PrEgabalin for Treatment Resistant generalised Anxiety disorder (PETRA)

A double-blind randomised controlled clinical trial to evaluate the addition of pregabalin to primary care patients who have not responded or partially responded to treatment with antidepressants.

Version	6.0
Date	18 November 2024
Sponsor	University College London (UCL)
Comprehensive Clinical Trials Unit Trial Adoption Group #	CTU/2021/381
Sponsor R&D ID #	143397
Trial registration #	ISRCTN 16993990
CTA #	20363/0458/001-0001
REC #	23/EM/0192
IRAS #	1007569

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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 PETRA 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 (Chan, Tetzlaff, Altman *et al*., 2013). The SPIRIT Statement Explanation and Elaboration document (Chan, Tettzlaff, Gotzsche *et al*., 2013) 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) is the trial sponsor and has delegated responsibility for the overall management of the PETRA trial to CCTU. Queries relating to UCL 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 petrasponsor@ucl.ac.uk

Funding

National Institute for Health and Care Research, Health Technology Assessment (NIHR HTA) reference number 134074.

Trial Registration

This trial has been registered with the ISRCTN Clinical Trials Register, where it is identified as ISRCTN 16993990.

Trial Administration

Please direct all queries to cctu.petra@ucl.ac.uk in the first instance; clinical queries will be answered by the Chief Investigator.

Coordinating Unit

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Structured trial summary

Acronym or short title	PETRA
Scientific Title	PrEgabalin for Treatment Resistant generalised Anxiety disorder (PETRA)
CCTU Trial Adoption Group #	CTU/2021/381
Sponsor R&D ID #	143397
CTA #	20363/0458/001-0001
REC #	23/EM/0192
IRAS #	1007569
Primary Registry and Trial Identifying Number	ISRCTN 16993990
Date of Registration in Primary Registry	19th September 2023
Secondary Identifying Numbers	NIHR HTA grant ref: 134074
Source of Monetary or Material Support	NIHR HTA
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	Patients with Generalised anxiety disorder (GAD) who have not responded to anti-depressants
Intervention(s)	Oral pregabalin or identical placebo. Participants will be randomised with a 1:1 ratio to pregabalin 50-300mg or placebo using a flexible dosing strategy that will mimic usual care. Participants will initially start at 50mg and may increase their dose up to a maximum of 300mg (where appropriate). Participants will be given clear instructions to titrate the dose starting: • Day 1-4 one tablet a day (50mg) • Day 5-9 two tablets a day (100mg) • Day 10-14 three tablets a day (150mg) • Day 15 onwards four tablets a day (200mg) At the PI discretion, study medication may be increased to 5 tablets a day (250mg) or 6 tablets a day (300mg). Participants will be advised to stop increasing the medication dose at the point they find it is satisfactorily effective, or if they experience adverse effects which are not tolerable up to a maximum of 4 tablets. They will continue taking the study medication until the tapering

	period (see below) starts at the 26-week follow up assessment. After completion of the 26-week assessment participants will reduce their study medication over the next 28 days. Participants will be given specific instructions for tapering depending upon the number of tablets they are taking.
Key Inclusion and Exclusion Criteria	INCLUSIONS • Meeting ICD-11 criteria for generalised anxiety disorder using the revised clinical interview schedule (CIS-R) • Scoring ≥12 on the CIS-R total score • Age 18-74 years (upper age limit to ensure the validity of our measures) • Currently taking an SSRI, SNRI or mirtazapine (at specified doses; the full list is in the trial guidance document that all investigators at sites have to follow) for a minimum of 8 weeks prior to randomisation and with good adherence as agreed with PI. • Treatment with at least one other antidepressant before their current antidepressant EXCLUSIONS • Currently taking pregabalin or use within the previous 1 month (i.e. wash-out of 1 month required) • Taking regular antipsychotics • Have bipolar disorder, psychosis, or alcohol misuse • Current or recent opiate dependence where there is a risk of pregabalin abuse • Current use of opiates with a daily dose of >15 morphine milligram equivalents • Creatinine clearance <30ml/min (measured by eGFR is acceptable) • Requirement to use home oxygen machines daily for respiratory problems. • Experience breathlessness and score ≥3 on the MRC Dyspnoea scale ('Stops for breath after walking about 100 metres or after a few minutes on the level' or 'Too breathless to leave the house or breathless when dressing or undressing') • Regular daily use of z drugs >3.75mg zopiclone or >10mg zolpidem • Regular daily use of benzodiazepines or regular night-time use >10mg diazepam or equivalent. • Currently receiving psychotherapy and within 6 months of starting therapy

	• Pregnancy, planned pregnancy and women who are breastfeeding • Unable to complete self-administered scales in English (some scales are not validated in other languages) • Taking part in another CTIMP
Study Type	Interventional Trial design including: • randomised • double blind (participants and researchers are blinded to allocation) • assignment (parallel) • Phase IV • Web-based computerised system to randomise with a 1:1 ratio • Nested qualitative study • Internal pilot at UCL site
Study setting	Primary care patients
Date of First Enrolment	August 2023
Target Sample Size	498
Trial Duration	45 months
Primary Outcome(s)	Anxiety symptoms measured with GAD7 at 12 weeks as a continuous score
Key Secondary Outcomes	• Anxiety symptom scores (GAD7) at all other follow up times (3, 6, 26, ~30 weeks) and GAD7 as a binary outcome (GAD7 ≥10) at follow up times (3, 6, 26, ~30 weeks). • Self-reported health and social care resource use, employment and time off work will be completed at 26 weeks (asking about the previous 6 months) using a bespoke health and social care Resource Use Questionnaire. • Medication prescriptions will be collected from primary care medical records covering 6 months pre and post randomisation. The following key secondary outcomes are repeated at all follow-up visits: • Depressive symptom scores using PHQ-9. • Self-reported global improvement, quality of life with SF-12 Health Survey and EQ-5D-5L. • Adverse effects of pregabalin and antidepressants adverse effects using scales from previous studies with additional items for pregabalin. • Adherence to study medication using a single item asking if they are still taking study medication and a 5-item scale used in the MIR and Cobalt studies. • Alcohol consumption using the AUDIT-PC. • Benzodiazepine use.

	After completion of the 26-week assessment and the taper period there will be a follow-up assessment 30 days after the 26-week assessment and we have called this the ~30 week follow up assessment. The comparison between the randomised groups will be double blind. Withdrawal symptoms that have been reported include agitation, irritability, insomnia, myalgia and palpitations and will be assessed using self-administered scales.
Nested Qualitative study	Some participants will be invited to a semi-structured interview that we have called the "6th additional interview" in the PIS and this will explore acceptability of taking and prescribing pregabalin for anxiety, from the perspectives of trial participants and GPs.

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
Glyn Lewis	DoP UCL	Chief Investigator
Larisa Duffy	DoP UCL	Trial Manager
David Kessler	University of Bristol	Professor of Primary Care
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Ekaterina Bordea	UCL CCTU	Health Economist

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 Management Group

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Grace Auld	UCL CCTU	Clinical Project Manager

Trial Steering Committee

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Rachel Phillips	Imperial College London	Independent Statistician
Ami Vadgama	UCL	Independent PPI
John Campbell	Exeter University	Independent GP
Caroline Sanders	The University of Manchester	Independent Qualitative Expert
Larisa Duffy	UCL DoP	Facilitator
Glyn Lewis	UCL DoP	CI
Nick Freemantle	UCL CCTU	Sponsor representative

Independent Data Monitoring Committee

Name	Affiliation	Role
Chris Burton	University of Sheffield	Independent Chair
Clare Robinson	Queen Mary University of London	Independent Statistician
Steven Marwaha	University of Birmingham	Independent Clinician

Trial Team

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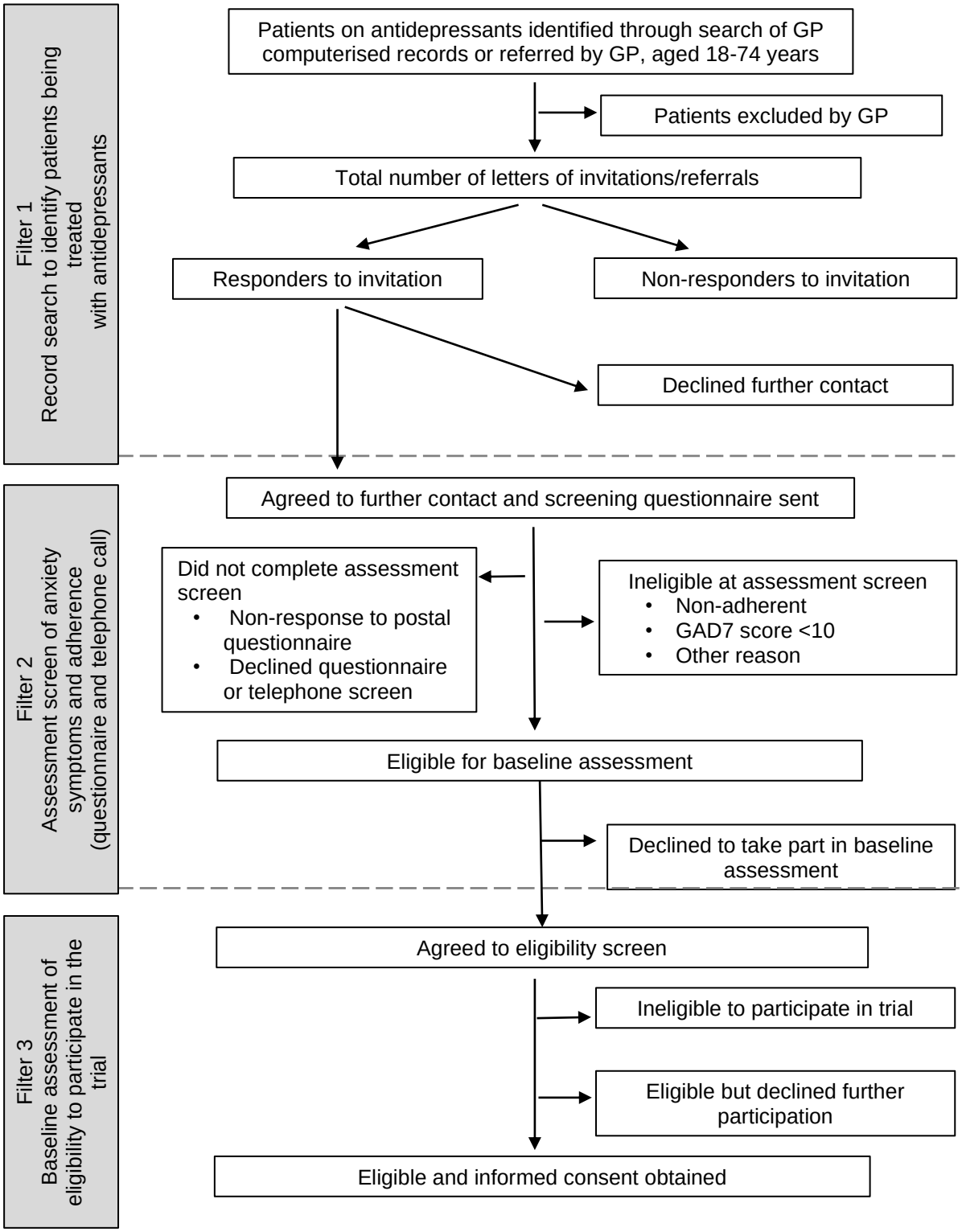
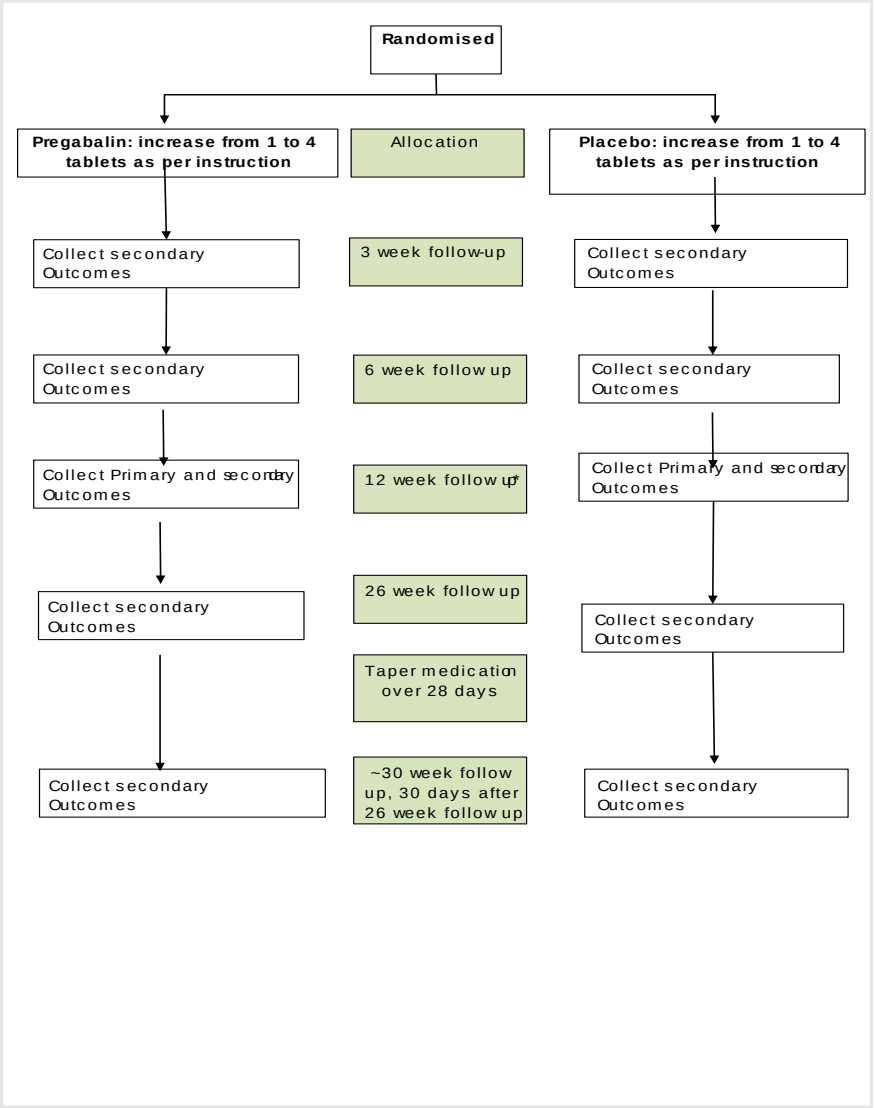
Trial Diagrams





*approximately 25 participants will also participate in a semi-structured interview we call the 6th additional interview in the nested qualitative study

Abbreviations

AE	Adverse Event
AR	Adverse Reaction
AUDIT PC	Alcohol Use Disorders Identification Test; Primary Care
BNF	British National Formulary
CA	Competent Authority
CCTU	Comprehensive Clinical Trials Unit at UCL
CI	Chief Investigator
CIS-R	Clinical Interview Schedule - Revised
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product
DSUR	Development Safety Update Report
EC	Ethics Committee
EDC	Electronic Data Capture
EU	European Union
EudraCT	European Clinical Trials Database
FSH	Follicle Stimulating Hormone
GAD	Generalized Anxiety Disorder
GAD-7	Generalized Anxiety Disorder Assessment-7
GCP	Good Clinical Practice
GP	General Practitioner
HE	Health Economist
HEAP	Health Economics Analysis Plan
HRA	Health Research Authority
IB	Investigator Brochure
ICD-11	International Classification of Diseases 11th Revision
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
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NAE	Notifiable Adverse Event
NHS	National Health Service
NIHR HTA	National Institute for Health and Care Research, Health Technology Assessment
NIMP	Non-Investigational Medicinal product
PHQ-9	Patient Health Questionnaire-9
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
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SF-12	12-Iterm Short Form Survey
SmPC	Summary of Product Characteristics
SNRI	Serotonin and norepinephrine reuptake inhibitors
SOP	Standard Operating Procedure
SNRI	Serotonin Noradrenaline Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

TMG	Trial Management Group
ToR	Terms of Reference
TSC	Trial Steering Committee
UCL	University College London
WoCBP	Women of Childbearing Potential

Glossary

Term	Definition
Benzodiazepines	A type of sedative medication
Generalised anxiety disorder	Persistent worrying or anxiety about a number of areas that are out of proportion to the impact of the events
Pregabalin	A Class C controlled substance and Schedule 3 drug, exempt from safe custody requirements, that is used to treat epilepsy, anxiety and pain
Women of Childbearing Potential	A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
Serotonin noradrenaline reuptake inhibitors	A class of drugs that are commonly used to treat anxiety and depression
Selective serotonin reuptake inhibitors	A class of drugs that are typically used to treat anxiety and depression
Z drugs	Medicines such as zopiclone (eszopiclone (Lunesta), zaleplon (Sonata)) and zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist). Zopliclone is the commonest prescribed

1 Background

1.1 Rationale

Generalised anxiety disorder (GAD) is characterised by at least 6 months of symptoms including disproportionate worry, nervousness, poor concentration and sleep disturbance. The prevalence of GAD is 6%, higher than depression (3%) in the UK (McManus *et al.,* 2016) but is less likely to present and be recognised in primary care. However, over the past few years the rate of GAD recorded in primary care has increased by 50% and especially in younger, working-age adults aged 18-35 years, in whom rates of presentation have more than doubled over the past decade (Slee *et al.,* 2021).

GAD is highly comorbid with other anxiety disorders and depression. Anxiety is best described as a continuum between "normal" levels and more severe clinically important anxiety that affects function. Our approach is to include comorbidities of depression and other anxiety disorders if people meet the diagnostic criteria for GAD. This better reflects the decisions that general practitioners (GPs) have to make if someone presents with generalised anxiety. Further, someone with other diagnoses will still benefit from any reduction in anxiety even if their comorbid condition is not influenced. Finally, reducing GAD symptoms could also lead to benefit for other comorbid conditions. For example, generalised anxiety can increase later depressive symptoms so treatments that improve anxiety symptoms could also reduce depressive symptoms (Jacobson and Newman, 2017).

Psychological treatments (e.g. cognitive behavioural therapy) and antidepressants are the main evidence-based options for GAD (NCCMH, 2011). The evidence so far is that psychological and pharmacological benefits are additive for most depressive and anxiety disorders (Cuijpers *et al.,* 2014) so optimising pharmacological treatment will also be of benefit for those receiving psychological treatments. The Covid-19 pandemic may have led to increased anxiety.

Access to psychological treatments is limited, with lengthening waiting, so research into improving the pharmacological treatment of anxiety is timely.

There is evidence that selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs) and mirtazapine (a noradrenergic and specific serotonergic antidepressant) are effective for people with GAD. After antidepressant treatment, about 50% of people still have significant generalised anxiety (Baldwin, Huusom and Maehlum, 2006; Baldwin, Waldman and Allgulander, 2011), even if there has been some improvement. There is currently no consensus and much clinical uncertainty about what pharmacological treatments should be used after non-response or partial response to antidepressants. We are only aware of one study that has investigated pregabalin as an adjunctive treatment in primary care (Rickels *et al.,* 2012) and this supports its use, but the treatment effect was relatively small and of unknown clinical importance. Furthermore, the study gave little information on how the participants were recruited and their clinical characteristics so the generalisability to the NHS or other health care settings is uncertain.

1.1.1 Explanation for choice of comparators

We are comparing active pregabalin with an identical placebo. This is so we can investigate the effectiveness and cost-effectiveness of pregabalin.

1.2 Objectives

1. To investigate whether pregabalin, in addition to an antidepressant, is an effective and cost-effective treatment for generalised anxiety disorder (GAD) in people who have not responded to antidepressant treatment
2. To investigate any adverse effects associated with combined treatment of pregabalin and antidepressants
3. To investigate withdrawal symptoms from pregabalin when it is used in combination with antidepressants
4. To investigate the acceptability of prescribing pregabalin in addition to antidepressants for GAD from the perspectives of patients and general practitioners using qualitative methods

1.3 Trial Design

A double-blind randomised controlled trial for people with generalised anxiety disorder, who have been treated with at least two antidepressants, one of which failed, and who are currently still taking the other antidepressant. Participants will be randomised with a 1:1 ratio, to pregabalin or placebo with both groups also receiving usual care from their general practitioner who will continue to prescribe their existing antidepressant.

There is also a qualitative study to explore acceptability of the intervention and implementation in practice.

1.4 Benefit Risk Assessment

Pregabalin is licensed for use in people with generalised anxiety disorder and is off patent in this indication. Its adverse effects are well described as it is commonly used clinically.

Dizziness, sedation, headache, dry mouth, fatigue, memory problems and poor concentration are most the commonly reported adverse effects. The existing randomised literature is limited in describing the frequency and importance of these side-effects. In particular, memory and other cognitive problems could be a serious adverse effect for people who are working or studying, particularly relevant given the increase in presentation in young people. Weight will be monitored, as there is potential for weight gain. Our dosing schedule is limited to a maximum of 300mg a day (of note, the maximum BNF dose is 600mg a day) and we will start people on a low dose of 50mg daily initially. Participants will increase their dose up to the recommended dose of 200mg a day. At the PI discretion, the dose may be increased further to either 250mg or 300mg if the participant is still experiencing anxiety at the recommended 200mg dose. This gradual titration, recommended dose of 200mg and limited maximum dose of 300mg is designed to reduce adverse effects.

Recently there have been reports that heroin and ex-heroin users have become dependent upon large doses (2-3g daily) of pregabalin. Pregabalin is now a Schedule 3 Controlled Drug. BNF advice is to taper over at least one week but there are case reports of difficult withdrawal from normal prescribing levels of pregabalin (~300mg) and we have had similar feedback from patient and public involvement (PPI) and from clinical experience. More data are available on gabapentin withdrawal, though still only from case-reports. It is important to investigate any

potential harms, including the risk of withdrawal effects. We are not aware of any empirical study of withdrawal from pregabalin that could inform clinical practice.

We will be carrying out a study that will withdraw the participants from pregabalin over 28 days. This will enable us to monitor any withdrawal effects and also to minimise any effects of withdrawal.

As pregabalin is a Controlled Drug, we will limit the amount of study medication that is prescribed at any one time to the participants. Participants will only be prescribed a sufficient number of bottles to ensure they have an adequate supply of medication to last them a month. We will also monitor the use of pregabalin and only provide a new prescription for study medication when the participant has used most of the medication to avoid a large supply being held by the participants.

Pregabalin should not be used during pregnancy because of the possibility of teratogenic effects. We will therefore not include pregnant women in the study and will also ask women of childbearing potential to use highly effective contraception and to conduct a pregnancy test at baseline. A pregnancy test will be repeated at the end of the tapering period. Participants will be offered to repeat a pregnancy test if any delayed or missed menses occur.

We will have an emergency unblinding system so that we can alert people to the content of the study medication should an emergency arise.

The exclusions are listed in section 3.2. Amongst the exclusions are people with substance abuse problems because of reports that opioid addicts can abuse pregabalin. Pregabalin is not metabolised by the Cytochrome P450 (CYP) system and interactions are mostly as a result of sedation and dizziness interacting with drugs that also lead to those symptoms. Although there is recent warning about respiratory depression in people who are currently on opioid medication and benzodiazepines, analysis of Clinical Practice Research Datalink (CPRD) primary care data show that at least 42% of people are co-prescribed antidepressants and opioids, benzodiazepines, or z-drugs. We also know that pregabalin is often co-prescribed with these other medications. Given the variability of dose, clinical conditions and other circumstances we have excluded people with a creatinine clearance of <30ml/day, and if they report breathlessness and score 3 or 4 on the MRC dyspnoea scale (of note, a maximum score is 4). Given the risk of respiratory depression in conjunction with opiates, we will exclude those regularly taking more than 15 morphine mg equivalents per day. We will allow people taking up to 10mg diazepam (or equivalent for other benzodiazepines) or 3.75mg zopiclone or 10mg zolpidem at night but those taking higher doses will be excluded. We will not include people regularly taking daytime benzodiazepines as this is a powerful anti-anxiety drug and our clinical focus is on examining the benefits of pregabalin, in part as an alternative to benzodiazepine that in any case are not recommended for long term use. As generalised anxiety is commonly comorbid with depression, we will have a PETRA Risk Management SOP that specifies the procedure to inform GPs, with the participants consent, about any suicidal thoughts reported in our research assessments. Table 1 summarises the risks, frequencies and mitigations of the Investigational Medicinal Products (IMP(s)).

Table 1. Summary of the risks, frequencies and mitigations of the Investigational Medicinal Products (IMP(s))

Name of IMP(s)	Potential risk	Risk Frequency	Risk Management
Pregabalin	1. Dizziness, somnolence, headache	Very common ((≥1/10)	The participant will be given instructions to increase the dose of the medication over the first 14 days as described in the protocol. If the participant experiences side effects, they will be advised to either remain on their current dose or reduce the dose if the side effects are not tolerable. The participant can discuss this with the PI who may also advise to stop the medication.
	2. Nasopharyngitis 3. Appetite increased 4. Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased 5. Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy 6. Vision blurred, diplopia 7. Vertigo 8. Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth 9. Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm 10. Erectile dysfunction oedema peripheral, oedema, gait abnormal,	Common (≥1/100 to <1/10)	The participant will be given instructions to increase the dose of the medication over the first 14 days as described in the protocol. If the participant experiences side effects, they will be advised to either remain on their current dose or reduce the dose if the side effects are not tolerable. The participant can discuss this with the PI who may also advise to stop the medication.

	fall, feeling drunk, feeling abnormal, fatigue 11. Weight increased		
	12. Neutropaenia 13. Hypersensitivity 14. Anorexia, hypoglycaemia 15. Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy 16. Syncope, stupor, myoclonus, loss of consciousness, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, mental impairment, speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, malaise 17. Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation 18. Hyperacusis 19. Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure	Uncommon (≥1/1,000 to <1/100)	The participant will be given instructions to increase the dose of the medication over the first 14 days as described in the protocol. If the participant experiences side effects, they will be advised to either remain on their current dose or reduce the dose if the side effects are not tolerable. The participant can discuss this with the PI who may also advise to stop the medication and consult their general practitioner for any further investigation or management.

	20. Hypotension, hypertension, hot flushes, flushing, peripheral coldness 21. Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness 22. Gastroesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral 23. Elevated liver enzymes 24. Rash papular, urticaria, hyperhidrosis, pruritus 25. Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness 26. Urinary incontinence, dysuria 27. Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain 28. Generalised oedema, face oedema, chest tightness, pain, pyrexia, thirst, chills, asthenia 29. Blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased		
	30. White blood cell count decreased 31. Amenorrhoea, breast discharge, breast enlargement, gynaecomastia 32. Renal failure, oliguria, urinary retention 33. Rhabdomyolysis 34. Jaundice	Rare (≥1/10,000 to <1/1,000)	The participant will be told to stop the medication and consult their general practitioner for further management.

	35. Stevens-Johnson syndrome, toxic epidermal necrolysis, cold sweat 36. Ascites, pancreatitis, swollen tongue, dysphagia 37. Pulmonary oedema, throat tightness 38. QT prolongation, sinus tachycardia, sinus arrhythmia 39. Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness 40. Convulsions, parosmia, hypokinesia, dysgraphia, Parkinsonism 41. Disinhibition 42. Angioedema, allergic reaction		
	43. Hepatic failure, hepatitis	Very rare (<1/10,000)	The participant will be told to stop the medication and consult their general practitioner for further management.
	44. Respiratory depression	Not known cannot be estimated from the available data)	The participant will be told to stop the medication and consult their general practitioner for further management. For participants who experience breathlessness and score 2 on the MRC Dyspnoea scale, the PI will review and consider reducing the dose. If they reach score 3 or 4 then they will discontinue

2 Selection of Sites/Investigators

2.1 Site Selection

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

2.1.1 Study Setting

We will recruit participants from primary care in England from GP practices across three regions: London, Bristol and the West Midlands. All participants will receive usual care from their general practitioner and will continue with their existing antidepressant. Participants will be recruited via 2 University sites (UCL and University of Bristol), and Keele University will act as a co-ordinating centre for participants recruited by UCL in the West Midlands region. GP practices may also be invited to participate via the Clinical Research Networks (CRNs). GP practices that are interested in participating will be asked to sign an Organisation Information Document (OID).

2.1.2 Site/Investigator Eligibility Criteria

To participate in the PETRA trial, investigators and trial sites, i.e. UCL and University of Bristol must fulfil a set of criteria that have been agreed by the Sponsor and PETRA Trial Management Group (TMG) and that are defined below.

Eligibility criteria:

1. A named clinician is willing and appropriate to take Principal Investigator (PI) responsibility
2. Suitably trained staff are available to recruit participants and collect data

Keele University will act as a co-ordinating centre for participants recruited in the North West Coast and the West Midlands region and must fulfil only the second of the eligibility criteria defined above.

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.

2.2 Site approval and activation

Site training will be performed prior to the activation of the UCL and University of Bristol sites and will include all processes for the trial including but not limited to protocol training, data management procedures, procedures for prescribing of investigational medicinal product, adverse event reporting procedures and expectations for monitoring visits. A log of Site Initiation Visit attendees will be kept in the TMF as a record of participants present. The Visit may occur in person or via Videoconference as outlined in the Quality Management and Monitoring Plan (QMMP).

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 participants until a letter for activation has been issued. On receipt of the signed Clinical Trial Site Agreement (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 UCL.

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

2.3 Co-ordinating centre approval and activation

Training will be performed prior to the activation of the Keele University co-ordinating centre and before recruitment of any participants in the North West Coast and the West Midlands region. A log of those attending the training will be kept in the TMF as a record of participants present. The training may occur in person or via Videoconference.

The trial manager or delegate will notify the Keele University co-ordinating centre of activation in writing.

The Keele University co-ordinating centre 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). Any deviation from the approved protocol must be documented, explained, and communicated to the trial team at UCL.

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. Meeting ICD-11 criteria for generalised anxiety disorder using the revised clinical interview schedule (CIS-R)
2. Scoring ≥12 on the CIS-R total score
3. Age 18-74 years (upper age limit to ensure the validity of our measures)

4. Currently taking an SSRI, SNRI or mirtazapine (at specified doses; the full list is in the trial guidance document that all investigators at sites have to follow), for a minimum of 8 weeks prior to randomisation and with good adherence as agreed with PI.
5. Treatment with at least one other antidepressant before their current antidepressant

3.2 Participant Exclusion Criteria

1. Currently taking pregabalin or use within the previous 1 month (i.e. wash-out of 1 month required)
2. Taking regular antipsychotics
3. Have bipolar disorder, psychosis, or alcohol misuse
4. Current or recent opiate dependence where there is a risk of pregabalin abuse
5. Current use of opiates with a daily dose of >15 morphine milligram equivalents
6. Creatinine clearance <30ml/min (measured by eGFR is acceptable).
7. Requirement to use home oxygen machines daily for respiratory problems.
8. Experience breathlessness and score ≥3 on the MRC Dyspnoea scale ('Stops for breath after walking about 100 metres or after a few minutes on the level' or 'Too breathless to leave the house or breathless when dressing or undressing')
9. Regular daily use of z drugs >3.75mg zopiclone or >10mg zolpidem
10. Regular daily use of benzodiazepines or regular night-time use >10mg diazepam or equivalent.
11. Currently receiving psychotherapy and within 6 months of starting therapy
12. Pregnancy, planned pregnancy and women who are breastfeeding
13. Unable to complete self-administered scales in English (some scales are not validated in other languages)
14. Taking part in another CTIMP

3.2.1 Women of Childbearing Potential

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Pregabalin use in the first trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin may cross the human placenta. Pregabalin is excreted into human milk however the effect of pregabalin on infants is unknown. Therefore, female participants of childbearing potential must not become pregnant and must agree to use a highly effective contraception whilst taking the IMP and for 30 days after stopping trial treatment. A highly effective method of birth control is defined as a contraceptive method that can achieve a failure rate of <1% per year when used consistently and correctly. Birth control measures should continue for the duration of trial treatment and can stop 30 days after the last IMP was taken.

Discussions of contraception and chosen method(s) of contraception should be clearly documented in the participants medical notes during the screening visit and prior to randomisation.

All women of childbearing potential will agree to undergo a urine pregnancy test at baseline, and again at the end of the tapering period. Participants will be provided with urine pregnancy test kits and instructions. Participants will also be provided with an additional pregnancy test

kit if any delayed or missed menses occur. A member of the research team at site will call the participant to verbally obtain the results of the pregnancy test. A picture of the results of this pregnancy test should be also provided to the research team at site. The result will be documented on the Case Report Form (CRF).

3.2.2 Birth Control Methods considered as Highly effective

Highly effective contraceptive methods include:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - injectable
  - Implantable (*low user dependency)*
- Intrauterine device (IUD) – (*low user dependency)*
- Intrauterine hormone-releasing system (IUS) – (*low user dependency)*
- Bilateral tubal occlusion – (*low user dependency)*
- Vasectomised male partner – (*low user dependency).* This is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP participant and that the vasectomised partner has received medical assessment of the surgical success. Investigators at sites must document azoospermia prior to the female participants' entry into the trial.
- Sexual abstinence, defined as refraining from heterosexual intercourse (i.e., with male partner) when this is in line with the preferred and usual lifestyle of the participant, during the entire period of administering the trial treatment.

(Taken from Clinical Trials Facilitation and Coordination Group, Recommendations related to contraception and pregnancy testing in clinical trials, v1.1, published on 21Sep2020

https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf?fbclid=IwAR3AY5Ha0ESDyqIBeUaYI9VTFWmx9bbt8NZ-80N-5ME6pkBb1UHvFsTwqlQ)

3.2.3 Male Participants

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy. In clinical practice, fertile male patients with partners who are women of childbearing potential are not required to use precautions to prevent pregnancy whilst taking pregabalin. Therefore, male participants will not be required to take precautions to prevent pregnancy whilst participating in the trial.

3.3 Recruitment

General practices, who have agreed to take part, across 4 geographical areas: London, Bristol, North West Coast and West Midlands, will carry out record searches to identify people who have been prescribed an antidepressant for at least 8 weeks and will contact potential participants with the participant information sheet and ask those interested to contact the

research team by all possible means, including a weblink. The initial contact will be via post, although GP practices may also text patients with a reminder to respond to the invitation letter. GPs and other primary care clinicians will also be invited to refer directly to the study team with patient agreement. A trained research assistant will then establish by phone some of the eligibility and exclusion criteria and screen with a GAD7 questionnaire to assess anxiety symptoms. This GAD7 screen will not be part of the eligibility criteria but is designed to increase the likelihood that participants will meet our eligibility criteria when they are assessed at the baseline visit. It is designed to improve the efficiency of the fieldwork. The consent will be obtained for the assessment of eligibility, supplemented by details from medical notes such as concerning renal impairment. For those potentially eligible for the trial, a baseline assessment will be performed online, or face to face in a general practice or at home or at University premises to establish eligibility.

We recognise that general practice is under considerable pressure at present, and we have designed this study to have minimal impact on the practice. For example, UCL and University of Bristol will be the Investigator sites (with Keele University acting as a co-ordinating centre for UCL participants recruited in the West Midlands region) and the practices will be research sites with no PI oversight required, this will minimise the paperwork for the practice.

We plan a 6-month internal pilot to estimate our recruitment rate and test the robustness of our procedures. The internal pilot will occur at the UCL site only so we can adapt and finalise any procedures before opening the University of Bristol site and activating the Keele University co-ordinating centre for UCL participants recruited from the West Midlands and North West Coast. Table 2 shows the internal pilot progression criteria.

Table 2. Internal pilot progression criteria

Progression criteria	Red	Amber	Green
Trial recruitment % complete	50%	70%	100%
Recruitment rate/region /month	4 randomisations per month	6	8
Number of GP practices opened	8	11	16
Total number of participants recruited	24	36	48

In addition to the recruitment targets given above, we will set a target of 90% for participants starting study medication, 80% for completing follow up assessments at the primary endpoint and as a measure of acceptability, we will require 70% of the participants to be taking study medication at the primary outcome assessment at 12 weeks. This will be reviewed at the end of the pilot and results presented to the Trial Steering Committee and Data Monitoring Committee.

3.4 Co-enrolment Guidance

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

3.5 Screening Procedures and Informed Consent

Patients will be provided with a Participant Information Sheet (PIS) and given sufficient time to read it fully (a minimum of 24 hours). Following a discussion with a medically qualified investigator or suitable trained and authorised delegate, any questions will be satisfactorily answered and if the participant is willing and has the capacity to consent and wishes to participate, informed consent will be obtained. This could be a paper consent form or e-consent and will be signed by a delegated member of site staff.

The local PI or clinical delegate will also review participants who have any cautions for pregabalin, for example renal impairment, co-existing chronic obstructive airways disease, and co-prescription of opioids, benzodiazepines, or z-drugs, and then decide if participants should be randomised. This will be done, when necessary, in consultation with the participant's GP.

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 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.

3.5.1 Process of informed consent

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

Written informed consent to enter and be randomised into the trial must be obtained from participants, if appropriate, 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 written 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.

Signed consent forms must be kept by the investigator and a copy given to the participant or family. The investigator and participant will have access to a copy regardless of method of consent used (paper or electronic). The consent process should be documented in the participants medical records. With the consent of the participant, a letter should be sent to the general practitioner informing him/her of the trial and the participant's involvement in it.

3.5.2 Consent procedure for the nested qualitative study

At the beginning of the study, trial participants will be asked to provide consent to participate in an optional interview conducted online after the 12-week visit. We will include participants from recruiting regions and maintain the blinding. We anticipate including at least 25 participants who have completed the week 12 visit and at least 10 participants who stopped study medication before 12 weeks (numbers depending upon data saturation).

3.5.3 Screening Visit

Once informed consent is obtained study assessments must be performed as detailed in Participant Timeline (section 5.2)

4 Trial treatments / Intervention

4.1 Introduction

Participants will be randomised with a 1:1 ratio to placebo or pregabalin (starting with 50mg and increasing to the recommended dose of 200mg) using a flexible dosing strategy that will mimic usual care to enhance retention.

4.2 Arm A: Active drug

4.2.1 Product

Pregabalin in 50mg tablets (sourced from any manufacturer with a marketing authorisation in the UK).

4.2.2 Regulatory Status

Pregabalin is a licensed drug and indicated for generalised anxiety disorder.

4.2.3 Dispensing & Storage

The Pharmacy Trials Unit at Bristol Royal Infirmary will act as the central pharmacy and will be responsible for dispensing and storage of pregabalin. More information regarding the distribution to participants can be found in the IMP Management Plan.

4.2.4 Dose Modifications, Interruptions and Discontinuations

(See also Section 4.7 for treatment discontinuation)

The study will allow flexibility in the dose to mimic clinical practice and to increase the acceptability of the intervention if people experience adverse effects. PPI input and prescribing experience indicate that there is a great deal of variation in the experience of adverse effects and in their tolerability. Clinical experience also indicates that increasing pregabalin slowly also increases the tolerability of any adverse effects. Allowing flexibility will increase retention of participants.

Participants will be given clear instructions to titrate the dose starting:

- Day 1-4 one tablet a day (50mg),
- Day 5-9 two tablets a day (100mg)
- Day 10-14 three tablets a day (150mg)
- Day 15 onwards four tablets a day (200mg)

The participants will be advised to stop increasing the medication at the point they find it is satisfactorily effective, or if they experience adverse effects which are not tolerable. Participants will be advised to contact their research team if any concerns that insufficient supply to last between study visits to enable timely delivery of their next medication supply. The medication instructions PIS will provide more information and contact details for the research team.

At the PI discretion, study medication can be increased beyond the recommended 4 tablets a day (200mg) to either 5 tablets a day (250mg) or 6 tablets a day (300mg). Participants should try the recommended dose of 200mg for a minimum of 2 weeks before the PI considers increasing their dose. If a PI is increasing a participant's dose above 200mg then it will be recorded in the study database.

For participants that increase their dose above the recommended dose of 200mg the dose should be titrated as follows:

- Four tablets a day (200mg) for at least 2 weeks before a dose increase is considered
- Five tablets a day (250mg) for at least 2 weeks before a dose increase is considered
- Six tablets a day (300mg) – maximum dose

All participants will continue taking the study medication until the tapering period (see below) starts at the 26 week follow up assessment. The participants dose will be gradually reduced over the tapering period to minimise withdrawal side effects.

If a participant experiences intolerable side effects, the dosage may be decreased to the previous dose level at any time during the double-blind period and will be documented. The GP will be informed of any dose changes.

In cases where participants have missed doses, these should be reviewed and discussed by the investigator at the research site to advise on the best dosing plan to remain on trial medication. Participants who discontinue study medication will be invited to all follow up assessments. Once participants have discontinued study medication, they will not be able to re-commence.

4.3 Arm B: Placebo

4.3.1 Products

As this is a double-blind trial, participants in Arm B (placebo) will be given the same instructions as per Arm A (Active drug), described in section 4.2.

4.3.2 Regulatory Status

N/A

4.3.3 Dispensing & Storage

Pharmacy trials unit at Bristol Royal Infirmary will act as the central pharmacy and will be responsible for dispensing and storage of identical placebo. More information regarding the distribution to participants can be found in the IMP Management Plan.

4.3.4 Dose Modifications, Interruptions and Discontinuations

See section 4.2.4 for details.

4.4 Concomitant Care

The participants will continue with their usual care with their GP while they are in the study.

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 there needs to be emergency unblinding and will take any further action as required.

4.6 Unblinding

The unblinding of participants will be done by the central pharmacy who will notify the participant's GP of the allocation so that further treatment can be discussed. The research team will remain blind to this information.

4.6.1 Routine Unblinding

Routine unblinding will occur when the participant has discontinued trial medication, and has completed all interviews at the end of the 30-week trial participation period and all data has been entered into the database

4.6.2 Emergency Unblinding

Unblinding may occur for any participant experiencing a medical emergency for which the clinical management will be facilitated by the unblinding of the participants 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.

In the event of unblinding becoming necessary, the central pharmacy will provide unblinding 24-hour 7 days a week. The 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 participant has been treated with active IMP without needing to unblind the participant.

Detailed information regarding unblinding is provided in the PETRA Unblinding Plan.

4.6.3 Unblinding for the Submission of SUSAR reports

All SAEs that are related to the trial medication (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 by the trial team, if the event is recorded as being a SUSAR then the following procedure will be used to unblind the SUSAR to determine if the participant was receiving active trial medication, and therefore, that the SUSAR needs onward reporting to the regulatory agencies:

- A member of the CCTU trial SUSAR Reporting Team will unblind the participant's trial treatment allocation via the central pharmacy.
- If the participant is revealed to the CCTU SUSAR Reporting team to be receiving active treatment, the CCTU trial SUSAR Reporting Team member will report the SUSAR via ICSR Submissions portal to the MHRA and REC as required.
- This information will not be forwarded to the UCL trial team or the sites. It will be kept in a separate file by the CCTU SUSAR reporting team.

4.7 Protocol Treatment Discontinuation

In consenting to the trial, participants are consenting to trial treatments, 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. Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
3. Withdrawal of consent for treatment by the participant
4. Significant deviation from the dosage regime
5. Pregnancy

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, we will withdraw that participant from the trial medication and ensure that they receive appropriate treatment outside the trial. The decision to withdraw will require a clinical judgement about the appropriateness of continuing with treatment.

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled.

All participants must be advised to taper the study medication and reduce the dose gradually if they want to stop the medication. 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. If the participant chooses to discontinue the trial treatment, we will provide them with specific instructions for tapering that can be altered at the discretion of the PI and depending upon the number of tablets they are taking.

The recommended tapering regimen is as follows:

If participant is taking 4 tablets:

- 9 days on 3 tablets

- 9 days on 2 tablets
- 10 days on 1 tablet.

If taking 3 tablets:

- 14 days on 2 tablets
- 14 days on 1 tablet

If taking 2 tablets:

- 1 tablet for 14 days

If taking 1 tablet:

- Can stop straight away

If at the discretion of the PI the participant is taking a higher dose of 5 tablets (250mg) or 6 tablets (300mg) then the recommended tapering regimen is as follows:

If participant is taking 6 tablets:

- 5 days on 5 tablets
- 5 days on 4 tablets
- 6 days on 3 tablets
- 6 days on 2 tablets
- 6 days on 1 tablet.

If taking 5 tablets:

- 7 days on 4 tablets
- 7 days on 3 tablets
- 7 days on 2 tablets
- 7 days on 1 tablet.

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

Data on participants who stop follow-up early will be kept and included in analysis.

Tapering phase

After the 26 week follow up assessment is completed participants will be given instructions to taper the study medication over the following 28 days. There will then be a further follow up assessment 30 days after the tapering period has started that we have called the ~30-week assessment. The instructions given to participants will be:

If someone is taking 4 tablets: they will be advised to have 9 days on 3 tablets, 9 days on 2 tablets and 10 days on 1 tablet. If taking 3 tablets: 14 days on 2 tablets, 14 days on 1 tablet. If taking 2 tablets: 1 tablet for 14 days. If taking 1 tablet: can stop straight away.

4.8 Accountability & Unused Trial Medication

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

Any unused medication should be disposed of upon discontinuation of trial medication via the following methods:

- Returned by participant to local pharmacy for disposal
- Returned to researcher at site for disposal (via local pharmacy or return to central pharmacy)
- Pre-paid envelopes may also be considered to allow participants to return trial medication directly to the central pharmacy (where necessary)

4.9 Adherence

The adherence to the study medication will be assessed at each follow up point. There is a structured assessment in the questionnaires at each follow up point.

5 Assessments & Follow-Up

5.1 Outcomes

We will collect outcome data by videolink or by phone/audio but on occasions will also use links to website questionnaires or in person interviews. This is to ensure that participants have a choice about the most convenient method for them.

5.1.1 Primary Outcome

Difference between anxiety symptoms (measured with GAD7 at 12 weeks post randomisation as a continuous score) (Spitzer *et al.,* 2006) between those participants who were allocated to receive placebo versus those who were allocated to pregabalin, accounting for the participant level baseline GAD7 score.

5.1.2 Secondary Outcomes

Anxiety and Depression

- Anxiety scores (GAD7) at week 3, week 6, week 26 and week 30.
- Dichotomised anxiety scores (present or absent based on a cut-off of GAD7 ≥10) at week 3, week 6, week 12, week 26 and week 30.
- Depressive scores (PHQ9) (Gilbody *et al.,* 2007) at week 3, week 6, week 12, week 26 and week 30.
- Panic symptoms (Spitzer, 1999)

Global Improvement & Quality of Life

- EQ5D5L (Herdman *et al.,* 2011) & SF-12 (Brazier and Roberts, 2004) at week 3, week 6, week 12, week 26 and week 30

Adherence

- Adherence to study medication will be assessed using a single item asking if they are still taking study medication and a 5-item scale used in the MIR and Cobalt studies. (Wiles et al 2013; Kessler et al 2018)

Withdrawal & Adverse Events

- Adverse effects of pregabalin and antidepressants – based on the Toronto scales for antidepressants (as used in GENPOD study (Crawford *et al.,* 2014)) with additional symptoms of pregabalin side effects (including waist circumference) and pregabalin withdrawal
- Withdrawal symptoms from pregabalin – these are included in the adverse effect scale above
- Stopping the study medication

Use of alternative anxiolytic methods

- Alcohol consumption (AUDIT PC) measured at every visit (Gómez *et al.,* 2005)
- Benzodiazepine use measured at every visit

Resource Use and Employment

- Primary care resource use (6 months pre and post randomisation)
- Antidepressant medication collected from primary care medical records (6 months pre and post randomisation)
- Self-reported health resource use (baseline and 26 weeks asking about previous 6 months) including psychological therapies.
- Self-reported social care resource use (baseline and 26 weeks asking about previous 6 months)
- Employment and time off work (baseline and 26 weeks asking about previous 6 months)

Cognitive Assessments

- Exploratory Assessments of reinforcement learning, working memory and general cognitive function (administered through a web browser using the Gorilla platform)

5.1.3 Nested Qualitative study

We will use qualitative methods to explore acceptability of taking and prescribing pregabalin for anxiety, from the perspectives of trial participants and GPs. Trial participants will be asked to consent, at the start of the study to be contacted to participate in an interview conducted after primary outcome is assessed at 12 weeks. We will recruit participants from across all 4 regions: London, Bristol, the West Midlands and North West Coast. We will interview from both groups, as still double blind at this stage, about 25 participants who completed the trial (up to 12 weeks) and about 10 who stopped study medication before 12 weeks, (numbers depending upon data saturation) (Saunders *et al.,* 2018). Participants will initially be selected at random but then sampling will be altered to ensure a diversity of participants are included.

Semi-structured interviews will be supported by a topic guide, which will be developed by the research team with input from the Lived Experience Group and modified iteratively during data collection and analysis. For trial participants, the topic guide will explore reasons for participation, decision to continue in or 'drop out' of the trial, previous and current experiences of managing anxiety, views on whether they thought they were taking active drug or placebo,

perceived side-effects, attitudes to, and acceptability of, the drug combination, effects on daily life and socialisation and whether they would continue this combination in the future.

GPs in participating practices, from across all 4 regions: London, Bristol, North West Coast and the West Midlands, will be advised that they will be invited to participate in an interview towards the end of the main trial. GPs may also be recruited using professional networks, social media and snowball sampling. The topic guide will allow an exploration of views on managing people with anxiety, the role of medication and talking treatments, views on pregabalin and the combination of drugs, acceptability of the combination, and barriers and facilitators to implementation of prescribing this drug combination in routine practice. We will interview about 15 GPs or until data saturation is achieved.

All interviews will be digitally recorded with consent and transcribed verbatim, the transcripts forming the data for analysis. An initial thematic analysis, using the principles of constant comparison (Clarke, V, Braun, V, Hayfield, 2015) will be carried out, within each dataset and then across the three datasets. This will be followed by a framework analysis using the Theoretical Framework of Acceptability (Sekhon, Cartwright and Francis, 2018) to understand acceptability of the intervention, and Normalisation Process Theory (May *et al.,* 2018) to understand barriers and facilitators to implementation of prescribing pregabalin in combination with antidepressants for people with anxiety in routine practice.

5.2 Participant Timeline

Figure 1. Participant Timeline

Visit Number	**SCREENING**	**BASELINE**						
Week	***-t***	**0**	**0 Randomisation**	**3**	**6**	**12**	**26**	**~30**
Informed consent		X						
Pregnancy test		X						X
Randomisation/Treatment group allocation		X						
Sociodemographic (background) questionnaire	X							
GAD-7	X	X		X	X	X	X	X
CIS-R		X						
History of anxiety and/or depression and treatment, smoking, negative childhood/adulthood experiences, events in past 6-months, social support		X						
AUDIT-PC				X	X	X	X	X
PHQ-9		X		X	X	X	X	X
SF-12 Health Survey		X		X	X	X	X	X
EQ-5D-5L		X		X	X	X	X	X
Medication adherence	X			X	X	X	X	X
Adverse events/physical symptoms		X		X	X	X	X	X
Questions about taking part in this research	X							
Global improvement		X		X	X	X	X	X
Suicidal ideation		X		X	X	X	X	X
Cognitive assessments		X		X		X		
Bespoke health and social care Resource Use Questionnaire		X					X	
Medication prescription (up to 7)			X	X	X	X	X	
Semi-structured interview with sub-sample of participants						X		
Semi-structured interview with up to 15 GPs								X

5.3 Participant Transfers

If a participant moves from the area or to another GP or doctor, then we will contact the new GP to explain the participants involvement in the trial. The original site will be responsible for the participant unless the participant moves to one of our other sites in which case the most appropriate site will take over responsibility.

5.4 Early Stopping of Follow-up

If a participant chooses to discontinue their trial treatment, they should always be followed up providing they are willing, that is, they should be encouraged to complete all remaining research assessments; if they do not wish to remain on trial follow-up, however, their decision must be respected, and the participant 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.

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

Participants may change their minds about stopping trial follow-up at any time and re-consent to participation in the trial.

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

(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 assistants about the best way to approach participants and to minimise loss to follow up. If one appointment is missed, the research assistant will still try to contact the participant for a subsequent time point.

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.

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 **Section 6.4** provides information on UCL trial team 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 3: Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SPC) or Investigator Brochure (IB) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: • results in death • is life threatening* • requires hospitalisation or prolongation existing hospitalisation** • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect • is another important medical condition***
* The term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g., a silent myocardial infarction) ** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE *** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above (e.g., a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation, or development of drug dependency).	

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
- Overdose of medication without signs or symptoms

6.2 Notifiable Adverse Events

6.2.1 Pregnancy

From the time of consent till end of tapering period, all pregnancies and suspected pregnancies that occur in female participants must be reported immediately of the site becoming aware to UCL Trial Team (cctu.petra@ucl.ac.uk) using the notification and follow-up of pregnancy form.

All confirmed pregnancies in the female partners of male participants should be reported to UCL trial team within 24 hours of the site becoming aware.

Before any additional outcome of pregnancy or pregnancy complications can be reported to UCL trial team, both pregnant female participants and the female partners of male participants must consent for follow-up in pregnancy. Outcomes should be reported to UCL trial team no later than 10 months after the initial report. Any complications of pregnancy including miscarriage, congenital abnormality or birth defect resulting from the pregnancy must be reported as an SAE to UCL trial team, within the timelines outlined in section 7.3.2 below.

6.3 Investigator responsibilities

AE of interest will be collected via the self-reported questionnaires at each follow up assessment. SAEs and SARs should be notified to UCL trial team immediately the investigator becomes aware of the event (in no circumstance should this notification take longer than 24 hours).

6.3.1 Investigator Assessment

6.3.1.1 Seriousness

The investigator responsible for the care of the participant must assess whether or not the event is serious using the definition given in Table 3. If the event is classified as ‘serious’ then an SAE form must be completed and UCL trial team notified immediately (within 24 hours).

6.3.1.2 Severity or Grading of Adverse Events

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

Grades 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 4. There are five categories: unrelated, unlikely, possibly, probably, and definitely related. If the causality assessment is unrelated or unlikely to be related, the event is classified as an SAE. If the causality is assessed as possibly, probably or definitely related, then the event is classified as an SAR.

Table 4: Assigning Type of SAE Through Causality

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

6.3.1.4 Expectedness

If there is at least a possible involvement of the trial medications (including any comparators), the sponsor will assess the expectedness of the event. If information of expectedness is provided by the investigator this should be taken into consideration by the sponsor. An unexpected adverse reaction is one that is not reported in the current and approved version of the SPCs for the trial, or one that is more frequently reported or more severe than previously reported.

6.3.1.5 Reference Safety Information (RSI)

The Reference Safety Information (RSI) for pregabalin for the PETRA trial is section 4.8 of the current approved SmPC. The RSI for the placebo for the PETRA trial is the 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 UCL trial team

UCL trial team must be notified of all SAEs as soon as site staff become aware of the event (in no circumstances should this notification take longer than 24 hours). The UCL trial team should be notified of any SAEs and other Notifiable Adverse Events (NAEs) occurring from the time of randomisation until 30 days after 26-week follow up, including SARs and SUSARs.

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/).

- The SAE form must be completed by the investigator (the clinician named 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. In the absence of the responsible investigator, an SAE form should be completed and signed by a member of the site trial team and sent by encrypted email to petrasponsor@ucl.ac.uk within 24 hours of the site becoming aware of the event. The responsible investigator should check the SAE form at the earliest opportunity, make any changes necessary. The SAE form should then be entered on the database, or signed and sent by encrypted email to petrasponsor@ucl.ac.uk. Detailed written reports should be completed as appropriate. Systems will 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 the primary event term, trial number and age when the event occurred during the trial, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be entered as soon as it becomes available.

SAE REPORTING
Within 24 hours of investigator 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 PETRA trial team at petrasponsor@ucl.ac.uk.

Follow-up: Participants must be followed up until clinical recovery is complete and 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 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, partial date of birth 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.

6.3.2.2 UCL Trial Team responsibilities

Chief Investigator (CI) or a medically qualified delegate will review all SAE reports received and will complete the assessment of expectedness in light of 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 UCL trial team becoming aware of the event; other SUSARs must be reported within 15 days.

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

In the UK an Annual Progress Report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

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.

6.3.2.3 Urgent Safety Measures

The UCL trial team 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 UCL trial team 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 PETRA 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 B (i.e., somewhat 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 PETRA 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 the PETRA 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 PETRA 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 will agree to allow trial-related monitoring, including audits, EC review and regulatory inspections, by providing access to source data and other documents as required. Participant consent for this will be obtained as part of the informed consent process for the trial. Health economic data will be collected from general practice records and trial team will have consent to access these. Health economic data may also be accessed remotely and we will rely on Clinical Research Network (CRN) support with data extraction.

7.3.2 Confidentiality

CCTU plan to follow the principles of the UK DPA regardless of the countries where the trial is being conducted.

Participant's data will be collected and kept securely. Personal identifiable data will include, name, address, email, phone numbers and NHS number, this is because participant will be in direct contact with researchers collecting the data. Personal identifiable data will be stored in

the UCL data safe haven and in equivalent secure locations according to the policies of the participating sites. 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. 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 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.

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 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 source document for the data elements listed below. These data elements will be recorded directly on the CRFs/eCRFs and therefore the CRFs/eCRFs will be regarded as source data. On occasions a research assistant might enter some data on behalf of the participant:

- *Participant questionnaires*
- *Cognitive assessments*
- *Treatment compliance data*
- *Trial Management Data*

7.5 Data Collection and Transfer Methods

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) 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 5.1). Data will be entered under this 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 PETRA 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 PETRA trial team at UCL, Bristol and Keele; delegated site staff 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.

All data will be handled in accordance with the Data Protection Act 2018, the EU General Data Protection Regulation (GDPR) 2016 (and subsequent updates and amendments).

7.7 Data Storage

Trial data will be stored in a database created specifically for the PETRA trial.

The database is hosted by OpenClinica. The data are 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/

The identification, screening and enrolment logs, linking personally identifiable information to the PIN, will be held securely in the UCL Data Safe Haven with access given to essential staff only. After completion of the trial the identification, screening and enrolment logs will be stored securely by the sites and the Keele University co-ordinating centre for 5 years after trial closure unless otherwise advised by CCTU.

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.

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 be 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.

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

We have estimated the minimal clinically important difference for the GAD7 as about a 20% reduction (Kounali *et al.,* 2020). From the Cobalt and MiR results at 6 months our MCID estimate is 1.6 or 1.9 GAD7 points and standard deviations (SDs) were 5.6 or 5.8. In those trials the correlation between baseline and 12-week GAD7 scores was 0.47 so this leads to an effective SD of 4.9. For a difference of 1.6 GAD7 points we need 199 per group for 90% power at the 5% significance level. Our target is 498 allowing for 20% attrition or other methodological challenges at 12 weeks, though we would expect to achieve substantially better follow up. For the withdrawal study, the power depends upon the position on the binomial distribution, but clinically important differences in withdrawal effects will be detectable. For example, we will have 85% power to find a difference between the groups where the control condition has a proportion of 2.5% of withdrawal symptoms and the pregabalin group 10%.

8.2 Assignment of Intervention

8.2.1 Randomisation Procedures

A PIN will be allocated to participants before the Screening assessment, the PI or delegate will enter the necessary participant characteristics required to uniquely identify each participant. 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 distribution pharmacy. The Trial team will not know the allocation but will be informed that the randomisation has occurred.

8.2.2 Randomisation Method

We will use a web-based computerised system to randomise with a 1:1 ratio, using a minimisation procedure to achieve balance between minimization groups. Minimisation groups will be specified in the Statistical Analysis Plan and in the randomization and minimization document for Sealed Envelope.

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 participants will be blind to allocation. A participant will be considered randomised at the point that they take their first IMP, and participants returning their untampered IMP will not be considered to have been randomised and thus will not be listed as lost to follow up.

8.2.5 Allocation Implementation

Once informed that an eligible participant has been identified and has consented to enter the trial, the random allocation of the participant 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 specified 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 and the Keele University co-ordinating centre, participants, the trial team at UCL and the blinded trial statistician will be masked to treatment allocation. The only exception being the delegated unblinded trial statistician, the third-party IMP licensed manufacturing facility and distribution pharmacy, unblinded monitor who will monitor the pharmacy and SUSAR reporting team (independent of trial team) at CCTU.

Blinding will be maintained by using matching medicinal preparation for pregabalin and placebo (matched size/appearance, taste of tablets and identical bottles). 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).

As the study is double-blind and the active drug and placebo will be of identical appearance, any change in the number of tablets will not in any way affect the blinding. Neither the participant, research assistant, PI or GP will know whether the participant is taking active or placebo and this will be impossible to find out without asking the pharmacy to “unblind”.

8.3 Statistical Considerations

8.3.1 Estimand Framework & Statistical Analysis Plan

Table 5. Estimand Framework

Characteristic of estimand	Definition and method of analysis
Population	Participants who have a diagnosis of generalised anxiety disorder, who have not responded to at least two antidepressant

	medications, who are currently still taking antidepressant medication, who are in the community, who agree to enter the trial and who do not fulfil exclusion criteria.
Treatment conditions	Pregabalin medication versus placebo in addition to care as usual `
Endpoint	Natural log of the score on the Generalised Anxiety Disorder scale at 12 weeks post randomisation
Summary measure	Mean difference between natural log of the score on the Generalised Anxiety Disorder scale at 12 weeks post randomisation between those randomised to placebo versus those randomised to pregabalin (adjusting for baseline scores).
Intercurrent Events	
i. Death before outcome	While alive policy
ii. Withdrawal from randomised medication (stays in trial)	Treatment policy
iii. Withdrawal from medication (leaves trial)	While in trial policy
iv. Increased use of alcohol	Treatment policy
v. Psychiatric admission	Treatment policy
vi. Commencement of psychological therapies	Treatment policy

Statistical Analysis Plan

A separate Statistical Analysis Plan will be pre-specified which will be held within the Statistics Master File (SMF). It will contain 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)

8.3.2 Interim Analyses

This study has an internal pilot with analyses to be conducted at 6 months to assess if the full RCT should proceed. The primary criteria of acceptability are:

i. Percent of trial recruitment complete
ii. Recruitment rate/site/month
iii. Number of GP practices opened
iv. Total number of participants recruited

Pilot data will be presented in grouped tables with frequency and percentages for the 4 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 will direct the unblinded statistician to provide reports as they require.

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

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

8.3.3 Statistical Methods – Outcomes

The primary analysis will be a generalised mixed model with identity link and Gaussian / mixed error structures, with log(e) GAD7 scores at 12 weeks as the outcome, accounting for baseline GAD7 scores using a repeated measures framework and also including minimisation factors used in the randomisation process. Natural logarithms will be used following our previous experience with the PANDA study(Lewis *et al.,* 2019) that suggested it was more efficient, and evidence that minimal clinically important differences for scales such as GAD fit a geometric model more closely. There will be two observations for each participant, the baseline and 12-week scores. These will be linked within a participant using a random intercept term. The model will be parameterised to identify baseline and post randomisation observation as one parameter, and random allocation as the second parameter. For the latter, all baseline measures will be coded as no treatment, and the post randomisation values will be classified as active or placebo. We will not make adjustments for repeated testing 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 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 (%).

We will carry out supportive analyses including the minimisation variables as explanatory variables. 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, 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 pregabalin patients while assuming an average outcome for missing control patients.

8.3.4 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: class of antidepressant medication at baseline

(SSRI, SNRI, other), baseline anxiety score (median GAD7 total score at baseline), and baseline depression score (median baseline total score PHQ9).

The principal approach we will take to analysing the withdrawal symptom phase of the study will, in principle, use the intention-to-treat principle and therefore regard the original randomised sample as the population of interest. However, we recognise that attrition could affect the interpretation of the comparison between active and placebo, especially if differential between the groups. We will therefore carry out supportive analyses to examine the likely impact of attrition including the potential use of mediation analyses and joint models.

8.3.5 Additional Analyses – Adjusted

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

8.3.6 Analysis Population and Missing Data

Outcomes will be analysed by means of Generalised Mixed Models without imputation of missing data. Measurements within individuals will be linked using a random intercept term. We will use two timepoints for the final analysis; baseline and primary timepoint at 12 weeks. An Intention-To-Treat (ITT) analysis will be carried out by randomisation group irrespective of medication compliance. The analysis population will consist of all those participants who were randomised. Mechanisms of missingness will be explored. The principal analyses will address a treatment strategy estimand, except death which will be while alive.

8.3.7 Analysis of the Nested Qualitative study

Analysis will be conducted by members of the qualitative research team at Keele University (Chew-Graham, Chipp and the study researcher), with input from the Lived Experience Research Group and wider research team. The results will be presented separately from the main study results.

9 Economic Evaluations

We will estimate the incremental cost per quality adjusted life year (QALY) gained for Pregabalin, usual care and their existing antidepressant compared to their existing antidepressant and usual care only from their GP over 26 weeks from an NHS health and social care perspective for direct costs related to anxiety. QALYs will be calculated from self-reported EQ-5D-5L and the algorithm recommended by NICE (https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l). Health and social care resource will be collected from GP medical records (primary care resource use) and self-reported bespoke questionnaires (community and secondary health care resource use associated with anxiety) at baseline and 26 weeks asking about the previous 6 months. Time off work will also be collected as part of self-completed questionnaires and costed using the human capital approach and mean wage from the Office of National Statistics.

9.1 Health Economic Analysis Plan

A full health economic analysis plan (HEAP) will be developed and signed off before the database lock. HEAP will contain the following sections:

- economic analysis background,

- outcomes,
- cost data,
- within-trial analysis,
- missing data and sensitivity analysis,
- secondary analyses,
- updating the HEAP.

Primary economic analysis will be within-trial analysis. There will be no economic modelling conducted as a part of the trial. 26-week time horizon is considered long enough to capture all important drivers of cost-effectiveness of pregabalin in patients with GAD.

9.2 Within-trial analysis

Primary analysis will be within-trial intention-to-treat analysis. Outcomes will be QALYs calculated using EQ-5D-5L. Secondary analyses will include (i) using the SF-12 and the SF-6D(18) algorithm to calculate QALYs; and (ii) including the cost of absenteeism.

The cost of pregabalin will be calculated using the BNF and trial data on usage. Other antidepressant medication use collected from GP files will also be costed using the BNF.

Health care resource use will be collected from GP records and self-reported bespoke questionnaires. The design of the questionnaires will be informed by our experience in previous trials in common mental health problems. Healthcare resource use will be costed using the Personal Social Service Resource Unit (PSSRU) and NHS Reference Costs (https://www.england.nhs.uk/national-cost-collection/).

We will report the mean incremental cost per QALY gained of Pregabalin, usual care and their existing antidepressant compared to their existing antidepressant and usual care only from their GP over 26 weeks for all analyses. The denominator and numerator of the incremental cost per QALY gained will be calculated using regression analysis, adjusting for baseline and stratification variables in line with the statistical analysis plan. Other potential coefficients for inclusion will be considered as part of a health economics analysis plan (HEAP), signed off before database close. 95% confidence intervals, cost-effectiveness planes and cost-effectiveness acceptability curves will be calculated based on bootstrapped results and using seemingly unrelated regression to account for the correlation between costs and QALYs. We will assess patterns of missing data, with the primary analysis mirroring the primary statistical analysis (complete case analysis adjusting for predictors of missingness), with sensitivity analyses using other methods including multiple imputation using chained equations (MICE) as set out in published guidance on accounting for missing data in cost-effectiveness analyses(Sterne *et al.,* 2009). These and other sensitivity analyses accounting for any uncertainty will be detailed as part of the HEAP. Subgroup analyses for costs, EQ-5D-5L utilities and QALYs will be conducted for class of antidepressant medication at baseline, baseline anxiety score and baseline depression score.

10 Regulatory & Ethical Issues

10.1 Compliance

10.1.1 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, sites, and the Keele University co-ordinating centre 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)
- The Human Medicines (Amendment etc.) (EU Exit) Regulations 2019 (SI 2019/775)

10.1.2 Site Compliance

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

Participating sites and the University of Keele co-ordinating centre will inform the UCL trial team 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).

10.1.3 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.

10.2 Ethical Approvals

10.2.1 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 that is clinically indicated and will work closely with the participants' GP to ensure the safety of the participants.

The randomised medication will be given to consenting participants in addition to existing care provided by general practitioners or other medical staff.

We will not be reimbursing for time and expenses when taking part in the study except for those who will be receiving the longer qualitative interviews. The participants in the trial will receive a £25 voucher for taking part and the general practitioners will receive £88 for taking part. We think this is an appropriate level of reimbursement given the time involved in these interviews.

We will be tapering the study medication at the end of this study and so the participants will be medication free. Their GP will be told their allocation after the end of the study so that participants can discuss future treatment with their GP.

The most serious possible adverse event would be the possibility of adverse effects on the foetus in pregnant women. We are excluding pregnant women and requiring all women of childbearing age to be on highly effective contraception for the duration of the study.

People with anxiety can experience thoughts of self-harm and suicide. A PETRA Risk Management SOP is in place to make sure that if such thoughts are expressed that we will inform their GP or other mental health teams so that appropriate action can be taken. Whenever a researcher becomes aware that a patient is at risk, the researcher will follow the PETRA Risk Management SOP. If participants become distressed, researchers will be able to offer support during the appointment and direct them to supportive services. Participants must provide written 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.

10.2.2 Ethics Committee Approval

Following main REC approval and Health Research Authority (in England) approvals and before initiation of the trial at either site or the University of Keele co-ordinating centre, the local information pack will be sent by UCL Trial team. The local information pack will contain the protocol, all informed consent forms, and information materials to be given to the prospective participant, the Organisation Information Document (OID), and the validated Schedule of Events Cost Attribution Template (SoECAT). Sites and the University of Keele co-ordinating centre will also be notified of any further substantial amendments 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 will 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 necessarily giving a reason and without prejudicing their further treatment.

10.3 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.

10.4 Other Approvals

The protocol will be submitted by those delegated at each participating site or to other local departments for approval as required. A copy of the local permissions (or other relevant approvals if required) and of the Participant Information Sheet (PIS) and consent form on local headed paper must be forwarded to the UCL trial team before participants are entered.

10.5 Trial Closure

Trial closure is defined as the date when all data have been received, cleaned and all data queries resolved at 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 UCL trial team 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 UCL Trial team will notify the HRA and the MHRA within 15 days, including the reasons for the premature termination.

11 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.

12 Finance

PETRA is fully funded by HTA, NIHR grant number 134074. It is not expected that any further external funding will be sought.

13 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 are several 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.petra@ucl.ac.uk

13.1 Trial Management Group

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and CCTU / UCL 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.

13.2 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.

13.3 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.

13.4 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.

14 Patient & Public Involvement and Engagement

Patient and Public Involvement and Engagement (PPIE) 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-applicant will arrange a Lived Experience Group to provide input when required during the study.

The interviews will be conducted by the qualitative researcher plus the lay co-investigator with experience in interviewing and qualitative methods.

15 Publication & Dissemination of Results

15.1 Publication Policy

15.1.1 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 the results to those participants who took part who express an interest in the findings.

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.

15.1.2 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.

15.1.3 Reproducible Research

We will publish a protocol paper in a peer reviewed journal so that the relevant information will be publicly available. At present our consent is for members of the research team to see participant data so we do not propose to make a participant level dataset publicly available. However, we will willingly collaborate with other scientists who wish to use the data and would like to join our research team.

16 Data and/or Sample Sharing

Data will be available for sharing after publication of the trial results. Researchers wishing to access PETRA 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.

17 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.

18 Protocol Amendments

Table 6. Summary of Protocol Amendments

Protocol version	Protocol date	Summary of changes
V1.0	01Jun2023	N/A
V2.0	22Aug2023	Changes to address comments raised during Combined Review by REC and HRA
V3.0	21Sep2023	Changes to amend Keele University from an investigator site to a co-ordinating centre
V4.0	01Nov2023	Cognitive assessments change from secondary outcome to exploratory assessments, emergency unblinding procedure clarified, corrections made to assessment timepoints in participant timeline
V5.0	23Sept2024	Updated the Inclusion and Exclusion criteria, provided recommendations/changes for medication dosage in cases of missed or skipped doses, and revised the unblinding information.
V6.0	18Nov2024	Non-substantial amendment to address formatting and typographical errors on Protocol SA06.

19 References

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19 Appendices

19.1 MRC Dyspnoea Scale

Scale	Severity of dyspnoea
0	No breathlessness except with strenuous exercise
1	Shortness of breath when hurrying on the level or walking up a slight hill
2	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
3	Stops for breath after walking about 100 metres or after a few minutes on the level
4	Too breathless to leave the house or breathless when dressing or undressing

Modified British Medical Research Council Dyspnoea scale