, Schulz R, Martire LM, Zdaniuk B, Glass T, Kop WJ, et al. The course of functional decline in older people with persistently elevated depressive symptoms: longitudinal survey from the Cardiovascular Health Study. Journal of the American Geriatrics Society 2005;53(4):569.
18. Coupland C, Dhiman P. Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ 2011;343:d4551.
19. McCrea RL, Sammon CJ, Nazareth I, Petersen I. Initiation and duration of selected SSRI prescribing over time: UK cohort study. British Journal of Psychiatry 2016;209:421-6.
20. Comijs HC, Nieuwesteeg J, Kok R, et al. The two-year course of late-life depression: 39 results from the Netherlands study of depression in older persons. BMC Psychiatry 2015;15:20.
21. Wilkinson P, Izmeth Z. Continuation and maintenance treatments for depression in older people. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD006727. DOI: 10.1002/14651858.CD006727.pub3.
22. Lewis G, Marston L, Duffy L, et al. Maintenance of discontinuation of antidepressants in primary care. New England Journal of Medicine 2021;385:1257-1267.
23. Azar, A.R., Chopra, M.P., Cho, L.Y., Coakley, E., and Rudolph, J.L. (2011). Remission in major depression: Results from a geriatric primary care population. International Journal of Geriatric Psychiatry, 26, 48–55.
24. Licht-Strunk, E., Van Marwijk, H.W.J., Hoekstra, T., Twisk, J.W.R., De Haan, M., and Beekman, A.T.F. (2009). Outcome of depression in later life in primary care: Longitudinal cohort study with three years' follow-up. British Medical Journal, 338, a3079
25. Herrmann, L.L., Le Masurier, M., and Ebmeier, K.P. (2008). White matter hyperintensities in late lifedepression: A systematic review. Journal of Neurology, Neurosurgery and Psychiatry, 79, 619–24
26. Alexopoulos, G.S., Murphy, C.F., Gunning-Dixon, F.M., Latoussakis, V., Kanellopoulos, D., Klimstra, S., Lim, K.O., and Hoptman, M.J. (2008). Microstructural white matter abnormalities and remission of geriatric depression. American Journal of Psychiatry, 165, 238–44.
27. Hickie, I., Scott, E., Wilhelm, K., and Brodaty, H. (1996). Subcortical hyperintensities on magnetic resonance imaging in patients with severe depression: A longitudinal evaluation. Biological Psychiatry, 42, 367–74.
28. O'Brien, J., Ames, D., Chiu, E., Schweitzer, I., Desmond, P., and Tress, B. (1998). Severe deep white matter lesions and outcome in elderly patients with major depressive disorder: Follow up study. British Medical Journal, 317, 982–4
29. Kohler, S., Thomas, A.J., Lloyd, A., Barber, R., Almeida, O.P., and O'Brien, J.T. (2010b). White matter hyperintensities, cortisol levels, brain atrophy and continuing cognitive deficits in late-life depression. British Journal of Psychiatry, 196, 143–9.
30. Sneed, J.R., Culang, M.E., Keilp, J.G., Rutherford, B.R., Devanand, D.P., and Roose, S.P. (2010). Antidepressant medication and executive dysfunction: A deleterious interaction in late-life depression. American Journal of Geriatric Psychiatry, 18, 128–35.
31. Depression in adults: treatment and management NG222 29 June 2022 (https://www.nice.org.uk/guidance/ng222

32. Devlin NJ, Krabbe PF. The development of new research methods for the valuation of EQ-5D-5L. Eur J Health Econ. 2013;14(Suppl.1):S1–3.

33. Beecham J, Knapp M. Costing psychiatric interventions. In: Thornicroft G, editor. Measuring mental health needs. London: Gaskell; 2001. p. 200–24. (EQ-5D-5L)

34. Curtis L, Burns A. Unit costs of health and social care 2022. Canterbury: Personal Social Services Research Unit, University of Kent; 2022.

35. Department of Health. 2021–2022 NHS reference costs. Department of Health, 2022.

36. Faria R, Gomes M, Epstein D, et al. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *Pharmacoeconomics* 2014; 32: 1157-1170.

37. StataCorp. Stata Statistical Software: release 18. College Station: StataCorp LP.

38. Zellner A. An efficient method of estimating seemingly unrelated regression equations and tests for aggregation bias. J Am Stat Assoc. 1962;57(298):348–68.

39. Fenwick E, Byford S. A guide to cost-effectiveness acceptability curves. Br J Psychiatry. 2005 Aug;187:106-8. doi: 10.1192/bjp.187.2.106. PMID: 16055820

40. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making. 1998 Apr-Jun;18(2 Suppl):S68-80. doi: 10.1177/0272989X98018002S09. PMID: 9566468.

41. Malterud K, Siersma VD, Guassora AD. Sample size in qualitative interview studies: guided by information power. Qualitative health research. 2016;26(13):1753-60.

42. Public Health England. SHAPE. No date; Available at: https://shapeatlas.net/.Noy C. Sampling knowledge: the hermeneutics of snowball sampling in qualitative research. Int J Soc Res Methodol. 2009;11(4):327–44.

43. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative research in psychology. 2006;3(2):77-101.

44. Fram SM. The constant comparative analysis method outside of grounded theory. Qualitative Report. 2013;18:1.

45. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC medical research methodology. 2013;13(1):1-8.

46. Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, et al. Shared decision making: a model for clinical practice. Journal of general internal medicine. 2012;27(10):1361- 7.

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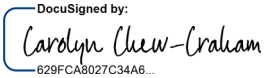
Carolyn Chew-Craham c.a.chew-graham@keele.ac.uk Security Level: Email, Account Authentication (Optional)	DocuSigned by:  629FCA8027C34A6... Signature Adoption: Pre-selected Style Using IP Address: 86.190.168.227	Sent: 06 May 2025 | 10:44 Viewed: 06 May 2025 | 10:47 Signed: 06 May 2025 | 10:47
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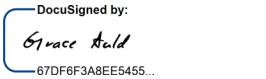
Grace Auld g.auld@ucl.ac.uk Clinical Project Manager UCL Security Level: Email, Account Authentication (Optional)	DocuSigned by:  67DF6F3A8EE5455... Signature Adoption: Pre-selected Style Using IP Address: 82.43.220.15	Sent: 06 May 2025 | 10:44 Viewed: 06 May 2025 | 11:52 Signed: 06 May 2025 | 11:52
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