Antidepressants Trial in Parkinson's Disease (ADepT-PD)

A Randomised Placebo-Controlled Trial of Escitalopram and Nortriptyline with Standard Psychological Care for Depression in Parkinson's Disease

Version	2.0
Date	4th September 2019
Sponsor	University College London (UCL)
Comprehensive Clinical Trials Unit	CTU/2017/285
Trial Adoption Group	
ReDA	18/0279
Trial registration	[ClinicalTrials.gov NCT03652870]
EudraCT	2018-002942-35
REC	19/LO/0288

Authorisation: Chief Investigator

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1 Administrative information

This document was constructed using the Comprehensive Clinical Trials Unit (CCTU) at UCL Protocol template Version 5. It describes the Antidepressants Trial in Parkinson's Disease (ADepT-PD), 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, 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 (2012) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials [1]. The SPIRIT Statement Explanation and Elaboration document [2] can be referred to, or a member of CCTU Protocol Review Committee can be contacted for further detail about specific items.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, Data Protection Act (DPA) 2018, General Data Protection Regulation (GDPR) 2016, and the National Health Service (NHS) UK Policy Framework for Health and Social Care. International sites will comply with the principles of GCP as laid down by ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC, the European Directive 2001/20/EC (where applicable), the EU Tissue and Cells Directives 2004/23/EC, 2006/17/EC and 2006/86/EC, and other national and local applicable regulations. Agreements that include detailed roles and responsibilities will be in place between participating sites and CCTU.

Participating sites will inform CCTU as soon as they are aware of a possible serious breach of compliance, so that CCTU can fulfil its requirement to report the breach if necessary within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

1.2 Sponsor

UCL is the trial sponsor and has delegated responsibility for the overall management of the Antidepressants Trial in Parkinson's disease (ADepT-PD) trial to CCTU. Queries relating to UCL sponsorship of this trial should be addressed to the CCTU Director or via the Trial Team.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	ClincialTrials.gov identifier: NCT03652870
Date of Registration in Primary Registry	28 August 2018
Secondary Identifying Numbers	ISRCTN: ISRCTN48548553 EudraCT#: 2018-002942-35 UCL R&D ID#: 18/0279 CTU Trial Adoption Group #: CTU/2017/285 IRAS#: 235544
Source of Monetary or Material Support	National Institute Health Research Health Technology Assessment (NIHR-HTA) Programme
Sponsor	University College London with sponsor duties delegated to CCTU.
Contact for Public Queries	adept@ucl.ac.uk
Contact for Scientific Queries	Professor Anette Schrag Address: UCL Institute of Neurology Royal Free Campus Rowland Hill Street NW3 2PF Email: a.schrag@ucl.ac.uk Telephone: 0207 794 0500 x34373
Short Title	Antidepressants Trial in Parkinson's Disease (ADepT-PD)
Scientific Title	A Randomised Controlled Trial of Escitalopram and Nortriptyline compared with placebo, and standard psychological care, for depression in Parkinson's disease
Countries of Recruitment	United Kingdom
Health Condition(s) or Problem(s) Studied	Depression in Parkinson's disease
Intervention(s)	Nortriptyline (target dose 100mg in patients aged 65 and under, or 50mg in patients aged over 65 or those with hepatic impairment), escitalopram (target dose 20mg in patients aged 65 and under, or 10mg in patients aged over 65 or those with hepatic impairment) or placebo, in addition to available standard psychological care.
Key Inclusion and Exclusion Criteria	Inclusion: 1. Patients with a diagnosis of idiopathic PD, based on a history and neurological exam performed by the enrolling investigator with presence of at least two of the three cardinal signs of PD: rigidity, bradykinesia, and rest tremor with no evidence of diagnostic alternatives. 2. Aged 18 to 85 years.

	3. Fulfilling diagnostic (*DSM-V*) criteria for a depressive disorder (i.e., major depressive disorder or persistent depressive disorder) or operationally defined subsyndromal depression (presence of two or more depressive symptoms at threshold or subthreshold levels, at least one of which has to include depressed mood or anhedonia. 4. Beck Depression Inventory-II (BDI-II) score ≥14. 5. Written informed consent provided. Exclusion: 1. Women who are pregnant, breastfeeding or of childbearing potential without effective contraception (hormonal or barrier method of birth control; or abstinence). Periodic abstinence (e.g.calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. 2. Patients who do not have sufficient understanding of the English language to be able to read and understand the self-completed questionnaires or patients who are unable to communicate answers to the self-rating questionnaires. 3. Patients with Montreal Cognitive Assessment (MoCA) score <16 or without capacity to consent. 4. Treatment with an antidepressant within 4 weeks of enrolment (except for a small dose of amitriptyline up to 30 mg for indications other than depression). 5. Patients with known severe liver failure. 6. Absolute contraindications to escitalopram or nortriptyline. These include: a. Patients with known QT-interval prolongation (defined here as >420ms) or congenital long QT syndrome. b. Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias. 7. Medications contraindicated on nortriptyline or escitalopram. These include: a. Non-selective and selective irreversible monoamine oxidase inhibitors (MAOIs) within 14 days. However, the antiparkinsonian selective reversible MAO-B inhibitors rasagiline, selegiline and safinamide are not contraindicated. b. Concomitant QT prolonging drugs, including domperidone, apomorphine at high doses (single dose or hourly rate of >6mg), certain neuroleptics (not quetiapine or clozapine), quinine, class IA and III antiarrhythmics (amiodarone, dronedarone and

	disopryamide), the antihistamines astemizole, mizolastine, the antimicrobial agents sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarian treatment),and some antiretrovirals. 8. Patients indicating active suicidal ideation or intent on the BDI-II item 9 and who, after clinical review of risk using the standardised Suicide Risk Management Protocol, need to be referred for immediate treatment. 9. Treatment with antiparkinsonian medication is not optimised and stable within 4 weeks of receiving the trial medication and there are plans to change up to primary endpoint (8 weeks). 10. Participation in another clinical trial of an investigational medicinal product or device within the last 30 days.
Study Type	A multicentre, double-blind, phase III parallel trial with an internal pilot study. Participants will be randomly allocated 1:1:1 to receive escitalopram or nortriptyline or placebo. The trial also includes a genetic sub-study. The participants will be asked if they will give an optional blood sample which will be analysed to try to identify genetic markers that may be associated with subtypes of PD (e.g. presence of depression and anxiety) or variation in treatment responsiveness. This genetic sub-study is funded by The Cure Parkinson's Trust.
Date of First Enrolment	01 November 2019
Target Sample Size	408 in full trial. The pilot study will have the aim to recruit 46 participants in the first 6 months from 10 sites and recruitment during this pilot study will be assessed to see whether the trial can continue as a three arm trial or be changed to a two arm trial (removing one of the active arms).
Primary Outcome(s)	Depressive symptoms as measured using the Beck Depression Inventory II (BDI II) at 8 weeks of treatment.
Key Secondary Outcomes	<u>Patient-reported outcomes</u> • Level of depression on the BDI-II at weeks 26 and 52 • Level of depression on the PHQ9 at weeks 8, 26 and 52 • Number of participants experiencing side effects (adverse events) as measured on the Modified Toronto Side Effects Scale, and reporting of other adverse events • Overall clinical effectiveness on the Global Clinical Impression scale (CGI) - change in health question • Anxiety symptoms on the Parkinson Anxiety Scale

	• Health related quality of life using the EQ-5D-5L questionnaire • Capability using the ICECAP-0 questionnaire • Health and social care resource use on the modified Client Service Receipt Inventory (CSRI) • Resources associated with paid carers using a modified version of the iMTA Valuation Of Informal Care Questionnaire (iVICQ) (asked alongside the CSRI) • Changes in concomitant medication <u>Clinician and patient-reported outcomes</u> • Motor and non-motor experiences on the MDS-UPDRS Part I and II, motor examination and motor complications on the MDS-UPDRS Part III and IV. Motor severity will also be video-recorded for rating by the central study team <u>Clinician-reported outcomes</u> • Cognitive function on the Montreal Cognitive Assessment (MoCA) • Levodopa-equivalence dose • Number of drop-outs <u>Carer-reported outcomes (only if participant has a carer)</u> • EQ-5D-5L and Carers Quality of Life Questionnaire for Parkinsonism • Time spent on informal care activities using the iVICQ (asked alongside the CSRI)

1.4 Roles and responsibilities

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

1.4.1 Protocol contributors

Name	Affiliation	Role
Professor Anette Schrag	UCL Institute of Neurology	Chief Investigator
Dr Camille Carroll	University of Plymouth Faculty of Medicine and Dentistry	Co-Applicant
Dr Caroline S Clarke	UCL Priment CTU	Health Economist
Dr Gordon Duncan	NHS Lothian	Co-Applicant
Dr Marc Serfaty	UCL Faculty of Brain Sciences	Co-Applicant
Dr Rachael Hunter	UCL Priment CTU	Co-Applicant
Dr Sophie Molloy	London North West University Hospitals NHS Trust, Department of Neurology	Co-Applicant
Professor Glyn Lewis	UCL Division of Psychiatry	Co-Applicant
Professor John Michael Whipps	Patient Representative	Co-Applicant
Professor Nick Freemantle	UCL CCTU	Co-Applicant/Statistician
Professor Richard G Brown	King's College London	Co-Applicant
Tola Erinle	UCL Priment CTU	Senior Data Manager
Kate Maclagan	UCL CCTU	Clinical Project Manager
Helen Knowles	UCL CCTU	Trial Manager

1.4.2 Role of trial sponsor and funders

Name	Affiliation	Role
Nick Freemantle	UCL CCTU	Overall supervision of UCL CCTU sponsorship Ultimate authority for the study conduct, report writing and decision to submit for publication will lie with the chief investigator.
NIHR-HTA	-	Funder

1.4.3 Trial Team

Name	Affiliation	Role and responsibilities
Felicia Ikeji	UCL CCTU	Clinical Project Manager
TBC	UCL CCTU	Trial Manager
Patrick Muller	UCL CCTU	Trial Statistician
TBC	UCL CCTU	Data Manager

1.4.4 Trial Management Group

Name	Affiliation	Role and responsibilities
Professor Anette Schrag	UCL Institute of Neurology	Chief Investigator
Professor Glyn Lewis	UCL Division of Psychiatry	Co-Applicant
Professor John Michael Whipps	Patient Representative	Co-Applicant
Professor Nick Freemantle	UCL CCTU	Co-Applicant
Professor Richard G Brown	King's College London	Co-Applicant
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Patrick Muller	UCL CCTU	Trial Statistician
Tola Erinle	UCL Priment CTU	Senior Data Manager
Dr Caroline S Clarke	UCL Priment CTU	Health Economist
TBC	UCL	Research Fellow

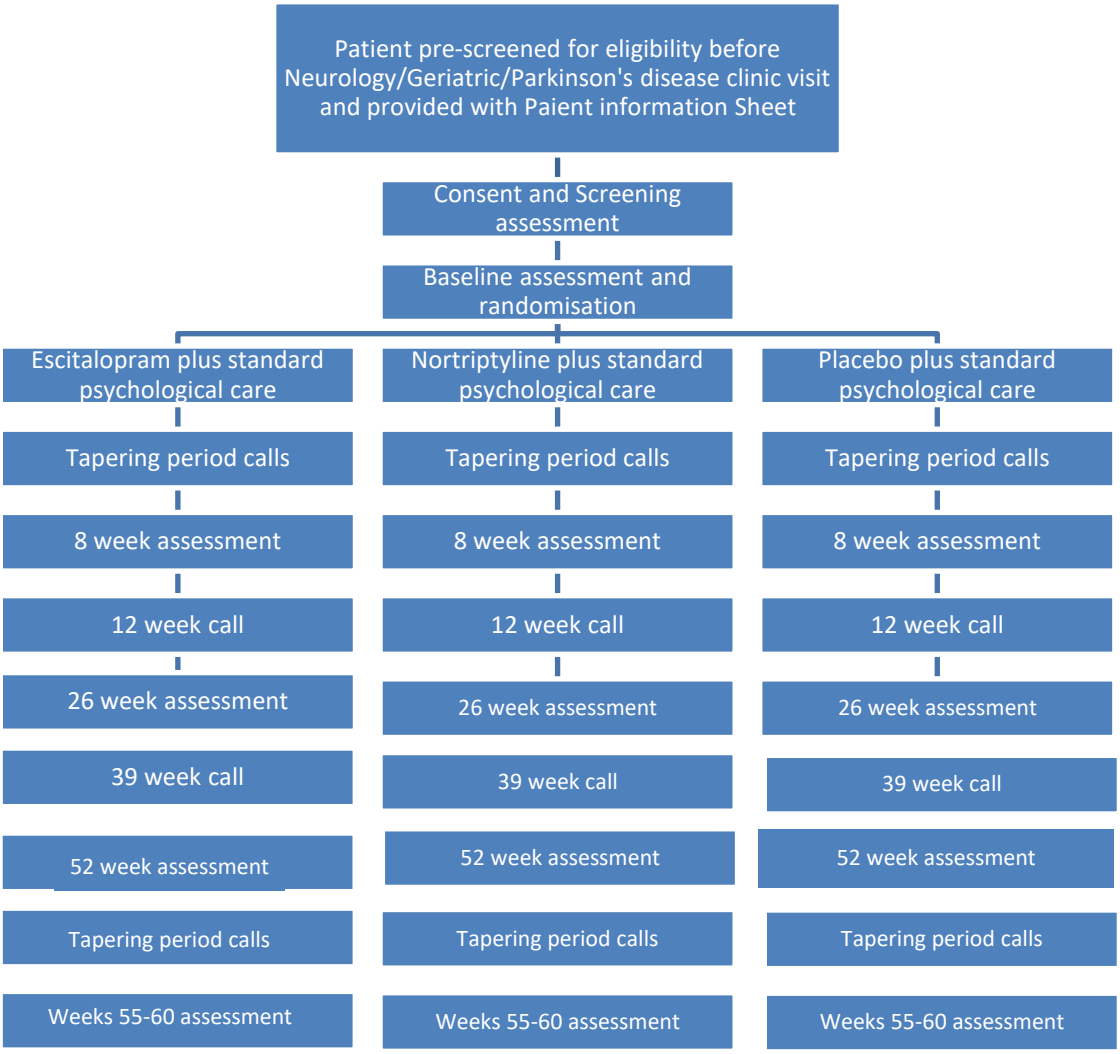
1.4.5 Trial Steering Committee

Name	Affiliation	Role and responsibilities
Professor Andrea Cipriani	University of Oxford	Independent Chair
Professor Anette Schrag	UCL	Chief Investigator, non-independent member
Dr David Okai	Oxford University Hospitals NHS Foundation Trust	Independent member
Smitaa Patel	University of Birmingham	Independent statistician
Professor Emma McIntosh	University of Glasgow	Independent health economist
Alan Leibert	Patient Representative	Layperson

1.4.6 Independent Data Monitoring Committee

Name	Affiliation	Role and responsibilities
Professor Per Odin	Lund University	Independent Chair
Dr David McNulty	University Hospitals Birmingham	Independent Statistician
Dr. David Nicholl	University Hospitals Birmingham	Independent member (clinician)
Dr. Pamina Mitter	University of Oxford	Independent member

2 Trial Diagram



3 Abbreviations

ACD	Acid Citrate Dextrose
AE	Adverse Event
AR	Adverse Reaction
BDI-II	Beck Depression Inventory - II
CA	Competent Authority
CBT	Cognitive Behavioural Therapy
CI	Chief Investigator
CGI	Clinical Global Impressions
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CCTU	Comprehensive Clinical Trials Unit at UCL
CSRI	Client Service Receipt Inventory
CTU	Clinical Trials Unit
CV	Curriculum Vitae
dPD	Depression in Parkinson's Disease
DPA	Data Protection Act
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSUR	Development Safety Update Report
EC	Ethics Committee
EQ-5D-5L	EuroQol EQ-5D 5-level health related quality of life questionnaire
EU	European Union
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HTA	Health Technology Assessment
IAPT	Improving Access to Psychological Therapies
ICECAP-O	ICEpop CAPability measure-Older people version.
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ITT	Intention to Treat
iVICQ	iMTA Valuation of Informal Carer Questionnaire
MDS-UPDRS	Movement Disorder Society – Unified Parkinson's Disease Rating Scale
MHRA	Medicines and Healthcare products Regulatory Agency
MOCA	Montreal Cognitive Assessment
mg	Milligrams
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net Monetary Benefit
QALY	Quality adjusted life year
PD	Parkinson's Disease
PI	Principal Investigator
PIS	Participant Information Sheet
PQOL-carer	Perceived Quality of Life scale – carer version
QA	Quality Assurance
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
PHQ	Patient Health Questionnaire
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
RSI	Reference Safety information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SSRI	Selective Serotonin Re-uptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCA	Tricyclic Antidepressant
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TSC	Trial Steering Committee
UCL	University College London

4 Glossary

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product.

Carer: a carer is anyone, including children and adults who looks after a family member, partner or friend who needs help because of their illness, frailty, disability, a mental health problem or an addiction and cannot cope without their support. The care they give is unpaid and occurs ≥ three time per week.

Case Report Form: a paper or electronic document designed to record all events within the study protocol required on each trial subject.

Drop-out: a participant who for any reason fails to continue in the trial until the last visit required of him/her by the trial protocol.

Escitalopram: an SSRI (selective serotonin reuptake inhibitor) used to treat clinical depression.

Hoehn & Yahr stage: A simple method of staging PD that can be applied to patients in either the ON or OFF medication state. For the purposes of the trial, Hoehn & Yahr staging will be assessed as part of the MDS-UPDRS assessment (in the ON medication state):

- Stage 0 - asymptomatic
- Stage 1 - unilateral invovement only
- Stage 2 - bilateral involvement without impairment of balance
- Stage 3 –mild to moderate involvement; some postural instability but physically independent; needs assistance to recover rom pull test
- Stage 4 - severe disability; still able to walk or stand unassisted
- Stage 5 - wheelchair bound or bedridden unless aided

Nortriptyline: a tricyclic antidepressant used to treat clinical depression.

On-Off periods: participants with advanced Parkinson's disease (PD) may not have good control of symptoms. These motor fluctuations usually happen when the medication taken to control PD (usually levodopa) is wearing off, but they can happen at other times too. This is called 'end of dose wearing off' or just 'wearing off'. An 'On period' is when a person's symptoms are controlled and when they feel at their most capable. An 'Off-period' is when Parkinson's symptoms come back and affect them the most. Practically define Off-period is the time before the first dose of antiparkinsonian medication is taken in the morning.

Parkinson's disease: a long term degenerative disorder of the central nervous system affecting the motor system.

Placebo: a substance used as a control. It has no therapeutic effect however it may provide psychological benefit.

5 Introduction

5.1 Background and Rationale

Parkinson's disease (PD) is a progressive neurological disorder that leads to increasing disability and functional decline. Currently no medications have been shown to halt or delay disease progression. One of the most common complications in patients with this diagnosis is depression which affects approximately 40% of patients with PD[3-7]. Depression is linked to functional impairment, cognitive decline and faster disease progression and are the main determinant of poor quality of life in PD[8-10]. Psychological therapies are used via standard access to appropriate psychological services in the NHS, but often antidepressant medications are required. Despite the high incidence of depression in this population, no conclusive evidence on appropriate choice of antidepressants in PD exists in the NHS, and the risk of worsening of parkinsonism[11-13] and aggravation of non-motor features of PD by antidepressants pose particular challenges in this population.

The most commonly used medications for the treatment of depressive disorders in the UK are selective serotonin re-uptake inhibitors (SSRIs), with NICE recommending that these are used in preference to other antidepressants[14-16]. Tricyclic antidepressants (TCA), which have mixed properties including serotonin reuptake inhibition and noradrenaline reuptake inhibition as well as anticholinergic and antihistamine actions, have similar efficacy to SSRIs[17-18]. The TCA nortriptyline has also been suggested to have neuroprotective properties in pre-clinical studies. However, TCAs are currently only recommended as second line treatments for depression in PD due to their increased risk of adverse reactions including orthostatic hypotension, dry mouth, constipation, urinary retention, memory impairment, hallucinations and confusion. They are particularly poorly tolerated in patients with cognitive impairment[17, 19-20].

Nevertheless, in depression in PD (dPD), TCAs have conventionally been used because their anticholinergic properties are considered beneficial for parkinsonian features, such as tremor, in early PD, and insomnia. Some trial evidence also supports efficacy of TCAs for depressive symptoms in PD[21-25]. SSRIs on the other hand, whilst supported by some trial evidence[26], are sometimes used cautiously in dPD, as cases of new onset parkinsonism or worsening of parkinsonism have been reported[11-13]. The reported effects of SSRIs on PD motor symptoms has varied between different studies[27-30], with some animal models[31] and case reports[32-33] suggesting parkinsonism as a reversible adverse effect of SSRIs, and suggesting deterioration of parkinsonism in some[28, 34-37] but not others[27]. Additionally, other side effects such as fatigue or postural hypotension can occur and may already be pre-existing in PD[36,38]. Furthermore, there have been reports about an increase in falls in patients on SSRIs[39], and very rarely serotonin syndrome has been reported[40]. The British National Formulary limits use of SSRIs and TCAs or advises caution in their use with the selective MAO-B inhibitors rasagiline and selegiline that are used in PD due to increased central nervous system (CNS) toxicity. Therefore, there remains concern that SSRIs worsen Parkinson's symptoms and that antidepressant treatment in dPD is not clinically effective.

Several systematic evidence reviews recommend the use of TCAs in dPD over SSRIs[25]. There is a lack of placebo-controlled trials, and overall surprisingly little evidence available on the effectiveness of antidepressants, either TCA or SSRI, in PD (see below), particularly in a real-life NHS setting rather than selected study populations of previous trials where age is typically relatively young and comorbidities

low, and little evidence that SSRIs are effective and better tolerated than TCAs. Only two trials comparing both an SSRI and a TCA in PD have been reported, both with small sample sizes (summarised below). There is therefore insufficient evidence and consequent uncertainty in the role of SSRIs and TCAs in the treatment of dPD, and as a result, depression in PD remains undertreated[41].

Clinical data - Previous trial evidence

Clinical effectiveness

Several meta-analyses on antidepressant medications for dPD have been published, most of which concluded that the small number of trials and methodological drawbacks preclude definitive conclusions about their efficacy and tolerability in dPD and further large trial evidence is needed[19, 42-45]. However, others concluded that there was evidence for benefit of SSRIs[26] or TCAs[25, 46] for dPD.

An up-to-date table of all identified RCTs using TCA or SSRI for dPD is below. Amongst the published trials, only two studies randomised patients to SSRI, TCA or placebo in a RCT; the studies by Menza *et al*[22] (nortriptyline and paroxetine) and Devos *et al*[47] (desipramine and citalopram). Both studies reported improvement of depression with both the TCAs and SSRIs compared to placebo, including improved anxiety, dysphoria, and vegetative symptoms and tolerability of the active agents, but the numbers were small. Among the published trials, both SSRIs (effect size 0.49; 95% CI 0.11 to 0.88) and TCAs (effect size 0.79; 95% CI 0.16 to 1.41) show improved symptoms of depression compared with placebo. Although TCAs show a numerically larger effect there is no systematic difference between the two treatments (p value for interaction =0.44). The trials contributing are very small and are likely to be unreliable, with only 107 patients randomised in SSRI trials and 44 in TCA trials.

Table 1. RCTs with an SSRI or TCA in depression in Parkinson's disease*

First author	Publication year	Study duration	Age range (yrs)	Diagnoses	Retention/Sample size per group	Study outcome measure	Findings
Devos D	2008	4 weeks	57–65	PD with MDD, MARDS >20	16/16 Placebo 13/15 Citalopram 16/17 Desipramine	MADRS	Improvement in all groups but both interventions better than placebo
Leentjens AFG	2003	10 weeks	67 ± 7.8	PD with MDD	6/6 Placebo 6/6 Sertraline	MADRS	50% reduction in both groups
Menza M	2009	8 weeks	62.2 ± 8.7	PD with MDD or dysthymia	11/17 Placebo 12/17 Nortriptyline 11/18 Paroxetine CR	HAM-D 17	Paroxetine not superior and may be inferior to nortriptyline
Richard I	2012	12 weeks	63.5 ± 10.7	PD with any depressive disorder	33/39 Placebo 34/42 Paroxetine 30/34 Venlafaxine	MADRS HAM-D 17 GDS	Improvement in treatment groups compared to placebo
Rios Romenets	2013	6 weeks	64.5–69.5	PD with insomnia	6/6 Placebo 6/6 Doxepin 6/6 CBT	BDI	No change in all groups
Wermuth L	1998	6 weeks	64 (44–79)	PD with MDD HAM-D >13	17/19 Placebo; 13/18 Citalopram	HAM-D 17	Reduction in both groups
Antonini A	2005	12 weeks	68.5-71.8	PD with MDD	11/15 Amitriptyline 12/16 Sertraline	HAM-D 17 PDQ-39	Reduction in both groups
Avila A	2003	90 days	70.4 ± 6.4	PD with MDD or dysthymia	7/7 Fluoxetine 6/9 Nefazodone	BDI	Improvement in both groups

*adapted from Bomasang-Layno et al, 2015

Cost effectiveness

Whilst evidence exists to suggest SSRIs are cost-effective compared with TCAs for major depression[18], no studies are available assessing the cost-effectiveness for an SSRI or TCA in dPD.

Rationale and risks/benefits: why is the research needed now?

As a result of the above summarised levels of evidence, some international treatment recommendations advocate the use of both TCAs and SSRIs in PD[48-49], whilst others state a preference for TCAs[25] or state there is insufficient evidence[50]. There is therefore an urgent need for conclusive trial evidence on the clinical effectiveness of SSRI and of TCA treatment in dPD in a real life setting in the UK, and for the cost-effectiveness of an SSRI and a TCA in the NHS setting to guide evidence-based treatment in the NHS.

This is a randomised trial in a NHS setting, comparing the clinical effectiveness and cost-effectiveness of the SSRI escitalopram, and of the tricyclic nortriptyline, to placebo, undertaken in a real-life setting in addition to standard psychological care. Based on the previous evidence from small trials, the hypothesis is that both SSRIs and TCAs are effective compared to placebo and the difference in efficacy

between TCAs and SSRIs is likely to be small, but that the tolerability of SSRIs is higher in this population than that of TCA due to the rate of adverse effects. The trial is designed to have statistical power to identify effects that are clinically important and slightly smaller than the pooled effects identified in the existing trials of SSRIs.

Results from an adequately powered, placebo-controlled trial in the NHS will provide conclusive evidence on the effectiveness (using both efficacy and tolerability) of escitalopram, one of the newer, most effective and best tolerated SSRIs, in patients with PD, combined with a cost-effectiveness analysis; this will allow for evidence-based treatment guidance of this common complication of Parkinson's disease in the NHS. In addition, it will provide evidence on the real-life effectiveness of nortriptyline, a TCA which is currently the most widely recommended antidepressant in dPD.

This study also has the potential to address the concern that worsening of Parkinson's symptoms is common with SSRIs and that antidepressant treatment in dPD is not effective or otherwise. Conversely, this study has the potential to support the notion that treatment with the TCA nortriptyline is associated with less severe parkinsonian features than placebo after one year.

5.1.1 Explanation for choice of comparators

Escitalopram is an SSRI similar to citalopram, the most widely used SSRI in the UK. Both citalopram and escitalopram, the S-enantiomer, are now off-patent with comparable costs and similar trial results. Until recently, escitalopram has been used less commonly in the NHS because it was more expensive. However comparative trial data in major depression (including non-industry funded research) suggest that escitalopram is more effective than citalopram with similar or lower rates of side effects[51-53], and that it is associated with increased probability of response in trials of older patients with dementia and agitation[54]. In addition, it has been reported that escitalopram has the highest probability of remission and is the most effective and cost-effective pharmacological treatment in a primary care setting[55].

Amitriptyline is the most widely used TCA in the UK, but is used predominantly at low doses for pain and insomnia in PD. The side effect profile of amitriptyline makes it poorly tolerated in patients with PD at higher, antidepressant doses. Nortriptyline is a metabolite of amitriptyline. However, unlike amitriptyline, nortriptyline has mainly noradrenergic effects, and weakly blocks dopaminergic reuptake. It also has fewer sedative, α1-blocking and anticholinergic effects than amitriptyline (by a factor of 8). It has been evaluated in multiple trials over several decades and its efficacy and adverse event profile in depressive disorders has been well studied. The trial evidence on TCA in dPD (see above) mainly reports on nortriptyline and desipramine (which is not available in the NHS). Whilst nortriptyline has a slightly higher cost than amitriptyline in the NHS, nortriptyline is a more appropriate medication for treatment of depression in this population. In addition, there is accumulating evidence from pre-clinical studies that nortriptyline may delay disease progression in Parkinson's disease[56].

5.2 Objectives

Principal:

Establish the clinical effectiveness and cost-effectiveness of *escitalopram* at 8 weeks compared to *placebo* in the treatment of depression in PD, in addition to standard psychological care in the NHS.

Establish the clinical effectiveness and cost-effectiveness of *nortriptyline* at 8 weeks compared to *placebo* in the treatment of depression in PD, in addition to standard psychological care in the NHS.

Secondary:

Establish whether there is a difference in adverse reactions between *escitalopram* and *nortriptyline.*

Establish the long-term (1 year) clinical effectiveness and cost-effectiveness of *escitalopram and nortriptyline* compared to *placebo* in the treatment of depression in PD, in addition to standard psychological care.

Establish the clinical effectiveness of escitalopram and of nortriptyline, compared to placebo on anxiety and other secondary outcome measures.

Establish whether after one year of treatment parkinsonism has deteriorated less in patients with Parkinson's disease with depression on nortriptyline than on placebo.

Establish whether after one year of treatment parkinsonism has deteriorated more in patients with Parkinson's disease with depression on escitalopram than on placebo.

5.3 Trial Design

The study is a multicentre, double-blind, parallel trial with an internal pilot study. Participants will be randomly allocated 1:1:1 to receive escitalopram or nortriptyline or placebo.

6 Methods

6.1 Site Selection

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

6.1.1 Study Setting

ADepT-PD will be conducted across specialist settings including Neurology, Care of the Elderly and Parkinson's disease clinics in the UK.

6.1.2 Site/Investigator Eligibility Criteria

Once a site has been assessed as being suitable to participate in the trial, the trial team will provide them with a copy of the ADepT-PD protocol and relevant Investigator Brochures/Summary of Product Characteristics.

To participate in the ADepT-PD trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the ADepT-PD Sponsor and/or Trial Management Group (TMG) and that are defined below.

Eligibility criteria:

- A named clinician is willing and appropriate to take Principal Investigator (PI) responsibility
- Suitably trained staff are available to recruit participants, enter data and collect samples

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing 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) as agreed in the site agreement. This includes confirmation of appropriate qualifications, by provision of a CV, familiarity with the appropriate use of any investigational medicinal products, agreement to comply with the principles of GCP, to permit monitoring and audit, as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related duties.

6.1.2.2 Resourcing at site

The investigator(s) should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (i.e. the investigator(s) regularly treat(s) the target population). They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to conduct the trial properly and safely.

Sites will be expected to complete a delegation of responsibilities log and provide staff contact details.

The site should have sufficient data management resources to allow prompt data return to CCTU.

6.2 Site approval and activation

On receipt of confirmation of capacity and capability, a signed site agreement, approved delegation of responsibilities log and staff contact details, 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. The Trial Manager or delegate will be responsible for issuing this after a green light to recruit process has been completed.

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

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

6.3 Participants

This is a pragmatic trial. The criteria for inclusion are as close to clinical practice as possible. Those with depressive symptoms in PD will be assessed for eligibility for participation.

6.3.1 Eligibility Criteria

Patients aged between 18 to 85 years with idiopathic Parkinson's disease.

6.3.1.1 Participant selection

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

6.3.1.2 Participant Inclusion Criteria

1. Patients with a diagnosis of idiopathic PD, based on a history and neurological exam performed by the enrolling investigator with presence of at least two of the three cardinal signs of PD: rigidity, bradykinesia, and rest tremor with no evidence of diagnostic alternatives.
2. Aged 18 to 85 years.
3. Fulfilling diagnostic (*DSM-V*) criteria for a depressive disorder (i.e. major depressive disorder or persistent depressive disorder) or operationally defined subsyndromal depression (presence of two or more depressive symptoms at threshold or subthreshold levels, at least one of which had to include depressed mood or anhedonia).
4. Beck Depression Inventory-II (BDI-II) score ≥14.
5. Written informed consent provided.

6.3.1.3 Participant Exclusion Criteria

No patients will be excluded based on PD motor severity but the following will be excluded:

1. Women who are pregnant, breastfeeding or of childbearing potential without effective contraception (hormonal or barrier method of birth control; or abstinence). Periodic abstinence (e.g.calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
2. Patients who do not have sufficient understanding of the English language to be able to read and understand the self-completed questionnaires or patients who are unable to communicate answers to the self-rating questionnaires.
3. Patients with Montreal Cognitive Assessment (MoCA) score <16 or without capacity to consent.
4. Treatment with an antidepressant within 4 weeks of enrolment (except for a small dose of amitriptyline up to 30 mg for indications other than depression).
5. Patients with known severe liver failure.
6. Absolute contraindications to escitalopram or nortriptyline. These include:
    a. Patients with known QT-interval prolongation (defined here as >420 ms[57]) or congenital long QT syndrome.
    b. Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias.
7. Medications contraindicated on nortriptyline or escitalopram. These include:
    a. Non-selective and selective irreversible monoamine oxidase inhibitors (MAOIs) within 14 days. However, the antiparkinsonian selective reversible MAO-B inhibitors rasagiline, selegiline and safinamide are not contraindicated.
    b. Concomitant QT prolonging drugs, including domperidone, apomorphine at high doses (single dose or hourly rate of >6mg), certain neuroleptics (not quetiapine or clozapine), quinine, class IA and III antiarrhythmics (amiodarone, dronedarone and disopryamide), the antihistamines astemizole, mizolastine, the antimicrobial agents sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarian treatment),and some antiretrovirals.
8. Patients indicating active suicidal ideation or intent on the BDI-II item 9 and who, after clinical review of risk using the standardised Suicide Risk Management Protocol, need to be referred for immediate treatment.
9. Treatment with antiparkinsonian medication is not optimised and stable within 4 weeks of receiving the trial medication and there are plans to change up to primary endpoint (8 weeks).
10. Participation in another clinical trial of an investigational medicinal product or device within the last 30 days.

6.3.1.4 Eligibility Criteria for Individuals Performing the Interventions

All assessments will be performed by suitably qualified members of the clinical trial team trained in the use of all relevant assessments used as part of the ADepT-PD trial. PI delegated roles and responsibilities for this trial will be documented in the ADepT-PD site delegation of responsibilities log. CVs and GCP certificates of all individuals working on the trial will be collected by the UCL CCTU ADepT-PD trial team to document their qualifications and relevant experience. Protocol specific training will be provided to participating sites prior to site activation.

6.3.1.5 Co-enrolment Guidance

Participants should not be enrolled in concomitant clinical trials of investigational medicinal products or devices but can participate in non-interventional studies.

6.3.1.6 Screening Procedures and Pre-randomisation Investigations

Written informed consent to enter and be randomised into the trial must be obtained from participants after explanation of the aims, methods, benefits and potential hazards of the trial and the optional genetic sub-study and **BEFORE** any trial-specific procedures are performed or any blood is taken for the sub-study. 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 standard of care. This includes administration of questionnaires used in clinical practice such as the Non-motor symptoms questionnaire, BDI-II, PHQ9, MDS-UPDRS, PDQ-39 or EQ-5D-5L.

Once consent has been provided, the following screening assessments will be carried out to evaluate patient eligibility:

- Evaluation of depressive symptoms according to DSM-V criteria using the modified Clinical Interview Schedule (CIS-R) assessment[58]
- Evaluation of severity of depression using the Beck Depression Inventory-II (BDI-II)
- Evaluation of cognitive function using the Montreal Cognitive Assessment (MoCA)
- ECG using a hand-held ECG device to rule out QTc prolongation
- Women of child bearing potential (i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile) urine samples will be tested to determine pregnancy status

6.4 Interventions

6.4.1 Products

- Active treatment escitalopram target dose: 20mg if 65 years and under; or 10mg if >65 years and in those with hepatic impairment
- Active treatment nortriptyline target dose: 100mg if 65 years and under, or 50mg if >65 years and in those with hepatic impairment
- Placebo

The initial dosage of study medication will be as follows:

- 5mg escitalopram increased by 5mg per day, at two-weekly intervals, to a maximum of 20mg escitalopram per day
- 25mg nortriptyline increased by 25mg per day, at two-weekly intervals, to a maximum of 100mg nortriptyline per day

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.

Standard psychological care will be provided according to the currently available, locally appropriate services (see standard care below).

Standard Psychological Care

People with depression are routinely treated in primary care by their GP. This may include referral to counselling or psychological treatments in England, usually to Communuity Mental Health Services e.g. Improving Access to Psychological Therapies (IAPT), although waiting times may be substantial. IAPT is not routinely available in Scotland where people may be referred to psychology services. Patients referred to IAPT are usually assessed within 4 weeks of referral and then placed on a waiting list for therapy, typically Cognitive Behavioural Therapy (CBT) or Interpersonal Therapy (the two main NICE recommended psychological treatments for depression), although other approaches may be offered locally. IAPT uses a stepped care approach with the least intensive modality used first based on the initial assessment, with more intensive and costly interventions used only as necessary. Depending on modality, treatment may involve 4-16 sessions over a period of 1-9 months. If patients are identified as depressed by their neurologist, they may be referred to their GP for management of their depression, or where they have complex problems and/or risk of suicide is deemed a concern, they may be referred to a liaison psychiatrist, if available, for specialist treatment of depression. The neurologist will be providing part of standard psychological care in terms of support and monitoring during routine consultations. IAPT services also allow self-referral.

We will record any psychological treatment provided to participants in the 6 months prior to and during participation in the trial. Patients who have received treatment with an antidepressant within 4 weeks of enrolment (except for a small dose of amitriptyline up to 30 mg for indications other than depression) will not be eligible for the trial.

6.4.2 Treatment Schedule

Doses of antidepressants are according to the British National Formulary guidelines. A dosing regimen that allows for a real-world titration in this population according to side effects has been chosen.

6.4.2.1 Treatment Allocation

Patients who meet eligibility criteria at the screening visit will be randomly assigned to receive 52 weeks of double-blind treatment with either escitalopram, nortriptyline or placebo in a 1-1-1 ratio before being tapered off the medication (over the following 1-4 weeks). To maintain study blinding, all study medications will be provided in bottles of identically appearing tablets.

If, following the pilot study (described in section 6.8.1.1), the decision is made to drop one of the active treatment arms, the trial will continue with two arms comparing either escitalopram/nortriptyline with placebo.

6.4.2.2 Medication titration

At Study start

Adult under 65

- For the first two weeks of double-blind treatment, participants will be instructed to take one tablet per day of study drug, containing either 5mg escitalopram, 25mg nortriptyline or placebo. All tablets are to be taken as a single dose in the morning.

- Thereafter, the daily study medication dosage will be increased by one tablet per day, at two-weekly intervals, to a maximum of four tablets per day unless a subject is experiencing intolerable side effects.

Adult over 65

- For the first two weeks of double-blind treatment, participants will be instructed to take one tablet per day of study drug, containing either 5mg escitalopram, 25mg nortriptyline or placebo. All tablets are to be taken as a single dose in the morning.
- Thereafter, the daily study medication dosage will be increased by one tablet per day, at two-weekly intervals, to a maximum of two tablets per day unless a subject is experiencing intolerable side effects.

The dose and intervals for escalation are consistent with the marketing authorisation of these drugs for the treatment of depressive disorders and with the doses used in the previous trials in Parkinson's disease.

A member of the local site research team will contact the participant by phone at each relevant time point to remind them when the dosage needs to be changed (if applicable) and to ask about side effects (AEs). In those >65 years and in those with hepatic impairment the dose will be increased to two tablets after 2 weeks only, from 5mg escitalopram to 10mg escitalopram or from 25mg nortriptyline to 50mg nortriptyline, not exceeding the British National Formulary maximum doses in those >65 years and in those with hepatic impairment.

If side effects continue, the dose may be decreased to the previous dose level at any time during the double-blind period.

Study medication compliance (i.e., number of unused tablets) will be recorded at all post-baseline visits.

During long-term follow-up

- After the primary endpoint at 8 weeks, all participants will continue on the same dose (*if applicable*) until the study visit at 52 weeks with an intermediate assessment at 26 weeks.
- If there is failure to respond to therapy and there is a clinical need to treat depression with an alternative agent, study medication will be tapered and stopped and alternative therapy introduced as appropriate by their GP/clinician (refer to study end).
- If there is a need to stop the study drug due to lack of efficacy or due to side effects, or the wish of the participant, participants will be encouraged to attend all study visits to obtain follow up assessments. For timing of assessments see Section 6.6 (Patient Timeline).

At trial end (52 weeks onwards)

- Following the study assessment after 52 weeks on medication, the trial drug will be tapered off in dose reductions of 25mg for nortriptyline and 5mg for escitalopram every two weeks (8 weeks for participants 65 years or under and 4 weeks for participants >65 years or those with hepatic impairment).

- A member of the local site research team will contact the participant at each relevant time point to remind them when the dosage needs to be changed.
- Blinding of the participants and study team will be maintained until the study medication has been withdrawn but an unblinded member of the trial team will communicate the treatment allocation to the GP (and not the participant or the trial team) if they request unblinding earlier.
- For those who may wish continued treatment at study end, liaison will be made with the GP to continue prescription following unblinding by an unblinded member of the trial team.

6.4.3 Dispensing

The trial medication will be supplied by the Royal Free Hospital Pharmacy Manufacturing Unit and packaged and labelled into bottles containing 185 tablets. After participants are randomised to receive trial medication, the PI or delegated research trial team member will complete an ADepT-PD prescription and order form which will be then emailed to the third party distributor who will send the trial medication directly to the trial participants. Participants who are aged 65 and under will receive 2 bottles of trial medication on a 3 monthly basis and participants aged 65 and over or who have a hepatic impairment will receive 1 bottle of trial medication on a 3 monthly basis.

Trial duration per participant

8 weeks on treatment to primary endpoint, then continued follow-up to 52 weeks on treatment to the secondary endpoint. The trial medication is then tapered off over the following 4-8 weeks and the final assessments will take place at 55-60 weeks (depending if the participant is aged 65 and under, or is aged over 65 or has a hepatic impairment).

Justification of trial duration per participant

The primary outcome will be assessed at 8 weeks, as this provides sufficient time for the titration of the antidepressant with a potential 2 week period on the maximum dose, whilst at the same time minimising the risk of drop-outs due to lack of response in the placebo group. However, we will continue the trial to overall duration of 52 weeks on their maximum dose before the participant is tapered off the trial medication (ending at 55-60 weeks) in order to determine long term effectiveness.

6.4.4 Dose Modifications, Interruptions and Discontinuations

Dose modification as a result of cardiac abnormalities

If cardiovascular symptoms, such as palpitations, syncope or seizures develop during treatment, the symptoms should be recorded as an adverse event (AE) and cardiac evaluation, including an ECG, should be undertaken to exclude a possible malignant cardiac arrhythmia; if QTc interval is >440ms for men and >470ms for women treatment should be withdrawn gradually.

Dose modification as a result of side effects

Dosage can be decreased because of AEs at any time during the double-blind period to the previous dosage level. If the dosage is reduced to zero, the participant should be withdrawn from the trial but

should remain in the trial for the purpose of follow up and data analysis, see section 6.6.1 (Early Stopping of Follow-up) for further details.

6.4.5 Accountability

The third party distributor will inventory and acknowledge receipt of all shipments of trial medication and complete a trial supplies receipt document, a copy of which will be retained by the third party distributor and the original returned to UCL CCTU. All trial medication must be stored in accordance with the manufacturer's instructions and it must be kept in a locked area with restricted access to designated trial personnel. The third party distributor will keep accurate records of the quantities of trial medication dispensed and sent to each participant. UCL CCTU trial personnel will periodically check the supplies of the trial medication held by the third party distributor to ensure accountability of all trial medication used.

Unused trial medication will be returned by each participant to their local site pharmacy at the end of their participation in the trial. The investigator or delegate will arrange for all unused trial medication to be destroyed according to local procedures after accountability and compliance assessments have been completed by the research team. Documentation confirming destruction will be provided to UCL CCTU.

6.4.6 Compliance and Adherence

Participants will be issued with a dosing diary to instruct them on the administration and timing of the trial medication on a daily basis, and also to record their daily uptake. A member of the local site research team will contact the participant by phone at each relevant time point to check that the participant has received the trial medication, ask about any side effects (AEs) experienced by the participant and to remind the participant when the dosage needs to be changed.

Participants will be encouraged to continue long-term follow-up to assess outcomes beyond the primary outcome time-point. Efforts will be made to collect follow-up assessments if participants have difficulty attending hospital appointments, e.g remotely via telephone.

In order to facilitate retention, the majority of assessments can be completed remotely to avoid drop-outs due to inability to attend. Assessments that are incomplete will not be excluded but will be accounted for during statistical analysis.

6.4.7 Concomitant Care

Standard psychological care will be provided according to the currently available, locally appropriate services (as described in section 6.4.1).

6.4.8 Overdose of Trial Medication

Measures will be taken to minimise accidental overdose of trial medication by providing adequate education to trial participants. Accidental or deliberate overdose of trial medication will be treated accordingly. The appropriateness of re-introduction of trial medication following an accidental overdose will be determined by the clinical investigator at the participating site. Any patient taking a deliberate overdose of trial medication will be withdrawn from the trial and will be followed-up unless they withdraw consent for follow-up.

Clinical data on escitalopram overdose are limited and many cases involved concomitant overdose of other drugs. In the majority of cases, mild or no symptoms were reported. Fatal cases of escitalopram overdose have rarely been reported with escitalopram alone. There is no specific antidote in the event of overdose. An airway needs to be established and maintained an airway, adequate oxygenation and respiratory function need to be ensured. Gastric lavage and the use of activated charcoal should be considered. Gastric lavage should be carried out as soon as possible after oral ingestion. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.

Clinical data on nortriptyline overdose show a mortality rate of 0-15%. Symptomatic and supportive therapy is recommended. Early transfer to a hospital with an intensive care unit is recommended. Activated charcoal may be more effective than emesis or lavage to reduce absorption, although combination therapy may be appropriate depending on time since ingestion.

6.4.9 Protocol Treatment Discontinuation

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

- Unacceptable treatment toxicity or adverse event
- Inter-current illness or requirement for medication that prevents further treatment with trial medication
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
- Withdrawal of consent for treatment by the participant

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. 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.

Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow up and data analysis, see section 6.6.1 (Early Stopping of Follow-up) for further details.

6.5 Outcomes

Participants with advanced PD may not have good control of symptoms. These motor fluctuations usually happen when the medication taken to control PD (usually levodopa) is wearing off, but they can happen at other times too. This is called 'end of dose wearing off' or just 'wearing off'. An 'On period' is when a person's symptoms are controlled and when they feel at their most capable. An 'Off-period' is when Parkinson's symptoms come back and affect them the most.

All assessments should be completed during an On-period. However, if the patient has off-periods at baseline and one-year follow up it should be attempted to also assess the participant during a practically defined Off-period e.g. before the first dose of antiparkinsonian medication, with an additional assessment of the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor assessments. This could be done during an assessment of the patient at home.

6.5.1 Primary Outcomes

At 8 weeks of treatment:

Depressive symptoms measured using the Beck Depression Inventory (BDI-II)[59-60] to assess clinical effectiveness against placebo.

6.5.2 Secondary Outcomes

At 8, 26 and 52 weeks of treatment:

Patient-reported outcomes

- Level of depression as measured using the Becks Depression Inventory (BDI-II) (at weeks 26 and 52) [58-59].
- Level of depression on the PHQ9.
- Number of participants experiencing side effects (adverse reactions) on the Modified Toronto Side Effects Scale[61-62] and reporting of other adverse events.
- Anxiety symptoms on the Parkinson Anxiety Scale[63].
- Quality of life on the EQ-5D-5L questionnaire[64-65]
- Capability using the ICECAP-O questionnaire[66-67].
- Health and social care resource use on the modified Client Service Receipt Inventory (CSRI)[68].
- Time spent by paid carers measured using a modified version of the iMTA Valuation of Informal Carers Questionnaire (iVICQ)[69] (asked alongside the CSRI).
- Changes in concomitant medication.

Clinician and patient-reported outcomes

- Motor and non-motor experiences on the MDS-UPDRS[70] Part I and II, and motor examination and motor complications on the MDS-UPDRS Part III and IV (including a recording of the participant's movements).

Clinician-reported outcomes

- Cognitive function assessed on the Montreal Cognitive Assessment (MoCA)[71].
- Overall clinical effectiveness on the Global Clinical Impression scale (CGI) - change in health question.
- Levodopa-equivalence dose.
- Number of drop-outs.

Carer-reported outcomes

The trial does not require that the participants have a carer, however, if a participant does have a carer (definition in section 4), the carer will be asked if they agree to complete the following questionnaires:

- Carer's quality of life using the EQ-5D-5L[63-64] and Perceived Quality of Life scale – carer version (PQOL-carer)[72].

- Impact on informal carers measured using a modified version of the iVICQ[69] (asked alongside the CSRI).

6.5.3. Additional assessment

At baseline and follow up visits, blood samples will be collected optionally for investigation of inflammatory markers which may play a role in response to treatment. The panel of inflammatory markers will be defined when collection of samples has been completed, but it is planned to use a standard multiplex panel including 10 cytokines and C-reactive protein. Blood samples will be centrifuged at the site and stored at -80 degree freezers locally before shipment to UCLH Laboratories, 6th Floor, Queen Square House, Queen Square, London WC1N 3BG at the end of the trial.

Following the 52 week assessment, the study drug will be tapered off as above, and the participants will be assessed at 55-60 weeks on the following measures:

- Reporting of AEs
- Changes in concomitant medications
- BDI-II
- MDS-UPDRS (Part I and II: Motor and Non-Motor Aspects of Experiences of Daily Living (nM-EDL) and part III (motor part))
- MoCA

6.5.4. Genetic sub-study

The trial also includes a genetic sub-study. The participants will be asked if they will give an optional blood sample which will be analysed to try to identify genetic markers that may be associated with subtypes of PD (e.g. presence of depression and anxiety) or variation in treatment responsiveness. Participants who do not wish to participate in the genetic sub-study will not be excluded from the main trial. Details of the genetic sub-study are included in Appendix 1.

6.6 Participant Timeline

	Screening/ Baseline Visit (week 0)[a]		IMP receipt call (week 1)	Escalation period calls (weeks 1-8)	8 Week Visit[b]	IMP receipt call (week 12)	26 Week Visit[b]	IMP receipt call (week 26)	IMP receipt call (week 39)	52 Week Visit[b]	Tapering period calls (weeks 55-60)	End of Study Visit (weeks 55-60)[c]
Flexibility of schedule ± days	0				+/-1 week		+/-2 week			-1 week		
Visit number	1				2		3			4		5
	Screening	Baseline										
Informed consent	●											
Eligibility screen	●											
CIS-R (including DSM-V)	●											
BDI II	●				●		●			●		●
MoCA	●				●		●			●		●
Demographics	●											
Medical history	●											
Concomitant medications (levodopa-equivalence dose)	●				●		●			●		●
Concomitant psychological therapies	●				●		●			●		
ECG	●				●		●			●		
Vital signs	●				●		●			●		
Pregnancy testing (if applicable)	●				●		●			●		
Blood sampling (optional)[d]	●				●		●			●		●
Randomisation		●										
Trial medication/dosing diary discussion[e]		●			●		●			●		

	Screening/ Baseline Visit (week 0)[a]		IMP receipt call (week 1)	Escalation period calls (weeks 1-8)	8 Week Visit[b]	IMP receipt call (week 12)	26 Week Visit[b]	IMP receipt call (week 26)	IMP receipt call (week 39)	52 Week Visit[b]	Tapering period calls (weeks 55-60)	End of Study Visit (weeks 55-60)[c]
Check receipt of trial medication			●			●		●	●			
Adverse events				●	●		●			●		●
MDS-UPDRS[f]		●			●		●			●		●
PHQ-9		●			●		●			●		
ICECAP		●			●		●			●		
Parkinson's anxiety scale		●			●		●			●		
CGI (change in health)					●		●			●		
EQ-5D-5L		●			●		●			●		
Modified Toronto Side Effects Scale		●			●		●			●		
Modified CSRI		●			●		●			●		
Modified iVICQ		●			●		●			●		
PQOL-carer[g]		●			●		●			●		
EQ-5D-5L carer[g]		●			●		●			●		
Pill count					●		●			●		●
Dose escalation / reduction reminders[h]				●							●	

[a] The Screening and Baseline assessments will occur on the same day.

[b] Where attendance at the trial site is not possible, efforts will be made to collect the information remotely (e.g. via telephone).

[c] The End of Study visit will take place at weeks 59-60 for participants aged 65 and under and at weeks 55-56 for participants aged over 65 (or with hepatic impairment).

[d] Optional genetic sub-study blood sampling (*refer to genetic sub-study guidance document*). will be taken at the screening/baseline visit (***but can be taken at a later visit if necessary***); **optional blood samples for analysis of inflammatory markers will be taken at every visit.**

[e] A member of the site trial team will provide the participant with a copy of the Dosing Diary which confirms how much trial medication the participant has to take daily and is also used for the participant to record the actual number of tablets they take each day.

[f] If the patient has Off-periods, at baseline and one-year follow-up, it should be attempted to also assess the participants during a practically defined Off-period e.g. before the first dose of antiparkinsonian medication, with an additional assessment of the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor assessments. This Off-period assessment could be done during an assessment of the patient at home.

[g] Only if participant has a carer.

[h] A member of the local site research team will contact the participant at the relevant times during the tapering periods (i.e. every 2 weeks when the dose is being escalated at the start of the participant's trial treatment and every week when the dose is being reduced at the end of the participant's trial treatment) to remind the participant when the dosage needs to be changed.

6.6.1 Early Stopping of Follow-up

If a participant chooses to discontinue their trial treatment, they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole trial, even though they no longer take the trial treatment. If, however, the participant exercises the view that they no longer wish to be followed up, this view must be respected and the participant withdrawn entirely from the trial. Participants who withdraw early from the trial will be asked to complete the BDI-II questionnaire to help evaluate their depressive symptoms at the time of withdrawal. CCTU should be informed of the withdrawal in writing using the appropriate ADepT-PD Withdrawal CRF. Data already collected will be kept and included in analyses according to the intention to treat principle for all participants who stop follow up early.

Participants allocated to a treatment group, but who withdraw prior to taking any trial medication (verified through the return of unused tablets), will not be considered to have been randomised as described in ICH E9[73]. Participants who withdraw from randomised therapy after randomisation is complete (i.e. participant has ingested trial medication) will be followed-up unless they withdraw consent for follow up.

6.6.2 Participant Transfers

If a participant moves area, making continued follow up at their consenting centre inappropriate, every effort should be made for them to be followed at another participating trial centre. Written consent should be taken at the new centre and then a copy of the participant's CRFs should be provided to the new centre. Responsibility for the participant remains with the original consenting centre until the new consent process is complete. The original consenting centre will be responsible for resolving any data queries relating to assessments performed up to the point of transfer to the new centre.

6.6.3 Loss to Follow-up

Efforts will be made to minimise loss to follow-up, such as tracing participants via their NHS number using NHS Digital records (Spine) (where they might have changed their GP) which supports the IT infrastructure for health and social care in England once approvals for access have been granted. Consent for this will be sought prior to the participant entering the trial.

6.6.4 Trial Closure

The end of the trial for individual participants will be the date of their last visit. Trial closure is defined as the date when all data has been received, cleaned and all queries resolved at all sites.

The REC and MHRA will be notified within 90 days of trial end. A summary report of the research will be sent to the REC and MHRA within 12 months of the end of the trial.

A site may be deemed ''closed'' once all trial-related activities at that site are reconciled and/or complete, all outstanding data queries have been resolved and a letter confirming that close down is complete has been sent to the site PI from UCL CCTU.

In terms of the funder, the end of the trial is the time of the provision of the final report.

6.7 Sample Size

The primary outcome is the change in depressive symptoms measured using the Beck Depression Inventory (BDI-II) after 8 weeks of trial treatment. In order to have 90% power and a significance level of 0.025 (for each comparison to preserve studywise alpha), 113 participants are needed per group to detect a 3-point BDI II difference [SD for change 6.35][58-59] for the escitalopram–placebo and the nortriptyline–placebo comparisons at 8 weeks. Allowing for 20% attrition, 136 participants will be required per randomised group (408 overall).

If, following the pilot study (described in section 6.8.1.1), one randomised group was dropped and the trial continues with two arms comparing either escitalopram or nortriptyline with placebo, then 230 participants would be required in total (115 per arm including 20% allowance for attrition or other challenges to the study assumptions) at 90% power with significance of 0.05.

With this sample size, the study will have 90% power (1-beta) to find a mean difference of 3 points on the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor subscale (part 3), with a nominal alpha of 0.025 for each active comparison, taking the effective SD from Athauda et al 2017[74].

For the estimation of adverse reactions we will use the Modified Toronto Side Effects Scale[62] which elicits rates of side effects. We will use estimation and provide 95% confidence intervals around the difference in percentage side effects for each item, however the width of these confidence intervals will depend upon their position on the binomial distribution. Thus, a trial with 136 subjects in each experimental condition will provide 95% confidence intervals on the comparison between active agents ±12% when the rate of events is around 50%, and ±7% when the rate of events is around 10%.

6.8 Recruitment and Retention

6.8.1 Recruitment

The study will recruit for an overall period of 23 months, including the 6-month pilot period, which is discussed in section 6.8.1.1. The aim will be to recruit from approximately 22 to 30 sites. Site selection and number of sites that need to be set up will be informed by the pilot phase results.

Recruitment will supported by the Parkinson's Portfolio Development Group, Parkinson's Excellence Networks and the Comprehensive Local Research Networks (CLRNs).

Recruitment from clinical lists

Patients identified as potentially suitable for this trial from a review of clinical lists (Neurology, Care of the Elderly and Parkinson's disease clinics) may be contacted using a standard letter from their PD clinician in order for the patient to be put in touch with the local research team. The written Participant Information Sheet (PIS) should be included with the approach letter and the letter will advise the patient to contact their local research team directly in order to register further interest in the trial.

Potentially suitable patients may also be approached directly by their clinician, specialist nurse or research nurse and, after being given a brief verbal outline of the trial, will be provided with PIS and then will be followed-up by the local research nurse as above.

Patients may be recruited to the study from research registers (e.g. the Royal Free research register) or other similar databases. In this case, potentially eligible patients will be contacted and provided with the PIS according to local protocol, to ascertain interest in the study.

Recruitment via publicity and word of mouth

Patients may learn about the study from patient support group publications or meetings (e.g. Parkinson's Trust), or internet sources (e.g. the approved trial website and other websites describing the trial such as Fox Trial Finder and Parkinson's UK). In such cases, interested patients will be signposted to the trial website for further information and for contact details of their nearest trial site.

All potential patients who contact the trial team through the above methods will be provided with a copy of the PIS and will later receive a telephone contact from a member of the site trial team to explain the trial. If the patient is likely to fulfil the eligibility criteria and chooses to take part in the trial, they will be invited for a screening/baseline visit.

6.8.1.1. Internal Pilot study: stop and progression criteria

The trial will include an internal pilot study in the first 6 months with the aim to recruit 46 participants, which could be achieved by recruiting 0.77 participants per month in 10 sites (over the first 6 months), whilst other sites are being set up. We expect all of the 10 sites to be open to recruitment and have recruited at least one participant at the end of month 6 and on average to have recruited 4.6 patients per site over that period of time.

The results of this pilot study will determine progression to the full trial. Aggregated data will be collected (at the end of month 6) on eligibility, uptake/recruitment, reasons for declining to participate where possible, adherence and attrition, as well as completion of outcome measures. The main progression criterion will be the ability to recruit:

- If recruitment is 70% (n=32) of the target in the first 6 months the trial will be continued in its entirety.
- If recruitment in the pilot study is 50-70% (n=23-31) at month 6, the TSC will review the recruitment data to determine if recruitment can be enhanced for the full trial.
- If recruitment is less than 50% (n≤22) at month 6, the nortriptyline treatment arm will be dropped in the full trial.
- Rate of clinically significant adverse reactions (ARs): If the rate of ARs necessitating withdrawal exceeds 30% in one of the active arms of the pilot study, the IDMC will review the adverse events to consider if that active arm should be dropped in the full trial.
- Loss to follow up before primary outcome: If >20% of participants do not complete the Week 8 visit assessment (primary endpoint), the TSC will consider stopping the trial.
- Adherence to study medication through pill count: If there is <60% adherence to trial medication, the TSC will consider stopping the trial.

If needed, according to the progression criteria listed above, IDMC and TSC meetings may be convened to provide advice on whether the results of the pilot study allow for the trial to either continue as planned, be modified to drop one of the treatment arms or to stop the trial completely. However, the HTA Programme will make the final decision on continuation. This decision making will not be an

automatic process and recruitment will continue after the first 6 months until a final decision on the continuation of the trial is reached by the HTA Programme.

6.8.2 Retention

The retention of participants in the trial to the primary outcome is fundamental to assessment of effectiveness and cost-effectiveness. The importance of attending scheduled follow up appointments until trial completion will be explained to all participants at the start of the trial to ensure that only those able to commit to the trial protocol are recruited.

Drop-outs may be due to lack of efficacy, adverse events, uncertainty about need to start non-trial antidepressant treatment outside of the trial or other factors related to medical issues or uncertainties in participants and clinical teams. A time point of 8 weeks has been selected to minimise this risk of excessive attrition; this allows for adequate titration to maximum dose at the primary outcome point but does not exceed the recommended time to judge the effect of an antidepressant in clinical practice. In addition to the longer-term outcome assessment at 52 weeks, a 26 week assessment is included for safety. Where attendance at the trial site is not possible, efforts will be made to collect the information remotely (e.g. via telephone). A clinical research fellow will provide the clinical guidance, respond to medical queries and support decision making to facilitate inclusion, monitoring and completion of the trial for all sites. All participants who withdraw from the study medication will be encouraged to attend the 26 weeks and 52 weeks assessments.

6.9 Assignment of Intervention

6.9.1 Randomisation

6.9.1.1 Sequence generation

A random sequence for trial arm allocation will be computer generated by the trial statistician and provided to the randomisation service provider (Sealed Envelope.com). The factors minimise on will include site, depression severity (BDI-II 14-19/20-63), Hoehn & Yahr disease severity staging in the ON medication stage (≤2.0/≥3.0or less), amitriptyline usage (yes/no), clonazepam/benzodiazepine usage (yes/no), gabapentin/pregabalin usage (yes/no) and pramipexole/dopamine antagonist usage (yes/no).

The trial statistician will generate unique kit identification codes for every active/placebo trial medication bottle which will be entered into the web-based, password-protected, secure web-based randomisation service provided by the independent data management company (“Sealed Envelope”) who have been commissioned by the Priment Clinical Trials Unit to support randomisation and data management for the trial. Priment staff members will follow Priment SOPs when developing the randomisation system in the Sealed Envelope database.

6.9.1.2 Randomisation concealment mechanism

The kit identification codes will be provided by the trial statistician to Sealed Envelope and the Qualified Person (QP) at the Royal Free Hospital Pharmacy (drug manufacturing site) who will ensure

that all trial medication bottles are labelled appropriately, and that the trial team and participants remain blind to treatment allocation. Sufficient numbers of labelled trial medication bottles containing (escitalopram/nortriptyline/placebo) will be dispensed following randomisation at visit 1 (Screening/Baseline), and every three months thereafter.

6.9.1.3 Randomisation Implementation

After the participant has provided written informed consent and their eligibility for the trial has been confirmed, randomisation will be performed by the PI, or delegated member of the clinical investigating team, at local sites using the Sealed Envelope randomisation service stated above. Eligibility and consent will be verified before each participant is randomised. The responsibility for enrolling and prescribing trial medication for the participant lies with the PI at each recruiting site. Eligibility decisions will be made in line with the approved protocol. Other delegated clinicians employed at the same clinical site as the PI may partake in patient enrolment and trial medication prescription provided appropriate training has been undertaken and approval is given by the PI. Person(s) delegated key tasks/roles must have full names recorded on the ADepT-PD delegation log.

Individuals at participating sites will be provided with a secure login to the sealedenvelope.com website, according to a delegation of responsibilities log. The users will be required to log into the website and answer eligibility questions before entering stratification data and being permitted to randomise a participant. The randomisation result will be shown directly online as a unique kit identification code, with an email confirmation to the user and also to the UCL CCTU trial team.

The investigator will provide details of the allocated unique kit identification number assigned to the participant on prescription and order forms which are then sent to a third party distributor to enable dispensation of trial medication. A full accountability trail will be maintained from receipt of trial medication by the third party distributor, prescribing of the trial medication by the local principal investigators, distribution of the trial medication to the participants by the third party distributor to the point of destruction of undispensed trial medication at the local site pharmacies. The third party distributor will remain blinded to trial arm (escitalopram/nortriptyline/placebo) allocation.

Randomisation will be considered complete when the participant ingests their first double blind therapy. Participants who withdraw before taking their first randomised tablets will be considered withdrawn prior to randomisation on the verification that their tablets are untampered.

At subsequent clinic follow up visits, the PI or delegate at each site will enter the participant's trial patient identification code into the Sealed Envelope randomisation service which will then provide the kit identification code for further trial medication bottle(s) to be dispensed.

The Royal Free Hospital Pharmacy Manufacturing Unit will ensure they supply sufficient number of escitalopram/nortriptyline/placebo tablets to ensure availability of adequately labelled trial medication bottles at the third party distributor for dispensing direct to the trial participants.

6.9.2 Blinding

Trial medications will be identical in appearance for both antidepressants and placebo. Site staff completing assessments will be kept blind to trial arm allocation, as will be the participants.

The trial medication kit identification code list will be prepared by the Priment senior data manager and provided separately to Sealed Envelope and to the Royal Free Hospital manufacturing site who will ensure that labelling of trial medication bottles occur in the correct manner with adequate safeguards in place, to ensure complete blinding of the trial medication to all investigators, participants and the pharmacy staff on the study.

The Sealed Envelope randomisation service is set up to enable the unblinding of individual patients, should the need arise. The trial medication kit labelling strategy employed ensures that the unblinding of an individual patient will not result in the unblinding of the entire trial arm.

Detailed information regarding allocation implementation and blinding is provided in the ADepT-PD IMP Management and ADepT-PD Randomisation and Unblinding Plan.

6.9.3 Emergency Unblinding

All recruited participants will be given an emergency contact card with details of the local clinical trial team, including emergency telephone number available 24 hours a day, 7 days per week. If necessary, emergency unblinding can occur at any time through the Sealed Envelope randomisation service which is accessible to all local teams 24 hours a day. Unblinding will occur for any participant experiencing a serious adverse event (SAE) if the clinical management of the SAE will be facilitated by the unblinding of the participant's treatment allocation. Unblinding will be carried out according to trial specific working practices. A member of the local clinical team will handle the unblinding process and, where possible, other members of the local clinical team not involved in the clinical management of the SAE should remain blinded. (The unblinding process will be fully documented and this documentation will be kept in a separate file to the investigator site file).

If the person requiring the unblinding is not the PI, or a delegated site team member, for example a non-site team healthcare professional, they will notify the local PI, or delegate, that an unblinding is required for a trial participant and a decision to unblind should be made in consultation with the PI or delegated site clinical team members if possible.

On receipt of the unblinded treatment allocation details, the PI or treating healthcare professional will treat the participant's medical emergency as appropriate. The local investigating team will notify CCTU (acting on behalf of the Sponsor) in writing as soon as possible after unblinding takes place detailing the reasons why unblinding was needed. It will also be documented at the end of the study in any final study report and/or statistical report.

Emergency unblinding should only take place for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the participant is receiving before the participant can be treated. Where possible, members of the research team not involved in the clinical management should remain blinded.

6.9.4 Unblinding for the submission of SUSAR (suspected, unexpected, serious adverse reaction) reports

All SAEs that are related to the trial medication (i.e. SARs) and are suspected to be unexpected, need to be submitted to the regulatory agencies within pre-specified timelines. When SAEs reports are received at the CCTU, if the event is recorded as being a SUSAR then the following procedure will be used to unblind the SUSAR to determine 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 using the Sealed Envelope randomisation service. This will be documented on the ADepT-PD Emergency Unblinding form.
- 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 on the e-SUSAR database available through the MHRA website or through Eudravigilance (including the unblinded information).
- This information will not be forwarded to the trial team at the CCTU or at the sites. It will be kept in a separate file by the CCTU SUSAR reporting team.

6.10 Data Collection, Management and Analysis

6.10.1 Data Collection Methods

Each participant will be given a unique trial Participant Identification Number (PIN). Data will be collected at the time-points indicated in the Participant Timeline (in section 6.6).

All relevant participant data will be collected by delegated members of the clinical team across participating sites. All data will be handled in accordance with the General Data Protection Regulation (GDPR) and the Data Protection Act (DPA).

Clinical team members across all participating sites will receive adequate training on the ADepT-PD protocol and associated questionnaires. They will also receive training on data collection which will be by direct entry onto source documentation (e.g. patient notes) and then transcribed onto paper case report forms (CRFs). These trial specific CRFs will be designed by the ADepT-PD trial team. The approved ADepT-PD CRF will be provided to all participating sites and will be used to record participant data collected during the trial. The CRFs will not bear the participant's name, instead the participant's initials, month and year of birth and unique participant identification number will be used for identification.

The following data are from standardised tools that have been extensively validated in previous clinical trials. The printed questionnaires completed at each visit will be the source documents which will be filed with the CRF:

- Becks Depression Inventory (BDI-II)
- Patient Health Questionnaire (PHQ9)
- Modified Toronto Side Effects Scale
- Global Clinical Impression scale (CGI) – change in health question only
- Parkinson Anxiety Scale

- EQ-5D-5L
- ICECAP
- Modified Client Service Receipt Inventory (CSRI) / Modified iVICQ
- MDS-UPDRS
- Modified Clinical Interview Schedule (CIS-R) (only at baseline)
- Montreal Cognitive Assessment (MoCA)
- EQ-5D-5L (carer completed; only if participant has a carer)
- Carers Quality of Life Questionnaire for Parkinsonism (only if participant has a carer)

Pseudonymised data will be collected from the trial sites using paper Case Record Forms (CRFs) and transferred to CCTU via secure portal/encryption. Copies will be kept at trial sites. The data will be entered into the database by a member of the ADepT-PD trial team and stored on secure servers. Training on paper CRF completion and storage for site staff listed on the delegation of responsibilities log will be provided at the site initiation meeting(s).

Data collection, data entry and queries raised by a member of the ADepT-PD trial team will be conducted in line with the CCTU and trial specific Data Management Standard Operating Procedure.

A screening and enrolment log, linking participant identifiable data to the pseudo-anonymised PIN, will be held locally by the trial site. This will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the trial the identification, screening and enrolment logs will be stored securely by the sites for 10 years unless otherwise advised by CCTU.

Clinical trial team members will receive trial protocol training. All data will be handled in accordance with the GDPR.

6.10.2 Data Management

A custom designed database will be created by the UCL Priment team (following Priment SOPs for database development) based on the data format in the paper CRFs and using Sealed Envelope's Red Pill database application and used to enter and store all trial data collected in the CRFs. The database will be stored on the Sealed Envelope servers based at Rackspace in London and backed-up at Amazon Web Services Ireland for the duration of the trial and will only be made available to external regulators if requested and specified users across participating sites. The servers are protected by firewalls. The database will be password protected and only accessible to members of the ADepT-PD trial team at CCTU and Priment, and external regulators if requested. Delegated users will be assigned a username and password for access. All data storage will adhere to GDPR and DPA.

The database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data and search facilities to identify validation failure/missing data. Data from the CRFs will be entered onto the ADepT-PD database under the unique participant identification number. This data entry will be performed by a member of the ADepT-PD trial team at CCTU. The data will be checked for missing items, inconsistencies and other pre-determined validation criteria. Any discrepancies noted will be sent as queries to the participating site for resolution. This processing of data will be detailed in the ADepT-PD Data Management Plan.

6.10.3 Non-Adherence and Non-Retention

Participants will be provided with a dosing diary to record uptake of trial medication for the duration of their time in the trial. Reasons for non-adherence to protocol will be noted in the medical notes and CRFs. Outcome data will continue to be collected on all contactable participants continuing to provide informed consent.

6.10.4 Statistical Methods

Statistical analysis will be undertaken by the Trial Statisticians at the UCL CCTU.

The primary analysis will be conducted on an intention to treat basis.

6.10.4.1 Statistical Analysis Plan

A detailed statistical analysis plan (SAP) will be produced prior to unblinded analysis and agreed by the TSC. This will detail the statistical methods used for description of demographic and baseline characteristics, assessing treatment compliance, evaluation of effectiveness of escitalopram/nortriptyline treatment on primary and secondary outcomes, and evaluation of safety.

The statistical analysis will be based on all participants as randomised, irrespective of subsequent compliance with allocated treatment (intention to treat analysis). Multivariate joint models will be used to explore the potential impact of differential loss to follow up should this occur.

A CONSORT diagram will be used to describe the course of patients through the trial. Baseline characteristics will be summarised by randomised group. Continuous variables will be summarised using summary statistics (mean, standard deviation, median, minimum, and maximum) by treatment group, and categorical variables will be presented using frequency distributions by treatment group.

6.10.4.2 Statistical Methods – Outcomes

The primary analysis will be the comparison of BDI-II, conditional on baseline score, between the escitalopram and the placebo group and between the nortriptyline and the placebo. As an exploratory analysis, we will provide an estimate of the difference in mean BDI II score and 95% confidence intervals between the two active treatments. Secondary analysis will describe the number of participants experiencing adverse events on the Modified Toronto Side Effects Scale. A comparison between the escitalopram and nortriptyline arms for the following secondary outcomes will also be described: motor examination (part III; with additional analysis during Off-periods), the combined part I and part II (motor and non-motor experiences), and the motor complications part of the MDS-UPDRS scores and their changes from baseline; of the global clinical impression (CGI) change in health score, the number of adverse events and of drop-outs; and all other secondary outcome measures. Secondary analyses of outcomes will be performed at 8 weeks and on those who have completed the 26 and 52 week assessments (blinded long term follow up with placebo group). Multivariate joint models will be used to explore the relationship between stopping treatment and the BDI II.

Descriptive analyses will be used to examine the baseline characteristics of the treatment groups. The treatment effect will be estimated using generalised mixed models, with random intercept terms for site (to account for dependency between measurements on different patients at a site) and for participant (to account for dependency between measurements from different times on a given participant). As part of the supportive analyses, generalised mixed models with repeated

measurements will be used to examine the treatment responses over time. We will examine the effects of dose received using instrumental variable methods based upon baseline participant characteristics. An additional supportive analysis will compare effect of any active treatment versus placebo on BDI-II score at 8 weeks. Results will be presented as estimates with 95% confidence intervals. All analyses will be carried on an intention to treat basis.

The primary and secondary analyses will be described in a hierarchy in the predefined statistical analysis plan, and alpha (type 1 error) will be spent down the hierarchy in order to establish which, if any, outcome variables are significant while preserving overall studywise alpha.

Confounders: We would expect any confounders to be randomly allocated between groups and therefore not affect our primary analysis. In the primary analysis, baseline values of the BDI II will be included as participant level explanatory variables. Differences in drop out between the groups will be addressed using joint (multivariate) models as described. Sites will be included as random intercept terms. If there are obvious differences in the baseline characteristics in the trial (unlikely given the numbers of subjects randomised) this could potentially introduce confounding. In those circumstances, we will therefore conduct sensitivity analyses that will including any variables that show imbalance between randomized arms as participant level covariates.

The project also provides the opportunity to understand the role of depression in PD, including the previously suggested increased rate of cognitive impairment of PD, and the possibility that those with depression have different clinical associations (e.g. increased rate of autonomic dysfunction). Following the predefined analyses on response to treatment, a data management steering committee chaired by the chief investigator will be formed to assess the merit of data analysis.

6.10.4.3 Additional Analyses - Subgroup

Planned sensitivity analyses of different disease stages (Hoehn and Yahr stages), severity of depression (BDI II categories of mild-moderate-severe), presence of anxiety and cognitive impairment will be performed. Further sensitivity analyses will be decided after the initial data analysis.

6.10.4.4 Additional Analyses – Adjusted

A comprehensive listing of analyses will be described in the statistical analysis plan.

6.10.5 Analysis Population and Missing Data

The primary and secondary analyses will be conducted following the intention to treat (ITT) principle, where all randomised patients are analysed in their randomised group whether or not they receive their randomised treatment. If there are missing data and a positive overall result, we will evaluate the sensitivity of the results to different assumptions about the missing data.

6.10.6 Economic evaluations

We will calculate the net monetary benefit (NMB) of (i) escitalopram plus standard psychological care, (ii) nortriptyline plus standard psychological care, and (iii) standard psychological care alone, to evaluate which of the three treatment options is the most cost-effective treatment of depression in PD. NMB will be calculated as the cost per quality adjusted life year (QALY) gained of each treatment option multiplied by a willingness to pay for a QALY gained. The primary analysis will be from a health and social care cost perspective and including participant data only, with secondary analyses including

carer data. The analysis will use trial data only, and will report the NMB at 8 weeks, in line with the trial's primary outcome measure, and at 52 weeks.

6.10.6.1 Health Economic Analysis Plan

Data to be used for economic analysis

No directly identifiable participant information will be used for this analysis. The analysis will use trial data on resource use and quality of life collected from participants and carers during the ADepT-PD randomised controlled trial, supplemented with published unit costs[75] and other information as required. The analysis will be done according to randomised groups, i.e. according to intention to treat.

Results to be reported

The primary analysis will concern resource use costs and quality of life of participants only. We will report the NMB of each arm, along with 95% confidence intervals for mean costs and QALYs calculated using bootstrapping. The results of the bootstrap will be presented on a cost-effectiveness plane. The bootstrap replications will also be used to construct cost-effectiveness acceptability curves to report the probability that an intervention is most cost-effective (i.e. has the highest NMB) for different values of willingness to pay for an additional QALY from a health and social care cost perspective using participant data only. A secondary analysis will report the NMB per years of full capability (YFC) gained calculated using the ICECAP-O and associated algorithm[76].

Outputs from the within-trial analysis – participants only

- Mean cost per participant of escitalopram in escitalopram arm
- Mean cost per participant of nortriptyline in nortriptyline arm
- Mean cost per participant of other medications and therapies, including standard psychological care, in each of the three arms
- Mean total health care cost per participant in each arm
- Descriptive statistics of EQ-5D-5L as completed by participants and associated algorithm to calculate utility score for participants
- Mean total participant-level QALYs for each arm
- Descriptive statistics for the ICECAP-O and the associated algorithm.
- Mean total participant-level YFC calculated using the relevant algorithm
- Primary result: mean NMB for each arm using participant data only, for a range of values of willingness to pay
    - 95% confidence intervals for all of the above, generated using non-parametric bootstrapping
    - Cost-effectiveness acceptability curves generated using bootstrapped results for QALYs and YFC.

Resource use and cost data

Participant resource use will be assessed using a shortened version of the Client Services Receipt Inventory (CSRI) and using the Concomitant Medications and Concomitant Psychological Therapies Logs and iVICQ for carer input. These questionnaires will be modified according to the needs of people with Parkinson's disease and a depressive disorder and will be administered at baseline (asking about the previous three months), 8 weeks, 26 and 52 weeks (each time collecting information on resources used since the last visit). These questionnaires will ask participants for details of primary, secondary and social care resource use related to depression.
Drug unit costs, including the cost of escitalopram and nortriptyline, will be taken from the British National Formulary (BNF). Other unit costs will be taken from nationally published sources and the literature and publicly available sources and applied to data collected in the trial.

Utility, capability and health related quality of life data

QALYs will be calculated as the area under the curve from the EQ-5D-5L UK-specific tariffs[63-64] and adjusting for baseline differences[77], using information from EQ-5D-5L completed by participants at baseline, 8 weeks, 26 weeks and 52 weeks. A similar method will be used to calculate YFC using the ICECAP-O.

Impact on informal/unpaid carers

A secondary analysis will include impact on informal/unpaid carers. We will capture the impact of the three treatments on the time spent by informal/unpaid carers on caring tasks, and on carers' health related quality of life. At baseline, 8 weeks, 26 weeks and 52 weeks we will administer a questionnaire asking about time spent assisting with a range of carer tasks (informal/unpaid and paid carers including both state and out of pocket funded) using a modified version of the iVICQ developed as part of the HomeHealth trial[78]. The iVICQ has been incorporated into the CRF for the CSRI for ease of completion. Unpaid/informal carer time will be costed using the Proxy Good Method, where time spent on specific tasks is valued at the hourly wage for if it was provided by paid carers. Carers (if the participant has a main carer) will be asked to complete the EQ-5D-5L at baseline, 8, 26, and 52 weeks so that it can be directly translated into QALYs using the area under the curve, and added to the cost-utility index, as recommended by Koopmanschap et al[79]. The total costs and QALYs for carers associated with each treatment group will be added to participant costs and QALYs, and NMBs reported.

Additional outputs from the within-trial analysis – carers

- Descriptive statistics of EQ-5D-5L as completed by carers and associated algorithm to calculate utility score for carers
- Mean total carer QALYs for each arm
- Mean time spent caring for the participant in each arm, and mean cost as calculated using the Proxy Good Method
- Secondary results: mean NMB for each arm using participant data and carer data, for a range of values of willingness to pay
    - 95% confidence intervals for all of the above, generated using non-parametric bootstrapping

- Cost-effectiveness acceptability curves generated using bootstrapped results

Sensitivity analysis and missing data

Assumptions made during the analysis will be tested for as part of the sensitivity analyses. Missing data will be dealt with as in the main statistical analysis, using multiple imputation as appropriate.

6.11 Data Monitoring

6.11.1 Data Monitoring Committee

The IDMC will be constituted of a minimum of 3 independent members who will each provide expert knowledge/advice on different aspects notably clinical expertise on depression in Parkinson disease, conduct of clinical trials and statistical analysis of trial data.

IDMC members will convene at scheduled time points throughout the duration of the trial to review interim trial data and safety data. Recommendations will be made by the IDMC to the TSC regarding continuation/ stopping of the trial based on safety data.

ADepT-PD also includes an internal pilot study with the aim to recruit 46 participants in the first 6 months of the trial. An IDMC meeting may be convened to review recruitment against the results of the pilot study to allow the IDMC to advice on whether the results of the pilot study allow for the trial to either continue as planned, be modified to drop one of the active treatment arms or to stop the trial completely.

An independent statistician will generate the summaries of trial results for the IDMC to review, ensuring that the trial team remain blinded to treatment allocation. Further details of the roles and responsibilities of the IDMC, including membership, relationships with other committees, decision making processes, and the description of stopping rules and/or guidelines where applicable, are described in detail in the ADepT-PD IDMC Terms of Reference (ToR).

6.11.2 Interim Analyses

No interim analysis will be performed apart from those required by the IDMC.

6.11.3 Data Monitoring for Harm

All Adverse Events (AEs) and SAEs occurring during the trial observed by the investigator or reported by the patient, whether or not attributed to the investigational drug, trial interventions or other trial-specific procedure will be recorded in the patient's medical records, and on the appropriate ADepT-PD CRFs. UCL CCTU will keep investigators informed of any safety issues that arise during the course of the trial.

6.11.3.1 Safety reporting

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

Table 1: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this 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 applicable product information (e.g. Investigator's Brochure for an unauthorised product or summary of product characteristics (SPC) for an authorised product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that at any dose: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or 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. Important AEs or ARs that may not be immediately life threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table (e.g. a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation, or development of drug dependency).

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
- Changes in the motor features of Parkinson's disease (which will be captured on the MDS-UPDRS)

6.11.3.2 Other Notifiable Adverse Events

6.11.3.2.1 Notification of pregnancy by female participants

Escitalopram and nortriptyline are contraindicated during pregnancy as safety in pregnant women has not been established. Female patients with a positive pregnancy test at screening are not eligible for inclusion in this trial and should not be randomised. Women on escitalopram or nortriptyline should not breastfeed. Female participants of child bearing potential will be advised to use an acceptable method of contraception throughout the duration of the study. In the event that a female participant becomes pregnant during the course of the trial, the trial medication will be discontinued. Pregnant female participants will remain in the trial (receiving **no** trial medication) and complete all trial follow up assessments as per protocol.

Pregnancy is not a serious adverse event. Following initiation of the trial medication, if a female participant becomes pregnant, the ADepT-PD Pregnancy notification form should be completed by the investigator at the site and forwarded to the ADepT-PD trial team at CCTU. CCTU notification should take place immediately, but no longer than 24 hours of the investigator becoming aware of the pregnancy. The pregnancy outcome may or may not be considered a SAE. Participants will be given a copy of the Pregnancy Monitoring Information Sheet (for trial participants) and will be asked to sign the Pregnancy Monitoring Consent Form (for trial participants) agreeing for data on the pregnancy to be collected. Pregnancy should be followed until the outcome is known (including any premature termination of the pregnancy) and information on the status of the mother and child. Pregnant participants will be followed up until birth, the ADepT-PD Pregnancy Notification & Follow-Up Form (capturing information for up to 6 to 8 weeks after birth) should be completed and forwarded to the trial team at CCTU. Any congenital malformations and/or birth defects are reportable as SAE.

6.11.3.3 Investigator responsibilities relating to safety reporting

All AEs and ARs, whether expected or not, should be recorded in the participant's medical notes and on the ADepT-PD Adverse Event Log. SAEs and SARs should be notified to CCTU immediately, using the ADepT-PD Serious Adverse Event Report, when the investigator becomes aware of the event (in no circumstance should this notification take longer than 24 hours). The SAEs and SARs should also be recorded in the participant's medical notes.

6.11.3.3.1 Seriousness assessment

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 1. If the event is classified as 'serious' then an ADepT-PD Serious Adverse Event Report must be completed and CCTU notified immediately (no longer that 24hours after the investigator becomes aware of the event).

6.11.3.3.2 Severity or grading of Adverse Events

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

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 AD refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

6.11.3.3.3 Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 2.

Table 2: Causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	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 or other concomitant treatment)	Unrelated SAE
Possibly related	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 or other concomitant treatment)	SAR
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	SAR
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

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

6.11.3.3.4 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 on the 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 approved version of the IB or SPCs for the trial, or one that is more frequently reported or more severe than previously reported. See the reference safety information (RSI) in section 4.8 of the current approved SPCs for the trial for a list of expected toxicities associated with escitalopram and nortriptyline. If a SAR is assessed as being unexpected it becomes a SUSAR (suspected, unexpected, serious adverse reaction) and the MHRA and REC reporting guidelines apply (see Notifications sections of the protocol).

6.11.3.4 Notifications

6.11.3.4.1 Notifications by the Investigator to CCTU

CCTU must be notified of all SAEs immediately (within 24 hours) when the investigator becomes aware of the event.

Investigators should notify CCTU of any SAEs and other Notifiable Adverse Events (NAEs) occurring from the time of randomisation until 30 days after the last protocol treatment administration,

including SARs and SUSARs. From this point forward the site will not actively monitor SAEs or NAEs but will notify the CCTU of any SARs and SUSARs if they become aware of them until trial closure.

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

The ADepT-PD Serious Adverse Event Report (SAE report) must be completed by the investigator (the clinician named on the delegation of responsibilities list who is responsible for the participant's care) who will provide the grading and causality for the event. In the absence of the responsible investigator, the SAE form should be completed and signed by a member of the site trial team and emailed as appropriate within the reporting timeline. The responsible investigator should check the SAE report at the earliest opportunity, make any changes necessary, sign and then email to CCTU. 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 trial participant identification number, 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 sent as soon as it becomes available.

The SAE report must be scanned and sent via secure portal/encrypted to the trial team at CCTU on **adept@ucl.ac.uk.**

Participants must be followed up until clinical recovery is complete 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 reports (clearly marked as follow-up) should be completed and scanned and sent via secure portal/encrypted to CCTU 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 participant identification number, initials and month and year of birth only. The participant's name should not be used on any correspondence and should be blacked out and replaced with trial identifiers on any test results (if applicable).

6.11.3.4.2 CCTU responsibilities

A medically qualified member of staff will be appointed as the sponsor clinical reviewer (usually the Chief Investigator (CI) or a medically qualified delegate) and will perform a clinical review of all SAE reports received. The sponsor clinical reviewer 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 competent authorities of other European member states and any other countries in which the trial is taking place) and the RECs as appropriate. Fatal and life threatening SUSARs must be reported to the competent authorities within 7 days of CCTU becoming aware of the event; other SUSARs must be reported within 15 days.

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

The trial manager or delegate at CCTU will submit Development Safety Update Reports (DSURs) to competent authorities.

6.11.4 Quality Assurance and Control

6.11.4.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the ADepT-PD 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; and other considerations.

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 is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

6.11.4.2 Central rating of motor severity

The recordings of movements (taken at the MDS-UPDRS assessments) will be sent to the central trial team for central rating of the motor severity by the CI.

6.11.4.3 Central Monitoring at CCTU

CCTU staff will review Case Report Form (CRF) data for errors and missing key data points. The trial database will also be programmed to generate reports on errors. Essential trial issues, events and outputs, including defined key data points, will be detailed in the ADepT-PD Data Management Plan.

6.11.4.4 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the ADepT-PD Quality Management and Monitoring Plan (QMMP). The QMMP will also 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.

6.11.4.4.1 Direct access to participant records

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

6.11.4.5 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in

the Compliance section of the protocol. Independent trial oversight complies with the CCTU trial oversight policy.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the ADepT-PD QMMP.

6.11.4.5.1 Trial Team

The Trial Team (TT) will be set up to assist with the developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TT terms of reference.

6.11.4.5.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination 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.

6.11.4.5.3 Trial Steering Committee

The TSC is the group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the CI, CCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

6.11.4.5.4 Independent Data Monitoring Committee

The IDMC is the only oversight body that has access to unblinded accumulating comparative data. 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 (including review of trial conduct and data) and authority will be covered in the IDMC terms of reference. The IDMC will consider data in accordance with the statistical analysis plan and will advise the TSC through its Chair.

6.11.4.5.5 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.

7 Ethics and Dissemination

7.1 Research Ethics Committee/Health Research Authority Approval

Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant will be submitted to the relevant REC and the Health Research Authority (HRA) for approval. Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents will be submitted for local permissions.

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 remains 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 must be recorded. After randomisation the participant must remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

7.2 Competent Authority Approvals

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is required in the UK. This protocol will be therefore be submitted to the MHRA in the UK for approval.

The progress of the trial, safety issues and reports, including expedited reporting of SUSARs, will be reported to the MHRA as required.

7.3 Other Approvals

The protocol, Participant Information Sheet (PIS) and informed consent forms on local headed paper, the REC/HRA and MHRA approvals, schedules of funding and activity (and other trial documentation as needed) will be submitted by those delegated to do so to the relevant NHS Trust R&D department of each participating site or to other local departments for approval as required in each country. The NHS Trust R&D department will conduct a local feasibility assessment to determine whether the NHS Trust has the capacity and capability to participate in the trial. No trial conduct can take place at a participating site until all approvals including the local capacity and capability approval are in place.

The protocol has received formal review and methodological, statistical, clinical and operational input from the CCTU Protocol Review Committee.

7.4 Protocol Amendments

The sponsor will ensure that essential documents, namely the trial protocol, PIS, informed consent forms, GP letter and submitted supporting documents have been approved by the appropriate regulatory body (MHRA), REC, and HRA prior to any participant recruitment. The protocol and all agreed substantial amendments will be documented and submitted for ethical and regulatory approval prior to implementation.

7.5 Consent

Patients and carers (if applicable) will be provided with separate Patient Information Sheets (PIS) and given sufficient time to read them fully. Following a discussion with a medically qualified investigator or suitable trained and authorised delegate, any questions will be satisfactorily answered and if the participant and carer (if applicable) are willing to participate, written informed consent will be obtained. During the consent process it will be made completely and unambiguously clear that the participant and carer (if applicable) are 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.

In accordance with the UK Clinical Trial Regulations, the risk/benefit profile of the trial will be regularly monitored. Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the PIS and the participant will be asked to sign an updated informed consent form. These will be approved by the REC prior to their use.

Capacity to consent will be kept under review throughout the trial. If a participant is judged to have lost capacity to consent then he/she will be withdrawn from the trial.

7.5.1 Consent for collection of data from pregnancy outcomes

Consent will be sought from all pregnant female ADepT-PD participants to allow collection of data from the outcome of the pregnancy (see section 6.11.3.2.1 for further details).

7.5.2 Consent in Ancillary Studies

Consent will be sought from all eligible ADepT-PD participants to participate in the optional genetic sub-study to identify genetic markers that may be associated with subtypes of PD (e.g. presence of depression and anxiety) or variation in treatment responsiveness (see Appendix 1 for details) and for use of their clinical data to support further analysis for future research.

7.6 Confidentiality

Data with personal information will be held coded and in a pseudo-anonymised fashion on a university network which is password protected. Access will be limited to the minimum number of individuals necessary for quality control, audit and analysis, including the CI, CPM, Trial Manager, Data Manager, Statistician and the Trial Management Team. Any data will be shared with co-investigators without identifying information.

7.7 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

7.8 Indemnity

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical 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.

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.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to UCL, upon request.

7.9 Finance

ADepT-PD is fully funded by an NIHR-HTA grant number 16/145/01.

The genetic sub-study is fully funded from The Cure Parkinson's Trust (project code HM012).

7.10 Archiving

The investigators agree to archive and/or arrange for secure storage of ADepT-PD trial materials and records for a minimum of 5 years after the close of the trial unless otherwise advised by the CCTU.

7.11 Access to Data

The CI, CPM, Trial Manager, Data Manager, Statistician and Trial Management Team will have full access to the trial data. Following the predefined analyses on response to treatment, requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the data management steering committee chaired by the chief investigator. Considerations for approving access are documented in the TMG Terms of Reference.

7.12 Ancillary and Post-trial Care

For those who may wish continued treatment at study end, liaison will be made with the GP to continue prescription following unblinding.

7.13 Publication Policy

7.13.1 Trial Results

The trial will be registered with international trials databases such as clinicaltrials.gov, and reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement for the results (http://www.consortstatement.org/). The protocol will be aimed to be published in an open access journal. The findings from this trial will be disseminated widely, primarily through publication in international academic journals and conferences. The findings will be publicised through media offices of the host institution UCL and Parkinson's UK, the large PD Patient Support organization in the UK and the NIHR itself, and will directly provide the results to those developing NICE's Public Health Guidance. Given that this will be the largest trial in this field, it is anticipated that the lack of sufficient evidence outlined in the currently available meta-analyses on the effect of the studies interventions, the results will influence national as well as international guidelines on the management of depression in PD.

The main outputs/impact of the research will be:

1. Results on the feasibility, acceptability, recruitment to an antidepressant trial in PD

2. Results on the clinical effectiveness of escitalopram compared to placebo at 8 weeks

3. Results on the clinical effectiveness of nortriptyline compared to placebo at 8 weeks

4. Results on the cost effectiveness of escitalopram and of nortriptyline at 8 weeks

5. Comparison of the rate of number of participants experiencing adverse events on the Modified Toronto Side Effects Scale on escitalopram compared to nortriptyline at 8 weeks

6. Evidence for the effectiveness of escitalopram and nortriptyline compared to placebo for anxiety in patients with depressive symptoms in PD

7. Evidence on the long-term effectiveness of escitalopram and nortriptyline for depression in PD

8. Evidence for the effectiveness of nortriptyline compared to placebo to reduce motor severity of PD at 1 year

The results of the trial will be disseminated regardless of the direction of effect.

7.13.2 Contributorship

Contributorship in published outputs (group and individual/authorship or named acknowledgement) will be recognised using the recommendations laid out by the International Committee of Medical Journal editors (ICMJE)[80].

7.13.3 Reproducible Research

The project also provides the opportunity to understand the role of depression in PD, including the previously suggested increased rate of cognitive impairment of PD, and the possibility that those with depression have different clinical associations (e.g. increased rate of autonomic dysfunction). Following the predefined analyses on response to treatment, a data management steering committee chaired by the chief investigator will be formed to assess the merit of data analysis. Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the data management steering committee chaired by the chief investigator

8 Ancillary Studies

None

9 Protocol Amendments

Protocol Version Number	Protocol Date	Summary of Changes
1.0	TBC	N/A

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11 Appendices

11.1 Appendix 1 ADepT-PD genetic sub-study (optional)

The participation information sheet for the ADepT-PD trial includes information on the optional genetic sub-study. The sub-study requires a blood sample to be taken (for genetic analysis) at screening/baseline or at any study visit. Participants will be given an opportunity to discuss the genetic sub-study with the local study team and to have any questions answered. Participants who do not wish to participate in the genetic sub-study will not be excluded from the main trial.

The informed consent form for the ADepT-PD trial includes the option for participants to agree to participate in the sub-study. Two 10ml blood samples (approximately 2 tablespoons) will then be taken, usually at the screening/baseline clinic visit; one 10mL blood sample in an EDTA sample tube for the extraction of inherited material by University College London Hospitals Neurogenetics Laboratory and one 10mL blood sample in an acid citrate dextrose (ACD) sample tube for the European Collection of Cell Cultures (ECACC), a UK based repository.

11.1.1 Aims of genetic sub-study

The aim of this sampling is to try to identify genetic markers that may be associated with subtypes of PD (e.g. presence of depression and anxiety) or variation in treatment responsiveness. The primary aim of this resource and of future work will be to enable targeting of the best treatments to specific patient groups.

Secondary outcomes will include:

- Correlation of high quality clinical data with genotype
- Investigation of pharmacokinetic variables linked to absorption, distribution, metabolism and excretion of therapeutic agents (ADME).
- Identification of research-engaged patients carrying specific genetic variants for future studies

11.1.2 Sample collection

Instructions for collection, packing and dispatching samples are included in the ADepT-PD genetic sub-study guidance document.

11.1.2.1 UCLH Neurogenetics laboratory sample

One sample will be collected in an EDTA tube, packaged and sent (along with a copy of the informed consent form for the genetic sub-study) by post at room temperature from individual study sites to UCLH Neurogenetics Laboratory, 6th Floor, Queen Square House, Queen Square, London WC1N 3BG, to be stored with other samples in a biobank within the Institute of Neurology. If the participant has consented to being contacted in the future, the participant's contact details will be forwarded to the team at UCLH Neurogenetics Laboratory. The inherited material (DNA and genes) will be extracted from the whole blood sample in accordance with the analytical plan agreed by the ADepT-PD genetic sub-study investigators (Professor Anette Schrag and Professor Huw Morris) and their teams. The inherited material will be stored in The Cure Parkinson's Trust DNA bank, a subset of the Clinical Neurological Disease Biobank and Neurogenetics Research Study (CANDAS) DNA bank, and used for genetic investigations into PD. The Neurogenetics laboratory will process, store and dispose of blood samples in accordance with all applicable legal and regulatory requirements, including the Human

Tissue Act, 2004 and any amendments thereto. Professor Huw Morris will be the custodian of the samples and any accompanying data.

11.1.2.2 ECACC sample

The second sample will be packaged and sent directly by post from individual study sites to ECACC, Genetic Support Services, Culture Collections, Public Health England, Salisbury, Wiltshire SP4 0JG, for preparation and storage of peripheral blood lymphocytes (PBLs) and potential future preparation of immortalised cell lines. This whole blood sample must be kept at room temperature in the ACD tube and must not be frozen or refrigerated.

The advantages of storing cell lines are the provision of an ongoing source of DNA for future studies and the facilitation of large-scale collaborative studies. ECACC will process, store and dispose of blood samples in accordance with all applicable legal and regulatory requirements, including the Human Tissue Act, 2004 and any amendments thereto. Cell lines/lymphocytes for cell line preparation will be stored at ECACC encoded by the ADepT-PD participant identification number, provided by the local trial site. To enable the cell line to be of optimal use to the research community, ECACC will also be provided with strictly limited participant details - specifically gender, ethnicity, year of birth and PD diagnosis. No further personal identifying details will be released to ECACC. Participants can request withdrawal of their samples from ECACC at any point.

11.1.3 Analyses

11.1.3.1 Genetic analysis

The initial genetic analysis will consist of high throughput genotyping of the LRRK2 G2019S mutation together with genotyping for the common glucocerebrosidase (GBA) variants associated with PD. It is estimated that approximately 5% of participants in the ADepT-PD trial will carry LRRK2 or GBA mutations. Clearly, specific drug trials and new hypotheses will lead to new areas of analysis and future work will hopefully include whole genome single nucleotide polymorphism (SNP) and, ultimately, exome/genome analysis.

11.1.3.2 Pharmacogenomic analysis

In collaboration with the ADepT-PD trial team and The Cure Parkinson's Trust, the UCLH Neurogenetics team will investigate whether specific major genetic sub-groups of PD or specific variants in candidate genes influence the outcome of PD drug trials in a preliminary pilot analysis. This will initially be a post-hoc analysis on a very small number of subjects.

11.1.3.3 Other analyses

Other analyses may include:

- Screening and analysis of potential pathogenic and anonymous genetic variations in sporadic and familial patients, with comparison to control samples. This will include DNA variants such as point mutations, gene re-arrangements, deletions/duplications, non-coding sequence change and DNA expansions. Analysis will include large-scale SNP analysis and sequence analysis.
- Analysis of phenotype modifiers i.e. analysis of gene variants which modify the disease by altering age at onset, or other disease phenotypes such as drug responsiveness, or secondary characteristics such as cognitive impairment and specific psychiatric features.

11.1.4 Sample and data sharing

All samples will be treated as a gift for research. UCL Neurogenetics department samples will be stored and used in ongoing and future projects by the ADepT-PD genetic sub-study investigators (Professor Anette Schrag and Professor Huw Morris) and their teams. Samples will form part of The Cure Parkinson's Trust DNA bank (currently within the CANDAS biobank) which will be made available as a resource for the Parkinson's research community through a vetted application process. A committee including core investigators, scientific, lay and charity representatives will review requests for data and sample access. These samples will be made available to responsible investigators in the UK and around the world for use in research, teaching, therapeutics and diagnostic purposes.

11.1.5 Confidentiality

Blood samples for the genetic sub-study will be labelled with the unique ADepT-PD participant identification number ensuring the pseudonymity of the participants who have provided the samples. At UCLH Neurogenetics Laboratory, brief clinical details will be stored with the genotype data including the full date of birth, gender, age at onset of PD, family history and ethnicity. Genotype results will be stored on a web-based, secure confidential database, including after completion of the ADepT-PD trial. Participants may ask for their information to be removed from this database at any time, in accordance with the GDPR.

Genetic sub-study samples will be linked to the main trial data held by Professor Schrag's team at the end of the trial via the unique ADepT-PD participant identification number to integrate genetic, clinical and trial outcome data as secondary analyses following the main trial. This is essential for analysis of phenotype modifiers - analysis of genes which modify the disease by altering age at onset or other disease phenotypes such as drug responsiveness, or secondary characteristics such as age at onset, response to therapy, and motor and psychiatric phenotype. Participants will be informed of this in the information sheet. Any information collected during the study will be kept confidential, aside from enabling the research team to inform participants about the development of new tests if participants have agreed to this as part of the consent process.

Pseudonymised (de-identified) information and DNA collected during the study may be transferred both within and outside the European Economic Area as part of ongoing collaboration with other researchers. This may include combining data from participants' samples with those of other patients in order to determine important factors related to Parkinson's. This information may be made available to other researchers to enable large-scale analysis and new discoveries. Pseudonymised (de-identified) data will be hosted centrally through a secure web-based database holding research data without personal details. This will meet high security standards and safety measures, including ISO27001 certification, and will enable sharing of data to approved groups. Participants are informed of this in the ADepT-PD patient information sheet and will consent to these specific aspects. Personal data will be held separately from research data on a separate, secure web-based database meeting the same security standards. Written records linking participant identification numbers with personal identifiable information (e.g. contact details for future communication) will be stored securely in locked filing cabinets.

11.1.6 Follow-up and future contact

During the consent process for the sub-study, participants will be asked if they would be happy to be contacted in the future to provide further samples or details about their Parkinson's or to learn about new tests or research studies for which they may be eligible.

11.1.7 Withdrawal

Participation in the genetic sub-study is voluntary and participants can chose to withdraw at any time. If participants decide not to take part or to withdraw from the genetic sub-study, participation and treatment in the main study will not be affected. If participants withdraw from the main study (withdrawal from treatment and/or withdrawal from follow-up), their data and samples will be retained for further use as described in the sub-study participant information sheet. If participants request that their samples and data be withdrawn from the genetic sub-study, every effort will be made to destroy samples and data that have been provided but in some cases this may not be possible, e.g. when further analyses have been carried out by collaborators.