Clinical Trial Protocol

Full Title:	A randomised, double-blind, placebo controlled trial of pramipexole in addition to mood stabilisers for patients with treatment resistant bipolar depression
Short Title/Acronym:	PAX-BD
Previous Versions:	Version 5.0, 29 Jan 2020 - Updated in response to COVID-19 Version 4.0, 10 Dec 2019 – updated with new sponsor name and logo Version 3.0, 31st July 2019 – in line with regulatory review requirements Version 2.0, 13 Jun 2019- submitted but not approved Version 1.0, 29 Nov 2018 – not submitted

Statement:

This protocol has regard for the HRA guidance.

RESEARCH REFERENCE NUMBERS

IRAS Number:	239794
EudraCT Number:	2018-2869-18
NHS REC Reference:	19/NE/0233
Research Registry & References:	ISRCTN72151939

RESEARCH SPONSOR

Sponsor Name:	Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust
Sponsor Reference:	RES-17-031

RESEARCH FUNDER(S)

Funder Name:	National Institute for Health Research (NIHR), Health Technology Assessment programme
Funder Reference:	16/154/01
Funder Disclaimer:	This study is funded by the NIHR Health Technology Assessment Programme. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.
Protocol Authors:	McAllister-Williams RH, Watson S, Smith D, Morriss R, Simon J, Geddes J, Chadwick T, Courtney P, Stokes P, Young A, Walker J, Wolstenhulme F, French D, Weetman C, Abouhajar A, Azim L, Hindmarch P, Duffelen N, Fouweather T, Harvey S

PROTOCOL APPROVAL SIGNATURE PAGE

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

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

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

Representative of the Research Sponsor

Name: Lyndsey Dixon

Position: Research and Development Manager

Signature: Date:

Chief Investigator

Name: Professor R. Hamish McAllister-Williams

Position: Professor of Affective Disorders

Signature: Date:

Senior Statistician

Name: Dr Thomas Chadwick

Position: Clinical Trials Statistician

Signature: Date:

Representative of the Newcastle Clinical Trials Unit

Name: Professor Helen Hancock/ Rebecca Maier

Position: Newcastle Clinical Trials Unit, Director/ Deputy Lead

Signature: Date:

PROTOCOL ACCEPTANCE SIGNATURE PAGE

Short Trial Title: PAX-BD **Site Name:**

Site I.D. Number:

Principal Investigator

I have carefully read and understood protocol version 6.0 dated 24/07/2020. I agree to conduct the study in compliance with Good Clinical Practice and all required regulatory requirements.

Name:

Position:

Signature:

Date:

KEY TRIAL CONTACTS

Chief Investigator	Professor R. Hamish McAllister-Williams Professor of Affective Disorders Northern Centre for Mood Disorders Institute of Neuroscience, Newcastle University Wolfson Research Centre Campus for Ageing and Vitality Newcastle upon Tyne NE4 5PL, UK Email: Hamish.Mcallister-Williams@ncl.ac.uk Telephone: +44 (0) 191 208 1370 Fax: +44 (0) 191 208 1387
Clinical Trials Unit	Newcastle Clinical Trials Unit Newcastle University 1-4 Claremont Terrace Newcastle Upon Tyne NE2 4AE
Senior Trial Manager	Ms Jenn Walker Email: Jenn.Walker@ncl.ac.uk
Trial Manager(s)	Ms Nicola Goudie Email: Nicola.Goudie@ncl.ac.uk Miss Georgiana Browne Email: Georgiana.Browne@ncl.ac.uk Dr Jenny McCaffery Jenny.McCaffery@newcastle.ac.uk
Trial Administrator	Dr Eva Maria Holstein Email: Eva.Holstein@ncl.ac.uk
Data Manager(s)	Mr Christopher Weetman Email: Christopher.Weetman@ncl.ac.uk
Collaborators/Co-Investigators	Professor Daniel Smith Professor of Psychiatry Institute of Health and Wellbeing The University Court of the University of Glasgow Email: Daniel.Smith@glasgow.ac.uk Professor Richard Morriss Professor of Psychiatry & Community Health Science University of Nottingham Email: Richard.Morriss@nottingham.ac.uk Professor Judit Simon Professor of Health Economics, Head of Department Department of Health Economics Centre for Public Health

Medical University Vienna – General Hospital AKH
Email: Judit.Simon@meduniwien.ac.at
Dr Stuart Watson
Clinical Senior Lecturer
Institute of Neuroscience
University of Newcastle Upon Tyne
Email: Stuart.Watson@ncl.ac.uk

Professor John Geddes
Director
NIHR Oxford Health Biomedical Research Centre
Oxford Health NHS Foundation Trust
Email: John.Geddes@psych.ox.ac.uk

Dr Thomas Chadwick
Clinical Trials Senior Statistician
Institute of Health and Society
Newcastle University
Email: Thomas.Chadwick@ncl.ac.uk

Mr Tony Fouweather
Clinical Trial Statistician
Institute of Health and Society
Newcastle University
Email: Tony.fouweather@ncl.ac.uk

Paul Courtney
Nurse Consultant
Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust
Email: Paul.Courtney@cntw.nhs.uk

Dr Paul Stokes
Clinical Senior Lecturer in Mood Disorders
Psychological Medicine
Institute of Psychiatry, Psychology and Neuroscience
Kings College London
Email: Paul.R.Stokes@kcl.ac.uk

Prof Allan H. Young
Chair of Mood Disorders
Psychological Medicine
Institute of Psychiatry, Psychology and Neuroscience
Kings College London
Email: Allan.Young@kcl.ac.uk

Sponsor

Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust
St. Nicholas Hospital
Jubilee Road
Gosforth

	Newcastle Upon Tyne NE3 3XT
	Lyndsey Dixon Email: Lyndsey.Dixon@cntw.nhs.uk Telephone: +44 (0) 191 246 7221
Funder(s)	National Institute for Health Research, Health Technology Assessment programme HTA Project 16/154/01 Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House Enterprise Road Southampton SO16 7NS
Out of Hours Contacts	Out of Hours Research Mental Health Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust Telephone: +44(0) 303 123 1145

Committees

Trial Management Group Chair	Professor R. Hamish McAllister-Williams, **Chief Investigator**
Data Monitoring Committee Chair	Professor Carl Clarke Professor of Clinical Neurology Department of Neurology City Hospital Sandwell and West Birmingham Hospitals NHS Trust Dudley Road Birmingham B18 7QH, UK Email: CarlClarke@nhs.net Telephone: + 44 (0) 121 507 4073
Trial Steering Committee Chair	Dr Jill Rasmussen General Practitioner Arlington Cottage Spook Hill North Holmwood Dorking, UK Email: Jill.Rasmussen@psi-napse.com Telephone: +44 (0) 130 688 3272

Trial Website

http://www.mood-disorders.co.uk/PAX-BD

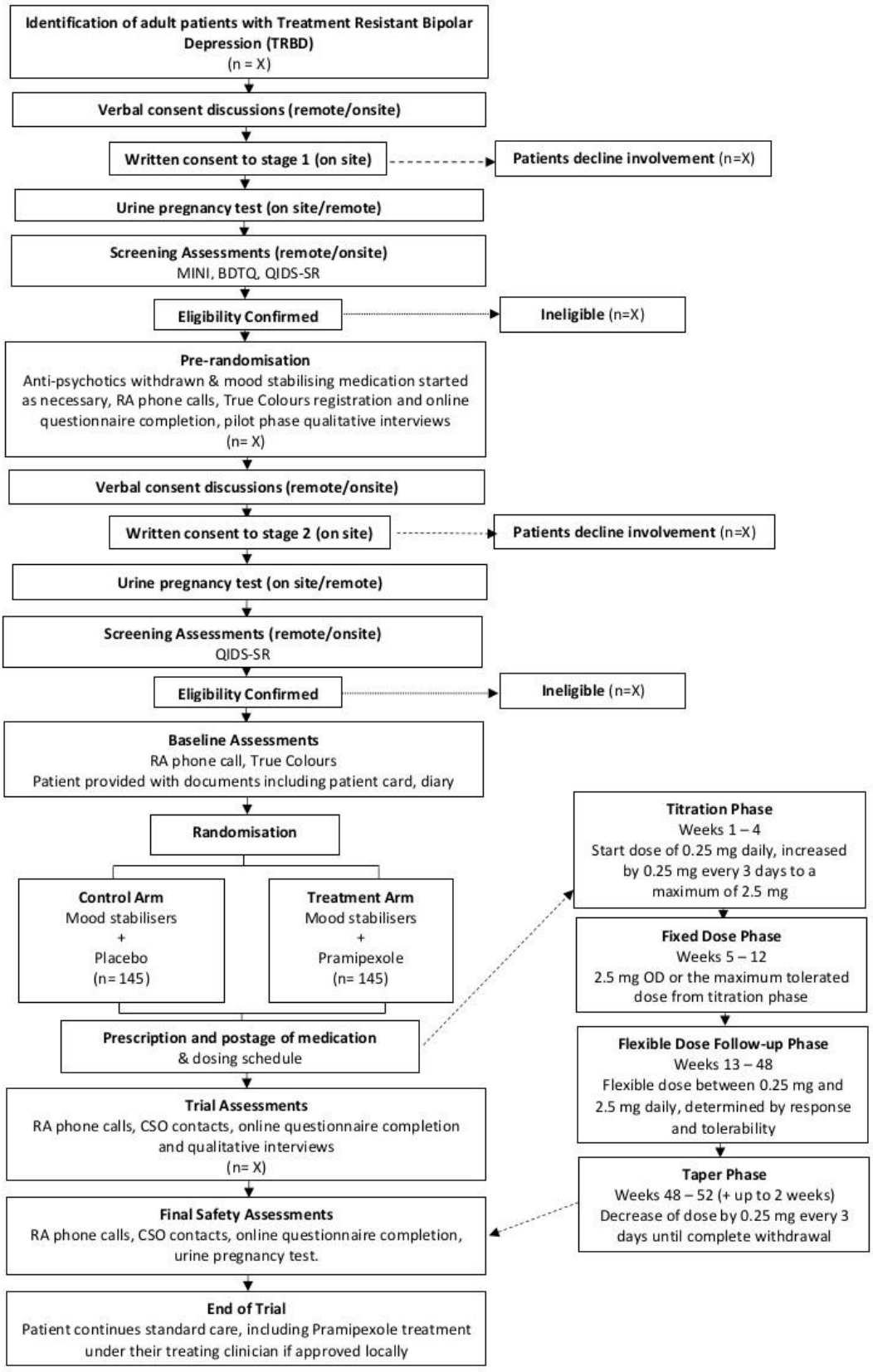
TRIAL SUMMARY

Trial Title	A randomised, double-blind, placebo controlled trial of pramipexole in addition to mood stabilisers for patients with treatment resistant bipolar depression	
Acronym	PAX-BD	
Protocol version and date	Version 6.0 24/07/2020	
Chief Investigator	Prof R. Hamish McAllister-Williams	
Sponsor	Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust	
Funder	National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (Ref: 16/154/01)	
Clinical Phase	Phase III	
Trial Design	Multi-centre, randomised, double-blind, placebo-controlled. Pre-randomisation phase to withdraw antipsychotics and commence mood stabilising medication if needed. Remote (online and phone) collection of outcome measures to facilitate UK-wide recruitment	
Trial intervention	Patient randomised in the ratio 1:1 to receive pramipexole or matching placebo in addition to mood stabilisers.	
Participant Population	Patients with Treatment Resistant Bipolar Depression (TRBD) (defined as failure of two NICE-recommended medications)	
Planned Sample Size	290 participants to be randomised. All participants followed up to 52 weeks (+ up to 2 weeks).	
	Objectives	**Outcome Measures**
Note: week 0 below refers to baseline after randomisation to trial medication		
Primary	To evaluate the clinical effectiveness of pramipexole versus placebo alongside standard mood stabilising medication, over 12 weeks, in the management of patients with treatment resistant bipolar depression.	Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR) at 12 weeks, co-varying for score at 0 weeks.
Secondary	To examine the impact of pramipexole treatment on mood and anxiety symptoms over 48 weeks, and pleasure symptoms over 12 weeks.	QIDS-SR weekly to week 48. Generalised Anxiety Disorder 7 (GAD-7) weekly to week 48. Snaith Hamilton Pleasure Scale (SHAPS) at week 0, 6 and 12. GAD-7 weekly to week 48.

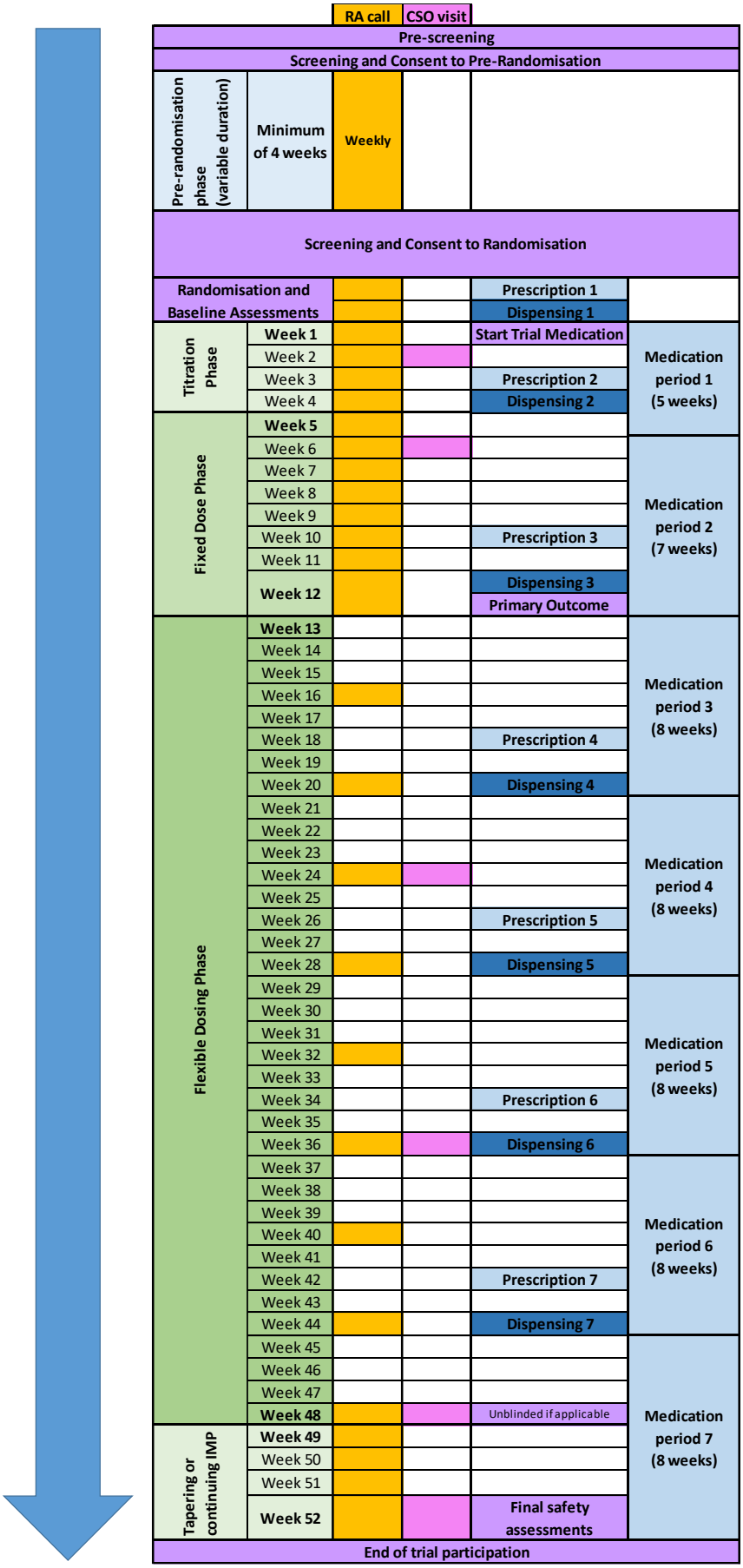
	To examine the impact of pramipexole on psychosocial function over 48 weeks.	Work and Social Adjustment Scale (WSAS) at weeks 0, 6, 12, 24, 36 and 48.
Secondary – Safety and Acceptability	To examine tolerability of pramipexole	Rates of AEs, SAEs and SUSARs will be reported describing severity, seriousness, causality and expectedness will be reviewed.
	To examine risk of switching to mania and occurrence of psychosis or impulse control disorders, which are known possible side-effects of pramipexole.	Altman Self Rating Scale of Mania (ASRM) weekly to week 48.
	To examine rates of impulsivity during treatment with pramipexole, using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease.	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS) weeks 0, 6, 12 and then 4 weekly to week 48 (weeks 16, 20, 24, 28, 32, 36, 40, 44 and 48).
	To examine side effects and overall acceptability of pramipexole treatment.	Treatment Satisfaction Questionnaire for Medication (TSQM) at Weeks 6, 12 and then 4 weekly to week 48 (weeks 16, 20, 24, 28, 32, 36, 40, 44 and 48). Adverse Events - reported weekly to week 12 and then 4 weekly to week 48 (weeks 16, 20, 24, 28, 32, 36, 40, 44 and 48.
	To examine adherence to medication to which patients are randomised.	Dose taken as reported during RA phone calls and from central trial medication accountability and reconciliation records.

Health Economics	To examine the quality of life, wellbeing, health and social care and broader societal costs of patients randomised to either pramipexole or placebo. To establish the incremental cost-effectiveness of pramipexole in comparison to placebo over 48 weeks.	EuroQoL 5 Dimension 5 Level (EQ-5D-5L) at start of pre-randomisation and weeks 0, 12, 24, 36 and 48. ICEpop CAPability measure for Adults (ICECAP-A) at start of pre-randomisation and weeks 0, 12, 24, 36 and 48. Oxford CAPabilities questionnaire-Mental Health (OxCAP-MH) at start of pre-randomisation and weeks 0, 12, 24, 36 and 48. The Health Economics Questionnaire (HEQ) at start of pre-randomisation and weeks 0, 12, 24, 36 and 48.
Comparison Analysis	To increase content validity by using gold-standard observer rated scales to measure participant scores on mania and depression to compare with previous studies in the field.	Young Mania Self-Rating Scale (YMRS) at weeks 0 and 12. Montgomery Asberg Depression Rating Scale (MADRS) at weeks 0 and 12. Quick Inventory of Depressive Symptomatology – Clinician Rated (QIDS-C) at weeks 0 and 12.
Investigational Medicinal Product(s)	Pramipexole (pramipexole dihydrochloride monohydrate)	
Comparator	Placebo	
Non-investigational medicinal products (nIMPs)	The Investigative Medicinal Product (IMP) will be administered in combination with mood stabilising medication (lithium, lamotrigine, valproate, carbamazepine). These are classified as non-Investigational Medicinal Products (nIMPs). The drug(s) used will be chosen by the patient's usual clinical team and used in line with guidance in the British National Formulary.	
Treatment Duration	48 weeks (+ up to 4 weeks for continuing or tapering at end of trial)	
Follow-up Duration	52 weeks (+ up to 2 weeks)	
Planned Trial Period	51 months	
Trial Sites	Up to 40 Trusts in the UK, including Mental Health Trusts in England	

TRIAL FLOW DIAGRAM



PATIENT FLOW DIAGRAM



CONTENTS

GLOSSARY OF ABREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
AR	Adverse Reaction
ANCOVA	Analysis of Covariance
ASRM	Altman Self Rating Scale of Mania
BAP	British Association of Psychopharmacology
BD	Bipolar Disorder
BDTQ	Bipolar Demographics and Treatment Questionnaire
CA	Competent Authority
CEAC	Cost-Effectiveness Acceptability Curves
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CSO	Clinical Studies Officers
CSRI	Client Service Receipt Inventory
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
DAWS	Dopamine agonist withdrawal syndrome
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSUR	Development Safety Update Report
eCRF	electronic Case Report Form
EQ-5D-5L	Health-Related Quality Of Life (Questionnaire)

EudraCT	European Clinical Trials Database
FSH	Follicle Stimulating Hormone (FSH)
GCP	Good Clinical Practice
GPhC	General Pharmaceutical Council
HDRS	Hamilton Depression Rating Scale
HEQ	Health Economics Questionnaire – amended CSRI
HRA	Health Research Authority
HTA	Health Technology Assessment
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to Treat
MADRS	Montgomery Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MINI	Mini-International Neuropsychiatric Interview
NCMD	Northern Centre for Mood Disorders
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
NIMP	Non-Investigational Medicinal Product

OxCAP-MH	Oxford Capabilities questionnaire – Mental Health
PI	Principal Investigator
PIS	Participant Information Sheet
POM	Prescription only medication
PPI	Public and Patient Involvement
QA	Quality Assurance
QC	Quality Control
QIDS-C	Quick Inventory of Depressive Symptomatology – Clinician Rated
QIDS-SR	Quick Inventory of Depressive Symptomatology – Self Report
QP	Qualified Person
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease–Rating Scale
RA	Research Assistant
R&D	Research & Development
RCPsych	Royal College of Psychiatrists
RCT	Randomised Control Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SHAPS	Snaith Hamilton Pleasure Scale
SMHRN	Scottish Mental Health Research Network
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure

SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TSQM	Treatment Satisfaction Questionnaire for Medication
TRBD	Treatment Resistant Bipolar Depression
UK	United Kingdom
UPDRS	Unified Parkinson's Disease Rating Scale
USM	Urgent Safety Measure
WSAS	Work and Social Adjustment Scale
YMRS	Young Mania Rating Scale

1. BACKGROUND

Bipolar disorder (BD) has a lifetime prevalence of 2.5% (1) and is associated with an 8-12 year reduction in life expectancy (2). Current UK NHS care pathways are defined by NICE clinical guidelines for the management of bipolar disorder (3). Patients with BD are symptomatic around 50% of the time, the vast majority of which is depression (4;5) for which NICE guidelines list 3 treatments: lamotrigine, quetiapine, & olanzapine (with or without fluoxetine) (6), with the latter two poorly tolerated due to weight gain and sedation (7;8). Around 70% of currently depressed BD patients in the UK are on at least one antidepressant (9) despite evidence that they lack efficacy (6), demonstrating the clinical challenge posed and that many patients have treatment resistant bipolar depression (TRBD). The prevalence of TRBD is unknown due to a lack of a consensus definition. However, around 50% of patients remain depressed at six months, and 30% at a year because of non-response, intolerance, or non-acceptance, of treatment (10), and current evidence-based treatment options for bipolar depression are extremely limited (11). As a result, TRBD is the major contributor to the enormous burden of disease associated with BD.

The potential role of pramipexole as a treatment for depressive episodes in BD is supported by a number of lines of investigation, including pre-clinical investigations in animal models. Antidepressant-like effects of pramipexole have been observed in animal models of depression and models known to be responsive to drugs with antidepressant efficacy, such as stress-induced suppression of sucrose intake in rats (11), the forced swim test (12;13), social interaction test (13) and olfactory bulbectomised rats (14). It has also been shown to increase hippocampal neurogenesis (12), an effect believed to be common to antidepressants (15;16). Pramipexole has extensive evidence for efficacy in Parkinson's disease (17), for which it has a marketing licence. A meta-analysis of pramipexole in Parkinson's disease reported improvement in depressive symptoms on the Unified Parkinson's Disease Rating Scale (UPDRS) (18). This led to a 12-week randomised double-blind placebo-controlled trial of pramipexole in patients with Parkinson's disease and significant depressive symptoms which reported a significant benefit that was independent of any motor improvements seen (19). Such findings, together with hypothesised roles for a hypo-dopaminergic state underlying bipolar depression (20) and naturalistic and open trial data (21-27) led to two RCTs in bipolar depression (28;29). Goldberg *et al* studied 22 patients (mainly type I)(28). All had failed to respond to at least two adequate trials of standard antidepressants during the current episode. They were treated with a mean of 1.7 mg/day (SD=1.3) pramipexole in combination with lithium or anticonvulsant mood stabilisers (NB: Pramipexole doses as published in the literature refer to the salt form). Mean improvement in HDRS scores at six weeks were 48% for pramipexole and 21% for placebo (p=0.05). Zarate and colleague's RCT included 21 patients with BD type II (29) who had failed at least one trial of a standard antidepressant. A mean dose of 1.7 mg/day (range 0.375 to 4.5 mg/day) pramipexole was given in combination with lithium or valproate. 60% of patients treated with pramipexole achieved a response (50% decrease in MADRS) at six weeks, compared with 9% taking placebo (p=0.02).

2. RATIONALE

Based on epidemiological data (30), over a 12-month period in excess of 1 million people in the UK will suffer from an episode of BD and for 95% of these individuals this will herald a lifelong relapsing and recurring illness. For the vast majority, this episode will be a depressive one (4;5), and at the end of a year 30% will remain ill because of non-response, intolerance, or non-acceptance of treatment (10) at least in part due to the limited treatment options currently available for bipolar depression (11). This high prevalence and rate of treatment resistance accounts for the estimated annual UK BD costs of £5.2B, with direct NHS costs of £342M, at 2010 prices (31;32). Patients are eligible for this trial if their current episode of bipolar depression has not responded to two adequate trials from the three NICE-recommended medications (6), or the additional evidence-based, though expensive, treatment lurasidone (33;34). A 'failed' trial will be defined as a clinically-determined inadequate response to an 'adequate trial' (at least eight weeks for lamotrigine) at an 'adequate dose' (based on current guidance), or an inability to tolerate or accept treatment. This reflects the current point of clinical equipoise, due to the limited number of treatment options available for TRBD and defines a point at which there is potential for significant change to clinical and cost trajectories.

The trial is an appropriately powered, pragmatic, randomised, controlled trial (RCT) with economic evaluation. The primary outcome is at 12 weeks and there is a 52-week follow-up period. Hence, the trial determines efficacy and longer-term cost-effectiveness in a real-world design. The use of a validated (35) self-reported primary outcome measure has successful precedents (36-39) and allows a patient-centric assessment and experience, as well as critically facilitating inclusion of a large and broad representative sample. The secondary outcome measures examine the broader potential for positive and negative impacts of treatment.

Economic evaluation will further allow consideration of the utility of this treatment regime. It will use the NHS/Personal Social Services perspective preferred by NICE with secondary analyses incorporating wider societal costs.

The PAX-BD trial therefore has the potential to have a major impact on the burden of disease experienced by patients and UK health services. A positive finding of cost-effectiveness coupled with a favourable tolerability profile is likely to have a profound impact on UK provision of care for patients with TRBD due to the current dearth of options available to clinicians. The roles held and experience of the PAX-BD team within UK psychiatry will facilitate dissemination and implementation of the PAX-BD findings.

2.1. Risk Assessment

Pramipexole is a dopamine agonist which is indicated in adults for treatment of idiopathic Parkinson's disease and restless leg syndrome. For the purposes of this protocol, pramipexole will be used in patients with treatment-resistant bipolar depression (TRBD).

This trial is categorised as Type B = "somewhat higher than the risk of standard clinical care".

Clinical experience with using pramipexole in participants with mood disorders suggests that tolerability issues tend to be encountered early (first 3-10 days) and are usually related to nausea. Other acute adverse events that are commonly reported included sleeplessness, sleepiness, increased anxiety, panic attacks, and increased sexual arousal, dizziness, tremors and irritability. Adverse event recording and reporting will also be undertaken by RAs at critical time points in conjunction with monitoring low blood pressure symptoms.

In the longer term, the intervention has also been recognised to induce mania and psychosis in some clinical populations, as well as impulse control disorders e.g. gambling, binge eating and hyper sexuality. There will be specific monitoring for such side effects with weekly completion of the ASRM to assess for mania and regular completion of the QUIP-RS to assess for impulse control disorders. The emergence of psychosis and suicide risk will also be assessed using a semi structured interview over the telephone conducted by the RAs. RAs will monitor for other side effects or any cause for concern via telephone calls to the patients, as well as reviewing the QIDS-SR, ASRM and QUIP-RS data for individual patients and communicate this to the patient's local clinical team.

During the pre-randomisation phase, some participants will be required to withdraw antipsychotics, as they may block the effect of pramipexole, and/or commence mood stabilising medication. At this time, they will be closely monitored by phone calls from the RAs and weekly monitoring of symptoms using the QIDS-SR, GAD-7 and ASRM for adverse events and destabilisation of underlying BD pertaining to changes in medication and stabilised before commencing pramipexole.

Adverse effects may occur when tapering or discontinuing dopamine agonists including pramipexole. Symptoms include apathy, anxiety, depression, fatigue, sweating and pain, which may be severe. At any point the pramipexole is withdrawn, discontinuation symptoms will be minimised by a gradual tapered withdrawal over up to 4 weeks. This will be monitored by weekly RA phone calls.

3. OBJECTIVES AND OUTCOME MEASURES

3.1. Primary Objective and Outcome Measure

To evaluate the clinical effectiveness of pramipexole versus placebo alongside standard mood stabilising medication, over 12 weeks, in the management of patients with treatment resistant bipolar depression. This will be assessed using the Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR) (40) scores for patients randomised to pramipexole compared to those randomised to placebo at 12 weeks, covarying for baseline QIDS-SR score.

3.2. Secondary Objectives

- To examine the impact of pramipexole treatment on mood and anxiety symptoms over 48 weeks, and pleasure symptoms over 12 weeks. This will be assessed using the Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR) and the Generalised Anxiety Disorder 7 (GAD-7) (41) scores, rated weekly from baseline to Week 48, and Snaith–Hamilton Pleasure Scale (SHAPS) (42) at weeks 0, 6 and 12.
- To examine the impact of pramipexole on psychosocial function over 48 weeks. This will be assessed using GAD-7 scores, rated weekly to week 48 compared to baseline, and the Work and Social Adjustment Scale (WSAS) (43) at Weeks 6, 12, 24, 36 and 48, compared to baseline.

3.3. Secondary Safety and Acceptability Objectives and Measures

- To examine risk of switching to mania and occurrence of psychosis or impulse control disorders, which are known possible side-effects of pramipexole, using the Altman Self-rating Scale of Mania (ASRM) (44) weekly to Week 48.
- To examine rates of impulsivity during treatment with pramipexole, using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS) (45) Weeks 0, 6, 12 and 4 weekly thereafter to week 48 (weeks 16, 20, 24, 28, 32, 36, 40, 44, 48)
- To examine side effects and overall acceptability of pramipexole treatment using the Treatment Satisfaction Questionnaire for Medication (TSQM) (46) at Weeks 6, 12 and then 4 weekly to week 48 (weeks 16, 20, 24, 28, 32, 36, 40, 44 and 48).
- To examine tolerability, rates of AEs, SAEs and SUSARs will be reported describing severity, seriousness, causality and expectedness.
- To examine adherence to medication to which patients are randomised, using dose taken as reported during RA phone calls and from central trial medication accountability and reconciliation records.

3.4. Health Economic Objective and Measures

To examine the quality of life, wellbeing, health and social care and broader societal costs of patients randomised to either pramipexole or placebo. To establish the incremental cost-effectiveness of pramipexole in comparison to placebo over 48 weeks. Health economics questionnaire (HEQ) capturing information on health and social services utilisation and broader societal costs (e.g. lost

productivity, informal care). In addition, the EQ-5D-5L (47) will capture health-related quality of life and the ICECAP-A (48;49) and OxCAP-MH (50, 51) instruments will capture broader wellbeing. All questionnaires will be completed at the start of pre-randomisation and at Weeks 0, 12, 24, 36 and 48.

3.5. Comparison Analysis Objective and Measures

To increase content validity by using gold-standard observer rated scales to measure participant scores on mania and depression to compare participant scores with previous studies in the field. This will be achieved using the Young Mania Self-Rating Scale (YMRS) (52) to capture presence of manic symptoms, and the Montgomery Asberg Depression Rating scale (MADRS) (53) and Quick Inventory of Depressive Symptoms- clinician rated (QIDS-C) (40) capturing severity of depressive episodes – administered at Weeks 0 and 12.

4. TRIAL DESIGN

The PAX-BD trial, a multi-centre, randomised, placebo-controlled trial of pramipexole versus placebo, in response to NIHR HTA commissioned call 16/154, will elicit whether pramipexole, co-prescribed with mood stabilising medication (lithium, valproate, carbamazepine, lamotrigine), is an effective treatment for TRBD.

Prior to starting the main trial, if patients are on an antipsychotic it will be gradually withdrawn under the supervision of the patient's treating clinician. Additionally, if patients are not on mood stabilising medication (as listed above), this will be started under the supervision of the patient's treating clinician. This will depend on the individual patient, whether they are on antipsychotic(s), and which one(s), and his/her situation. A local Clinician Manual with guidance regarding these medication changes will be provided to all participating sites, although clinicians will retain clinical responsibility for decisions taken. A target of 290 patients will be randomised (1:1 ratio) to receive either pramipexole or placebo, in addition to ongoing mood stabilising medication.

There is limited evidence to guide dosages of pramipexole for the treatment of bipolar depression. The dosage schedule described below was based on information in the SmPC for pramipexole in the treatment of Parkinson's Disease, the two small RCTs of pramipexole for bipolar depression (Zarate et al. 2004 (29) and Goldberg et al. 2004 (28)) and, most influentially, the largest published case series of patients with treatment resistant depression treated with pramipexole (n=42 of whom 18 had bipolar depression: Fawcett et al. 2016 (27)).

The SmPC for pramipexole for the treatment of Parkinson's Disease recommends a schedule of starting with a dose of 0.375mg a day (taken as 0.125mg three times daily), increasing by 0.375mg/day after 5-7 days, then in 0.75mg/day steps every 5-7 days. The recommended maximum is 4.5 mg/day.

The Zarate et al. RCT (29) treated patients using a more conservative dosage schedule than the SmPC, limiting all increases to 0.375mg every 5-7 days. In this study, 10 patients were treated with pramipexole with an average dose of 1.7mg. The Goldberg et al. RCT (28) utilised smaller dosage steps of 0.25mg (0.125mg twice a day) but occurring more frequently of every 3-5 days. The average dose of pramipexole used was identical to that in the Zarate study (1.7 mg/day).

Fawcett et al. (27) describe the treatment of patients in naturalistic practice using a dosage schedule that was developed from the combined experience of the authors. It was similar to that employed in the Goldberg et al. RCT (28) being 0.25mg/day increases every 3 days. The paper includes recommendations for clinicians using pramipexole for patients with treatment resistant depression. These include that pramipexole can be taken once a day in the evening, with this leading to better tolerability. Theoretically once daily dosing may also help increase adherence. On the basis of data suggesting a reduction in dopamine receptors with age, Fawcett et al. used steps of 0.5mg/day every 3 days for patients aged over 45 years.

The table below compares the dosage scheduled from the sources described above by illustrating the **potential** dose (depending on tolerability) achieved at 14 and 28 days of treatment. Ranges in doses reflect the range in frequency of dose increments included in recommendations/studies.

Source	Dose after 14 days	Dose after 28 days	Target dose	Maximum dose	Average dose
SmPC for Parkinson's Disease	0.75 to 1.5 mg/day	2.25 to 3.75 mg/day		4.5 mg/day	
Zarate et al. 2004 (29)	0.75 to 1.125 mg/day	1.5 to 2.0 mg/day		4.5 mg/day	1.7 mg/day (n=10)
Goldberg et al. 2004 (28)	0.75 to 1.25 mg/day	1.5 to 2.5 mg/day	2.5 mg/day	5.0 mg/day	1.7 mg/day (n=12)
Fawcett et al. 2016 (27)	Under 45s: 1.25 mg/day Over 45s: 2.5 mg/day	Under 45s: 2.5 mg/day Over 45s: 5.0 mg/day	2.0 mg/day	5.0 mg/day	2.46 mg/day (n=42*)

* - note this average is based on 42 patients in total: 24 with unipolar depression and 18 with bipolar depression.

As can be seen in the table, despite the difference in dosage schedules, the dose achieved after 14 days averages around 1 and that at 28 days around 2 mg/day or above, excluding the higher doses used for patients over the age of 45 in the Fawcett case series (27).

The dosage schedule for PAX-BD is based on that reported by Fawcett et al. 2016 (27), being a report of the largest collective of patients with bipolar depression. The schedule used for under 45 year old patients was chosen (i.e. 0.25mg/day increments in dose every 3 days). This leads to doses at 14 and 28 days that are within the range that would be achieved if using the schedule included in the SmPC for Parkinson's Disease (see table above). The maximum dose in the PAX-BD study (2.5mg/day) is lower than in the two previous RCTs (28,29) but higher than the actual average achieved in these two studies and the Fawcett case series (27). The faster titration rate used by Fawcett for patients over 45 is not used to simplify prescribing across a large RCT and because the slower titration rate still allows patients of all ages to reach a dose above the average used in other studies.

The trial team, participants and their treating mental health team will not know whether the participant is receiving pramipexole or placebo; the trial is 'double-blind'. The effectiveness of pramipexole after 12 weeks will be assessed, and patients will continue to be monitored by trial researchers for 48 (placebo) or 52 weeks (+ up to 2 weeks) (pramipexole) even if they discontinue the trial medication, giving real-life information on the use of this treatment.

The effect on depressive symptoms and quality of life will be assessed, along with side-effects and whether any other treatments were needed. Assessments will be self-reported using an online system completed by participants, who will be supported by prompts. These methods have worked well in previous studies such as CEQUEL (54) and patients approve of their use. The system allows more frequent (weekly) self-ratings of BD symptoms and thus gives a more complete picture of long-term symptom control. Where necessary, paper versions will be provided. Participants will be telephoned approximately every 4 weeks to assess concomitant medication use, symptoms and side-effects.

4.1. Internal Pilot

PAX-BD includes a 12 month internal pilot. Data from the pilot will be presented to a PPI group for discussion and further insights, as well as the Trial Management Group. These insights will then be presented to the DMC and TSC. A decision will be made as to whether any alterations to the protocol or remedial action is required. Identified good practice from the internal pilot will be shared across all sites.

The pilot comprises the following elements:

1. Staff Interviews

Staff qualitative interviews will be conducted by the trial RAs with a sample of PIs, clinicians and CRN staff at participating sites that are open to recruitment. Verbal consent will be obtained from staff over the phone prior to the interview.

Barriers to recruitment will be identified using a framework analysis designed for depression RCTs.

2. Pre- randomisation Phase

Data from the first 20 participants who have entered into the pre-randomisation phase will be used to examine:

- the proportion of participants on antipsychotics and on mood stabilisers at the point of consent
- the time taken to withdraw antipsychotics and its success rates (to include reviewing the number of participants who fail to be withdrawn)
- the time taken to establish participants on an alternate mood stabiliser and its success rate (to include reviewing the number of participants established on mood stabilisers)
- the proportion of participants still in the pre-randomisation phase after 3 months

Telephone qualitative interviews will be conducted by the trial RAs or study qualitative researcher with a sample of participants who withdraw/ are withdrawn during the pre-randomisation phase, or who are not randomised, and have consented to be contacted for interview. There will be one interview per patient and RAs/qualitative researcher will examine reasons for discontinuation and patient experiences.

3. Titration and Fixed dose phase (randomisation through to week 12):

The first 20 participants randomised will be followed during the titration and fixed dose phase up to the primary outcome at 12 weeks to explore:

- retention rates
- reasons for discontinuation

There may be a need to potentially adjust the doses for patients with early side effects to enhance longer term tolerability. A key question that will be addressed is whether any adjustment of the dose escalation is needed and/or whether greater flexibility is required in the titration schedule.

Telephone interviews will be conducted by the trial RAs/qualitative researcher with a sample of trial of participants who are randomised to the trial and reach week 12, and have consented to be contacted for interview. There will be one interview per patient after the week 12 primary outcome, and as close to this time point as possible. Further telephone interviews will take place with a sample of participants who stop taking trial medication prior to week 12, who have consented to be contacted for interview and have not withdrawn consent.

Sample size for qualitative interviews will be determined by reaching data saturation, estimated to occur at around 10 staff interviews, 20 participants at pre-randomisation and 20 participants post-randomisation.

4.2. Progression from Internal Pilot: Funder Stop Go Criteria

The trial funder "stop" criteria are, relative to recruitment of the first participant into the pre-randomisation phase of the trial, ≤ 50 participants randomised (to either arm) at 12 months with a ≤70% retention of those randomised at the primary outcome time point of 12 weeks. At 12 months post-consent to pre-randomisation of the first participant, the TMG will review the number of participants randomised and the percentage retention at 12 weeks. These numbers will be passed to the DMC and TSC, for verification as to whether they meet the trial stopping criteria or not. Recruitment and retention rates will be reviewed on an ongoing basis by the TMG throughout the trial.

5. TRIAL SETTING

The trial will be carried out at up to 40 secondary care mental health services across England, Scotland, Wales and Northern Ireland. Set-up of trial sites will be staggered over approximately 6 months, including Site Initiation Visits.

6. ELIGIBILITY CRITERIA

Eligibility must be assessed by a medically qualified doctor, after receiving written informed consent to take part in study, and this assessment documented in the participant's medical records. Only personnel formally delegated by the local Principal Investigator to assess eligibility may perform this task.

A further eligibility assessment will be performed at the randomisation phase, after receiving written informed consent to take part in the main study and prior to randomisation.

If it is determined during post-consent eligibility assessments at either phase, that a participant does not meet the trial's eligibility criteria, the patient will not proceed and medical delegates will record the reason for exclusion. These results will be reported in a CONSORT diagram.

For the purposes of this trial a woman is considered of child-bearing potential i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

6.1. Eligibility Criteria

6.1.1. For Pre-randomisation

Patients must fulfil all of the following criteria to enter the pre-randomisation phase:

Inclusion Criteria:

1. Currently under the care of secondary care mental health services at screening with a plan for the patient to remain in secondary care throughout the period of the trial.
2. A decision made by the patient's clinical team that a change in medication is indicated.
3. A current diagnosis of Bipolar Disorder (type I or II), defined as in DSM-5, which is supported by the use of the Mini-International Neuropsychiatric Interview (MINI) (55).
4. Currently depressed, i.e. meeting DSM-5 criteria for a Major Depressive Episode assessed via MINI and with a current QIDS-SR >10.

5. Current episode of depression failed to have responded to adequate trials, or lack of tolerability or patient declined/clinically inappropriate, of two different NICE recommended medications (quetiapine, olanzapine (with or without fluoxetine), lamotrigine) or lurasidone. Adequacy of treatment trial defined using a custom designed 'Bipolar Demographics and Treatment Questionnaire' (BDTQ).
6. Aged 18 or over at the point of consent.
7. Willing and able to provide written informed consent prior to any trial procedures taking place.
8. In the opinion of the investigator, is able to follow the trial prescription instructions and is able to manage 8 weeks supply of trial medication without risk of overdose.
9. The patient, if female and of child-bearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin (β-hCG)]*.
10. Women of child-bearing potential are required to use a highly effective contraceptive method during the pre-randomisation and post-randomisation phase of the trial. Highly effective methods of contraception include:
    - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
    - progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
    - intrauterine device (IUD)
    - intrauterine hormone-releasing system (IUS)
    - vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success)
    - bilateral tubal occlusion
    - sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject)

* Urine beta-HCG pregnancy tests should be conducted in line with local clinical policies, either sending the urine sample to the local clinical laboratory or by a suitably trained individual using a clinically approved pregnancy test strip

Exclusion Criteria:
Patients must not meet any of the following criteria to enter the pre-randomisation phase:

1. DSM-5 defined severe substance use disorder.
2. Current psychotic symptoms as assessed using the MINI.
3. History of retinal disease.
4. Current cardiovascular symptoms or significant concerns around cardiovascular disease.
5. History of significant renal disease (for example within the last 6 months eGFR is less than 50ml/min/1.73m^2 or there is a concern that eGFR is deteriorating and may be expected to fall below 50 during the course of the study).
6. Any known sensitivity to trial drug including its excipients.
7. Current pregnancy or planned pregnancy during the trial period, or breastfeeding.
8. Starting specific psychotherapy from four weeks before randomisation through to Week 12 post-randomisation.

9. Currently taking part in another clinical trial that would interfere with the outcomes of PAX-BD (site team to check with the CI and Trial Management Group if in doubt).
10. Confirmed diagnosis with potential confounding factors such as Parkinson's disease, restless leg syndrome (where restless legs syndrome has been formally diagnosed by a sleep clinic).
11. Significant clinical concern regarding impulse control behaviours

6.1.2. **At Randomisation:**

Patients must fulfil all of the following criteria to be randomised in to the trial:

Inclusion Criteria:

1. Currently depressed, i.e. meeting DSM-5 (56) criteria for a Major Depressive Episode and with a current QIDS-SR >10.
2. A minimum of two telephone phone calls with a trial RA and two on-line weekly symptom ratings have been completed during the pre-randomisation phase
3. On mood stabilising medication (lithium, valproate, carbamazepine, lamotrigine)
4. All regular psychotropic medication, including mood stabilisers, at a stable dose for a minimum of four weeks
5. The patient, if female and of child-bearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin (β-hCG)]*.
6. Women of child-bearing potential are required to use a highly effective contraceptive method during the post-randomisation phase of the trial. Highly effective methods of contraception include:
   - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
   - progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
   - intrauterine device (IUD)
   - intrauterine hormone-releasing system (IUS)
   - vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success)
   - bilateral tubal occlusion
   - sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject)
7. Willing and able to confirm written informed consent at the point of randomisation, after the pre-randomisation period.

* Urine beta-HCG pregnancy tests should be conducted in line with local clinical policies, either sending the urine sample to the local clinical laboratory or by a suitably trained individual using a clinically approved pregnancy test strip

Exclusion Criteria:

Patients must not meet any of the following criteria to be randomised in to the trial:

1. Psychotic symptoms over the preceding 4 weeks.
2. Any known sensitivity to trial drug including its excipients
3. Any deterioration in physical or mental health since pre-randomisation that means there is a clinical concern to proceed with the study.
4. On an antipsychotic at the point of randomisation.
5. Current or planned pregnancy during the trial period, or breast feeding.
6. Starting specific psychotherapy from four weeks before randomisation through to Week 12 post-randomisation.
7. Currently taking part in another clinical trial that would interfere with the outcomes of PAX-BD (site team to check with the CI and Trial Management Group if in doubt).
8. Confirmed diagnosis with potential confounding factors such as Parkinson's disease, restless leg syndrome (where restless legs syndrome has been formally diagnosed by a sleep clinic).
9. Significant clinical concern regarding impulse control behaviours
10. Any study team's concern regarding the patient's ability to remain engaged in the study collecting self-ratings of their symptoms.

7. TRIAL PROCEDURES

The PAX-BD protocol is designed to allow flexibility regarding face to face versus remote completion of study related tasks. The only exception to this is the final part of the consent discussion and physical signing of the consent form at Stage 1 and Stage 2 which must be done in person.

Possible delivery options for study related tasks are described throughout section 7. For any tasks that will continue to be carried out face to face, sites must ensure that they continue to follow local guidelines and policies, including in relation to COVID-19 for example contacting participants prior to attendance at site, the use of PPE at site etc.

7.1. Schedule of Events

	Screening	Pre-randomisation	Screening/ Randomisation	Baseline (Wk 0)	Treatment week (Post-randomisation)																										Tapering[8,9,10]	
					1	2	3	4	5	6	7	8	9 - 11	12	13 - 15	16	17 - 19	20	21 - 23	24	25 - 27	28	29 - 31	32	33 - 35	36	37 - 39	40	41 - 43	44	45 - 47	48	49 - 51	52 (+ up to 2 weeks)
Informed consent	X[1]		X[2]																													
Demographics	X																															
Medical history	X		X																													
Eligibility assessment[3]	X		X																													
BDTQ	X																															
MINI	X																															
QIDS-SR (Paper)	X		X																													
Pregnancy test	X		X																													X
Antipsychotics withdrawn & mood stabilisers started		X																														
Randomisation			X																													
RA phone call		X[4]		X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X[11]	X
AE recording		X[4]		X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X[11]	X
CSO[5] contact						X				X				X						X						X							X
IMP/Placebo admin					Titration phase. 0.25mg OD ↑ by 0.25mg every 3 days to 2.5mg OD or max. tolerated				Fixed dose phase. 2.5mg OD or max. tolerated from titration.				Flexible dose phase between 0.25 and 2.5mg/day.																				Tapering phase ↓ by 0.25 mg every day	
Dispensings			X					X						X				X				X				X				X			
Safety and Tolerability SOP[6]					X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X[11]	X
Concomitant Medications		X[4]		X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X[11]	X
DAWS Screening																																X[11]	X
QIDS-SR[6]		X[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[11]	X
ASRM[6]		X[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[11]	X
GAD-7		X[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[11]	X
SHAPS				X						X				X																			
WSAS				X						X				X						X						X						X	
TSQM										X				X		X		X		X		X		X		X		X		X		X	
QUIP-RS				X						X				X		X		X		X		X		X		X		X		X		X	X
YMRS				X										X																			

	Screening	Pre-randomisation	Screening/ Randomisation	Baseline (Wk 0)	Treatment week (Post-randomisation)																										Tapering[8,9,10]	
					1	2	3	4	5	6	7	8	9 - 11	12	13 - 15	16	17 - 19	20	21 - 23	24	25 - 27	28	29 - 31	32	33 - 35	36	37 - 39	40	41 - 43	44	45 - 47	48	49 - 51	52 (+ up to 2 weeks)
MADRS & QIDS-C				X										X																			
Participant Diary					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[11]	X
Qualitative Interviews (pilot phase only)		X												X																			
Self-reported demographics		X[7]																															
EQ-5D-5L		X[7]		X										X						X					X						X		
ICECAP-A		X[7]		X										X						X					X						X		
OxCAP-MH		X[7]		X										X						X					X						X		
HEQ		X[7]		X										X						X					X						X		
Participant Voucher														X											X								X
Unblinding																															X[12]		
End of study info sheet					X The End of Study Information Sheet needs to be given out at an appropriate time i.e. at week 46 to allow the participant time to consider the document before the week 48 contact or if they withdraw/discontinue study treatment they should be given the document at this point																													

[1] Consent is received to enter the pre-randomisation phase

[2] To be randomised to trial medication

[3] See section 6 for inclusion and exclusion criteria

[4] Weekly through pre-randomisation phase and until participant begins trial medication

[5] CSO or other delegated person at site – this will involve collection of medication returns and urine samples following social distancing guidelines (see section 7.7.2)

[6] A positive response to screening questions on the Safety and Tolerability SOP, item 12 (Thoughts of death or suicide) on the QIDS-SR, or the ASRM will trigger application of the PAX-BD Suicide, Mania and Psychosis, or Impulse Control SOP as appropriate.

[7] Completed at the beginning of the pre-randomisation phase

[8] If a participant stops taking medication for any reason during the trial, RA phone calls including DAWS screening will take place weekly during tapering. If participant has withdrawn from the trial, final safety assessment including pregnancy test for women of child-bearing potential will take place when participant has been drug-free for 2 weeks.

[9] Final safety assessments will take place at week 52 or when participant has been drug-free for 2 weeks (whichever is later).

[10] Week 49-52 schedule of assessments for tapering not applicable for participants who have been unblinded and are taking placebo. Participants receiving placebo will receive a final 'thank you' RA phone call following unblinding medication. No further safety assessments, including pregnancy test, will be undertaken for these participants.

[11] Weekly through tapering phase.

[12] Unblinding to take place after week 48 assessments only for participants who have indicated that they would wish to continue taking pramipexole after the end of the trial, if they were found to be receiving it.

7.2. Summary of Trial Assessments

The following trial assessments will be either completed by the patient or conducted during the pre-randomisation phase and following randomisation, baseline and during treatment, as indicated in the schedule of events (section 7.1).

7.2.1. Data Collection System

Data will be collected at trial contacts, through scheduled contact with trained trial RAs and via participant self-reports on True Colours.

Use of True Colours for self-reports promotes participant safety and allows easy collection of trial data. In terms of safety, participants' ratings will be reviewed regularly by trained RAs who will alert a psychiatrist to high ratings and/or sudden changes in ratings to facilitate early intervention if required. True Colours has been shown to be acceptable to patients both as part of routine care and during clinical trials.

Phone call and other contact data will be recorded using electronic Case Report Forms (eCRFs) on the clinical data management system MACRO™ and the Participant Schedule Excel Spreadsheet. Participant identification on the eCRFs and Participant Schedule Spreadsheet will be through a unique trial identifier number.

At the start of the post-randomisation phase, participants will be provided with a participant diary in which to record the dose of medication taken each day, as well as record any concomitant medications and adverse events.

7.2.2. Questionnaires

Questionnaires (including measuring symptoms of depression, mania, pleasure, impulse control) will be administered at times specified in the schedule of events (section 7.1) specifically:

Demographics and Medical History – Self Report
The demographics questionnaire is a self-report measure which includes DOB, gender, height, weight, smoker/non-smoker and education level.

Bipolar Demographics and Treatment Questionnaire (BDTQ)
The Bipolar Demographics and Treatment Questionnaire (BDTQ) will be used to confirm participants have failed two NICE recommended treatments for bipolar depression and are treatment resistant, thereby meeting the PAX-BD eligibility criteria. This tool is based on the MGH Antidepressant Treatment Response Questionnaire (57) and informed by the consensus threshold definition for TRBD (58). The BDTQ asks participants to confirm a diagnosis of bipolar disorder (type 1 or type 2), indicate when the current episode of depression started and the highest dose of each medication taken within that period. Participants are also able to rate the efficacy of each intervention on a 1-10 Likert scale.

The Mini-International Neuropsychiatric Interview (MINI)
The Mini-International Neuropsychiatric Interview (MINI) is a structured diagnostic interview to assess if a person meets DSM-5 diagnostic criteria for various mental illnesses. The MINI is divided into modules, each corresponding to a diagnostic component; at the start, a set of screening questions are asked by the clinician with positive responses triggering the administration of the full interview in that section. At the end of each module, clinicians are permitted to indicate whether the diagnostic criteria

has been met based on responses. In PAX-BD, the MINI will be used as an aid for clinicians when assessing participant eligibility and confirming that participants meet DSM-5 criteria for BD and a current episode of depression and excluding those meeting criteria for a severe substance use disorder or presence of (or recent) psychotic symptoms. For the assessments needed in PAX-BD, the MINI will take 20-30 minutes to administer, depending on the range of questions asked and modules requiring completion.

Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR) – Self Report

The Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR) is a 16-item self-reported measure of depressive symptom severity which is derived from the 30-item Inventory of Depressive Sympatomalogy (IDS). The scoring system for the QIDS converts responses to 16 separate items into the nine DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) symptom criterion domains. The nine domains comprise of: 1) sad mood; 2) concentration; 3) self-criticism; 4) suicidal ideation; 5) interest; 6) energy/fatigue; 7) sleep disturbance (initial, middle, and late insomnia or hypersomnia); 8) decrease/increase in appetite/weight; and 9) psychomotor agitation/retardation. Each response is on a 0-3 Likert scale ranging from low to high severity and responses are based on the participants experience over the preceding seven days. The total score ranges from 0 to 27.

Altman Self-rating Mania Scale (ASRM) – Self Report

The Altman Self-Rating Mania Scale is a short, 5-item self-assessment questionnaire that assesses mood, self-confidence, sleep disturbance, speech, and activity level over the previous seven days and can be helpful in assessing the presence and severity of manic or hypomanic symptoms in accordance with the DSM-5 criteria. Responses are on a 0-4 Likert scale ranging from low to high severity, with frequency quantified by using 'occasionally' meaning once or twice; 'often' meaning several times or more and 'frequently' meaning most of the time. A score of 0 indicates the absence of manic symptoms and the total sum of the scores range from 0-20.

Generalised Anxiety Disorder 7 (GAD-7) – Self Report

The Generalised Anxiety Disorder 7 (GAD-7) scale is a 7-item self-reported measure of anxiety. The scale uses a normative system of scoring and assessment is derived from the total score across all seven items.

Snaith–Hamilton Pleasure Scale (SHAPS) – Self Report

The Snaith–Hamilton Pleasure Scale (SHAPS) is a standardised self-report questionnaire measuring participants' current hedonic capacity. This comprises 14-items covering the domains of social interaction, food and drink, sensory experience, and interest/pastimes. Response options include 'Definitely Agree', 'Agree', 'Disagree', and 'Strongly Disagree' with the disagree responses being scored as 1, and the agree responses being scored as 0; the final score ranges from 0-14. The higher the score, the higher the level of anhedonia (the inability to experience pleasure).

Work and Social Adjustment Scale (WSAS) – Self Report

The Work and Social Adjustment Scale (WSAS) is a self-reported 5-item outcome measure assessing degree of functional impairment based on impairment in functionality related to work, home management, social leisure, private leisure and personal or family relationships. Severity of impairment is measured on a 0-8 Likert scale ranging from 'Not at all' to 'Very severely'. The total WSAS score is calculated by adding up all of the items. A WSAS score above 20 appears to suggest

moderately severe or worse disturbance of function. Scores between 10 and 20 are associated with significant functional impairment but less severe clinical symptomatology. Scores below 10 appear to be associated with non-clinical populations.

Treatment Satisfaction Questionnaire for Medication (TSQM) – Self report

The Treatment Satisfaction Questionnaire for Medication (TSQM) is a 14-item questionnaire that includes 4 domains focusing on effectiveness, side effects, convenience, and global satisfaction of the medication over the preceding 2–3 weeks, or since the patient's last use. Item scores are combined to give 4 domain scores, which are transformed to a scale of 0-100, providing an overall rating of the patient's satisfaction with the medication.

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS) – Self report

The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS) is designed to measure severity of impulse control disorders symptoms in relation to the use of dopamine agonists in Parkinson's Disease. There are 4 items each related to compulsive gambling, buying, eating and sexual behaviour and three related behaviours (medication use, punding and hobbyism). It uses a 5-point Likert scale to gauge the frequency of behaviours that occurred in the preceding four weeks. Responses for each of the domains are on a 0-4 Likert scale of frequency of behaviours over the past four weeks with 0 being never and 4 being very often (6-7 days/week). The total QUIP-RS score range from 0-112.

Young Mania Self-Rating Scale (YMRS) – Over the phone

The YMRS is an observer-rated tool used to assess manic symptoms at baseline and over time. The scale is administered as a semi-structured clinical interview by a trained professional and covers core symptoms of mania, with each item given a severity rating. The interview usually takes 5-20 minutes to complete.

The YMRS comprises 11-items pertaining to core symptoms of mania with five defined grades of severity. Four items (irritability, speech, thought content and disruptive/aggressive behaviour) are double weighted to accommodate for poor cooperation from severely unwell participants. For some items, several keys are given for one grade of severity, though the presence of only one is required to qualify for the corresponding rating. Keys are provided for guidance and can be ignored by the professional if necessary, thus whole or half points on scales are possible when participants do not follow the progression indicated by the keys. Scores are allocated based on the participant's subjective report of their condition over the past 48 hours, and the clinician's observations during the interview, with the latter being more weighted. This interview is usually administered at baseline and at time-points thereon for comparison of participant progression across manic symptoms.

Montgomery-Asberg Depression Rating Scale (MADRS) – Over the phone

The MADRS is an observer-rated tool used to assess the severity of depressive episodes in participants with mood disorders. The scale is administered as a semi-structured clinical interview by a trained professional and covers core depressive symptoms sensitive to change with medical intervention. The interview usually takes 15-30 minutes to complete.

The MADRS comprises 10-items relating to core symptoms of depression; apparent sadness, reported sadness; inner tension; reduced sleep; reduced appetite; concentration levels; lassitude; inability to

feel; pessimistic thoughts; and suicidal thoughts. Nine items are based on the participant's report and one item is on the rater's observation during the interview. Each item is rated on a 0-6 Likert scale of severity, with the focus being on mood symptoms of depression, rather than somatic. The clinical interview typically begins with broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5). This interview is usually administered at baseline and at time-points thereon for comparison of participant progression across depressive symptoms. Higher scores indicate increasing depressive symptoms, with the total sum of scores ranging from 0 to 50.

Quick Inventory of Depressive Symptomatology – Clinician Rated (QIDS-C) – Over the phone
As QIDS-SR rated by the RA during telephone contact.

PAX-BD Safety and Tolerability SOP - Over the phone
This informs the inclusion of screening questions for impulse control behaviours, manic and psychotic symptoms, and other potential side effects of pramipexole. The PAX-BD study team have a responsibility to minimise risks as much as possible. RAs will assess reported events and reactions according to this SOP and take appropriate action proportionate to seriousness.

PAX-BD Suicide, Mania and Psychosis SOP/Impulse Control SOP - Over the phone
These SOPs will be triggered by a positive response on Item 12 (Thoughts of death or suicide) on the weekly QIDS-SR, or a positive response to screening questions on the Safety and Tolerability SOP or the ASRM. Study RAs will monitor for this and proceed by contacting participants via telephone to conduct a semi-structured interview assessing suicide risk. Any cause for concern discerned by RAs will be recorded and disclosed to the participant's local treatment team thereafter. QUIP-RS will be monitored for a 2-point increase in score from baseline on one of six domains (gambling, sexual behaviour, eating, buying, medication use and hobbyism-punding) to trigger the Impulse Control SOP.

7.2.3. Health Economics Questionnaires

Questionnaires measuring health economics outcomes will be administered at times specified in the Schedule of Events (section 7.1), specifically:

The Health Economics Questionnaire (HEQ) – Self Report
The Health Economics Questionnaire (HEQ) will be used for resource use data collection. Its development was based on previous versions of the Client Service Receipt Inventory (CSRI) instrument (59;60), a widely-used and validated instrument for collection of resource use data in mental health. Collected data will include all hospital and community health and social services, medication, productivity losses, informal care and patient's travel expenses.

EuroQoL 5 Dimension 5 Level (EQ-5D-5L) – Self Report
The EQ-5D-5L is a measure for health-related quality of life for patients in clinical settings consisting of two sections (47). The first comprises five items covering five dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Severity of impairment is measured on a 1-5 Likert scale ranging from 'No problems' to 'Unable'. Participants are required to choose one response statement for each item that best reflects how severe each health dimension is on the day. A score of 1 indicates the absence of an impairment and the total sum ranges from 5-25.

In the second section, the participant is presented with the EQ visual Analogue scale (EQ VAS) ranging from 0-100, 0 being 'The worst health you can imagine' and 100 being 'The best health you can imagine'. Participants are required to indicate how good or bad their health is on that day, and write the corresponding figure.

ICEpop CAPability measure for Adults (ICECAP-A) – Self Report

The ICECAP-A is a self-reported global measure of adult wellbeing covering five domains: attachment, stability, achievement, enjoyment and autonomy (61). The ICECAP-A comprises five items for each of the domains, with each response option being on a 1-4 Likert scale ranging from high to low severity respectively. The participant is asked to choose the statement which best reflects their overall quality of life at the time of completion. A score of 5 indicates full capability and the total sum of scores range from 5-20.

Oxford CAPabilities questionnaire-Mental Health (OxCAP-MH) (50) – Self Report

The OxCAP-MH is a 16-item, multi-dimensional, self-reported instrument developed for outcome measurement in mental health research (50). The items cover facets of individual wellbeing capability: overall health, enjoying social and recreational activities, losing sleep over worry, friendship and support, having suitable accommodation, feeling safe, likelihood of discrimination and assault, freedom of personal and artistic expression, appreciation of nature, self-determination and access to interesting activities or employment. Each response is on a 1-5 Likert scale ranging through various measures of severity. The participant is asked to choose the statement which best reflects their overall quality of life at the time of completion. Overall results are scored on a 0–100 scale with higher scores indicating better capabilities.

7.3. Patient Screening

7.3.1. Patient identification

The PIs at each site will promote the study to their fellow clinicians. Suitable patients will be identified by clinicians at sites using patient clinic lists and databases, and/or research registers, assisted by Clinical Studies Officers (CSOs) or other staff from the Clinical Research Networks (CRNs) where possible. In Scotland, this will include members of the Bipolar Disorder Research Group, part of the Scottish Mental Health Research Network (SMHRN).

Sampling will be opportunistic, focusing on patients currently under the care of secondary mental health services. The trial will also be advertised to patients directly via a postal invitation letter and summary leaflet, recruitment posters and flyers in secondary care clinics, websites, social media and via patient support groups (e.g. the Bipolar Organisation). The CRN will assist with publicity of the trial. The trial RAs will work closely with the CSOs (or equivalents) at sites to share knowledge gathered as the study progresses.

7.3.2. Provision of Study Information

Potentially eligible patients can be given the study documents by a member of the clinical team at one of their standard clinic visits. They will ask the patient for verbal consent to use their preferred contact details for a member of the study team to get in touch and see if they are interested in taking part or have any questions. Patients will be given a Participant Information Sheet to consider. This will include

contact details of the local study team and RAs should the participant wish to make contact sooner and ask any questions.

As outlined in section 7.3.1, the first approach can also be made via provision of an invitation letter and summary sent by post. Patients then have the option to contact either the clinical or research team at site, if they would be interested in receiving further information about the study, including receiving a copy of the full participant information sheet (PIS). For patients that are interested in receiving a copy of the PIS, this can be provided either by post, email or at a standard clinic visit.

All patients will be given a minimum of 24 hours to consider participation to ensure they understand what the study involves and the risks for them.

A member of the study team will contact the patient and if the patient wishes to proceed, a screening contact will be arranged.

Routine care will continue for all patients alongside trial participation.

7.3.3. Screening Contact

Patient Consent

The screening contact will be arranged with the patient and the PI or medical delegate, to take place at a location convenient to them. This could be at clinic when the patient would be attending a standard clinic appointment, at the patient's home or can take place via telephone/teleconference or videoconference.

Informed consent discussion, including pregnancy discussion

Patients will be encouraged to ask questions about the trial and consider whether they wish to participate, including the optional qualitative telephone interviews.

During the screening contact, local PIs (or medical delegate) will document the patient as potentially eligible against the inclusion and exclusion criteria for consent at screening.

The patient will be informed of his/her right to withdraw from the trial at any time without being subject to any resulting detriment, by revoking his/her informed consent.

Discussions regarding contraception will take place during the informed consent process to ensure all women of child-bearing potential are aware of the risks of becoming pregnant whilst taking part in trial. These female participants will be asked to confirm which contraception methods will be used for the duration of the trial. These discussions must be documented in the participant's medical records.

Written informed consent

Written informed consent will be received by the PI, or delegate, after discussion of the trial and answering any questions the patient has to their satisfaction.

As outlined above, the Informed consent discussion can take place via telephone/teleconference or videoconference. If this method will be followed it is important to note while all of the initial consent discussions (including pregnancy/contraception discussions), answering of questions and obtaining initial verbal consent that the participant would like to consent to take part can take place via telephone/videoconference, the participant must still attend at site in order to sign the consent form

in person. Signing of the consent form could also take place at the participants home however it must be noted that consent has to be received by a medically trained, GMC registered doctor, delegated this task via the delegation log. This should take place no later than 72 hours after the telephone/videoconference has taken place with the participant.

This visit should take place following appropriate local policies regarding face to face patient contact including local COVID-19 policies. The aim is that this should be completed as promptly as possible, in order to limit face to face contact between patients and site staff but not at the expense of the patient being able to ask any further questions they might have about the study.

The original signed Consent Form will be filed in the Investigator Site File (ISF) and a copy filed in the patient clinical notes. Copies of the PIS used will also be filed in the ISF and clinical notes. Consent must be received prior to any trial specific assessments.

A copy of the completed consent form will also be sent by site to the secure NCTU email nctu.paxbd.conf@nhs.net – this is for safety monitoring purposes. You must use an nhs.net account to send this document. For sites that do not have nhs.net accounts, another secure method may be used but this must be discussed with and agreed by the NCTU Trial Manager(s) prior to use. For participants who do not consent to this, or where sites are not able to facilitate this, the consent proforma must be completed and sent to NCTU instead, via the same email method.

Only adults with capacity to give informed consent and sign the consent form will be recruited. To take part in the trial participants will need to be able to complete study questionnaires and diary, and understand written medication instructions, and therefore patients who are unable to read (e.g. blind, illiterate etc.) will not be consented.

In the case of protocol amendments or information becoming available which may affect the participant's willingness to continue in the trial, it may be necessary to re-consent the participant on an updated consent form (after necessary regulatory approvals are obtained).

Assessments

After patient consent, the PI or local delegate will administer the following assessments in order to assess eligibility:

- A urine sample pregnancy test for all female participants of child-bearing potential.
- Medical history and assessment of diagnosis/diagnoses according to DSM-5 criteria, assisted by the use of the MINI
- BDTQ
- QIDS-SR (paper)

Completion of the MINI and BDTQ can be completed either over the phone/via videoconference with the participant or via a face to face visit at site. Likewise the medical history and assessment of diagnosis can be completed either over the phone/via videoconference or via a face to face visit and/or in combination with a review of the participant's medical notes.

The QIDS-SR should be self-completed by the participant. It can be completed via a face to face visit. If a face to face visit at site is not possible in order to complete this questionnaire, then ideally a copy of the QIDS-SR should be posted or emailed to the participant. Participants can then either provide their answers securely via email or over the phone/via videoconference with a CSO if the

questionnaire has been posted. This questionnaire will also be made available via the study website allowing patients to access this in advance of a screening telephone call/videoconference. If it has not been possible for the participant to review a copy of the QIDS-SR in advance (i.e. no internet access, paper copy lost in post etc) and videoconference is also not an option (where the questionnaire could be displayed via screen share) then as a last resort the questionnaire can be completed over the phone with the questions read out to the patient by the site team.

If the consent form is completed via attendance at the participant's home or at site, the MINI, QIDS-SR and BDTQ assessments could also be completed as part of this visit, after the consent form has been fully signed. This would lengthen the visit time so should only be done in instances where both the participant and site team are comfortable with this and it meets local policies regarding face to face contact, including COVID-19 policies. If the participant and/or site team would prefer to keep face to face contact to a minimum then one of the options listed above can be used after the consent visit has been completed.

Collection of Urine Samples:

Urine samples for pregnancy testing can be collected at site, via an on-site screening contact, where possible.

If it is not possible for the sample to be collected during an on-site visit, then the sample pot will need to be sent out to the participant by post or given in advance (for example when the participant attended to consent, at a standard clinic visit etc). The sample can then be:

a) collected from the patients door by member of the site team (for example the CSO) - without going in the patients' house to observe social distancing guidelines

b) delivered in person by the participant to site (for example if they are attending for a standard clinic visit)

c) Posted back to the site team by the participant (using a pre-paid envelope provided)

It is imperative that the sample is analysed quickly (ideally no later than 48 hours after collection) to ensure the validity of the results. Therefore ideally options A or B should be used wherever possible. Where neither of these are possible, as a last resort option C can be used.

If this latter option is used, and sites local policy is for pregnancy tests to be carried out by the clinical laboratory, sites must be aware that there is an increased risk of the sample not being received by their Lab Department within the necessary timeframe for the sample to be useable and provide valid results, in line with local lab guidelines. If this is the case a further sample may need to be provided.

7.3.4. Confirmation of Eligibility for Pre-Randomisation Phase

Once results are received from all assessments undertaken as part of screening, eligibility will be confirmed by the PI at site, or delegated medically qualified clinician, and documented using the inclusion and exclusion criteria to enter the pre-randomisation phase. The PI or delegated clinician will inform the patient if they are eligible to take part in the trial by phone, videoconference or at clinic, depending on the appropriate routine contact with that patient.

For participants confirmed as eligible, a member of the site team will telephone the study RAs with the participant details including study ID number, full name, phone number and/or email address, as

well as the contact details of the patient's secondary care mental health clinician (and care co-ordinator if applicable).

Patients who do not wish to take part in the study, or do not meet the eligibility criteria for pre-randomisation, will continue with their standard treatment pathway and will be considered as 'screen failures'. These patients will not take part in the trial and no further data will be collected. These patients will be recorded on the screening log with reasons documented wherever possible.

7.3.5. Current Health Care Provider Contact

The participant's GP and the participant's secondary care mental health clinician will be sent a Health Provider Information Sheet letter and copy of the PIS to inform them the patient is taking part in PAX-BD. They will be asked to alert the local PI if they become aware of any issues that may prevent the participant from taking part in PAX-BD. The secondary care mental health clinician will continue to hold clinical responsibility for the patient during the study and will be asked to remain in contact with the local study team.

7.3.6. First RA Telephone Call

Within the first week after eligibility is confirmed for pre-randomisation, a trial RA will contact the participant by telephone to introduce him/herself, thank them for taking part, confirm validity of records held and answer any further questions the participants may have.

The RA will ask the patient what medication they are currently taking and record this information.

They will check with the participant that they are able to access the online self-reported outcome system, True Colours. If not, arrangements will be made for the participant to access paper copies which will be handed to the CSOs or other available member of the study team.

The participant will be given guidance to register with True Colours and the RAs will check the participant has successfully registered.

Additional phone calls may be arranged to provide further support if requested.

7.4. Pre-Randomisation Phase

The pre-randomisation phase will allow patients to have their antipsychotics withdrawn and mood stabiliser initiated if necessary. In addition, the pre-randomisation phase establishes if the patients are able to adhere to the weekly online mood ratings using the True Colours system. Doses of all regular psychotropic medication need to be stable for a minimum of four weeks prior to randomisation.

7.4.1. Antipsychotics Withdrawn & Mood Stabilising Medication Started

Local PIs and medical delegates will identify participants on antipsychotics and, together with the patient's secondary care mental health team, assist them to fully withdraw from antipsychotics. If not currently prescribed, all participants will commence a suitable mood stabilising medication (lithium, valproate, lamotrigine or carbamazepine). The participant must have been on mood stabilising medication, at a stable dose, for a minimum of four weeks prior to randomisation.

The clinical care for each patient during this time will be the responsibility of the patient's secondary care mental health clinical team. Local clinicians will be responsible for the everyday management of their patients' treatment, while being aware that they are in a clinical trial. Advice and support is available from the local PI, the CI and clinical collaborators.

7.4.2. Participant Completion of True Colours Assessments

At the start of the pre-randomisation phase, participants will enter information on True Colours to capture their demographics and medical history.

During the pre-randomisation phase, participants will be required to complete weekly assessments (QIDS-SR, GAD-7 and ASRM) using the True Colours system in line with the Schedule of Events (or provided with paper versions if required).

The participant will also use True Colours to complete Health Economic data on the HEQ, EQ-5D-5L, ICECAP-A and OxCAP-MH questionnaires, for comparison with data collected during the treatment period. These Health Economic measures will be carried out once at the start of the pre-randomisation phase.

Guidance on using the True Colours system will be provided by phone call by a trial RA.

7.4.3. Trial RA Telephone Calls

Throughout the pre-randomisation phase, RAs will contact participants weekly to confirm progress.

The RAs will:

- address any issues or missing data on True Colours with the participant
- guide the participant through completion of forms/missing data if required
- ask how the participant is managing withdrawal from antipsychotics and commencement on mood stabiliser
- confirm and record what medication is being taken
- record any adverse events
- Remind the participant as appropriate that they must complete a minimum of two phone calls and two True Colours assessments in order to be randomised

The RAs will communicate with the relevant site PI or medical delegate when a participant is potentially eligible for randomisation. This will allow the site team to arrange for the Randomisation Information Sheet to be sent to the participant (given at a standard clinic visit, posted, or emailed) and for the screening and randomisation contact to be arranged as soon as possible, but not less than 24 hours after the participant has received the Randomisation Information Sheet. If the period until the contact is longer than a week, the participant will continue to receive weekly RA phone calls until the contact.

If telephone contact cannot be made with the participant, the RAs will alert the site PI or medical delegate. The local study team will consider whether the participant is suitable to continue in the pre-randomisation phase or whether they should be withdrawn and continue under the care of their usual treating clinicians outside of the trial.

7.5. Randomisation phase

7.5.1. Screening and Randomisation contact

A screening and randomisation contact will be arranged with the PI or local medical delegate on the delegation log as soon as possible after receiving confirmation from the RAs that the patient is potentially eligible for randomisation. The contact can take place at a local clinic, at the patient's home, via telephone/teleconference or videoconference depending on what is more convenient.

Consent to be randomised

The Randomisation Information Sheet will be discussed with the participant and any questions answered. Participants will be reminded that there are some further assessments and tests before they can be confirmed as eligible to proceed to randomisation. During the informed consent discussions, female participants of childbearing potential will be reminded of the risks of becoming pregnant whilst taking part in the trial and asked to re-confirm which contraception methods will be used for the duration of the trial. These discussions must be documented in the participant's medical records.

As with the Pre-Randomisation Stage, the Informed consent discussion can take place via telephone/teleconference or videoconference. If this method will be followed it is again important to note while all of the initial consent discussions (including pregnancy/contraception discussions), answering of questions and obtaining initial verbal consent that the participant would like to consent to take part can take place via telephone/videoconference, the participant must still attend at site in order to sign the consent form in person. Signing of the consent form could also take place at the participants home however it must be noted that consent has to be received by a medically trained, GMC registered doctor, delegated this task via the delegation log. This should take place no later than 72 hours after the telephone/videoconference has taken place with the participant.

This visit should take place following appropriate local policies regarding face to face patient contact including local COVID-19 policies. The aim is that this should be completely as promptly as possible, in order to limit face to face contact between patients and site staff but not at the expense of the patient being able to ask any further questions they might have about the study.

Written informed consent will be received and documented from participants by the PI or local medical delegate, delegated that duty on the site delegation log, for commencement to the randomisation phase. Consent for the qualitative telephone interviews is optional for participants.

As with Stage 1, the original signed Consent Form will be filed in the Investigator Site File (ISF) and a copy filed in the patient clinical notes. Copies of the Randomisation Information Sheet used will also be filed in the ISF and clinical notes. Consent must be received prior to any trial specific assessments.

A copy of the completed consent form will also be sent by site to NCTU for safety monitoring purposes (via the same secure email method outlined for Stage 1). For participants who do not consent to this, or where sites are not able to facilitate this, the consent proforma must be completed and sent to NCTU instead, again via the same secure email method.

Eligibility Assessment and Confirmation

Consent to randomisation must be received prior to any trial specific assessments or tests to assess eligibility.

After patient consent, the PI or local delegate will administer the following assessments in order to assess eligibility:

- A urine sample pregnancy test for all female participants of child-bearing potential.
- QIDS-SR (paper)

As with the Pre-Randomisation Stage, the QIDS-SR should be self-completed by the participant. If a face to face visit at site is not possible in order to complete this questionnaire, then a copy of the QIDS-SR should be posted or emailed to the participant. Participants can then either provide their answers via email or over the phone/via videoconference with a CSO/delegated team member if the questionnaire has been posted. This questionnaire will also be made available via the study website as another way for patients to access this in advance of a screening telephone call/videoconference. If it has not been possible for the participant to review a copy of the QIDS-SR in advance (i.e. no internet access, paper copy lost in post etc) and videoconference is also not an option (where the questionnaire could be displayed via screen share) then as a last resort the questionnaire can be completed over the phone with the questions read out to the patient by the site team.

If the consent form is completed via attendance at the participant's home, the QIDS-SR assessment could also be completed as part of this visit, after the consent form has been fully signed. This would slightly lengthen the visit time (e.g. by around 5 mins). This should be taken into account regarding face to face contact, including COVID-19 policies. If the participant and/or site team would prefer to keep face to face contact to a minimum then one of the options listed above can be used after the consent visit has been completed.

Regarding collection of the urine sample please see 'Urine Sample Collection' within section 7.3.3.

The PI or delegated clinician assessing eligibility will arrange for other pre-treatment tests that they consider to be necessary for the safety of their patients.

Once all required assessments, tests etc have been carried out, the PI or delegated clinician will inform the patient if they are eligible to take part in the trial by phone, videoconference or at clinic, depending on the appropriate routine contact with that patient.

Eligibility must be confirmed by the PI at site, or delegated clinician, and documented using the inclusion and exclusion criteria for randomisation. These eligible participants will be randomised anonymously to receive either pramipexole (active treatment) or placebo. Reasons will be recorded wherever possible for patients who do not proceed to randomisation. Patients who do not proceed to randomisation will remain under the care of their usual treating team outside of the trial.

7.5.2. **Randomisation**

Randomisation should take place as soon as possible and no more than 2 weeks after a participant has been confirmed as eligible. If randomisation does not take place within 4 weeks of confirmation of eligibility, eligibility must be reconfirmed, including pregnancy test for women of child-bearing potential. Eligible participants will be randomised by a delegated and trained member of the research team at each site using the Sealed Envelope system (a central, secure, 24-hour web-based randomisation system with concealed allocation). Eligible participants will be randomised in a 1:1 ratio to receive either pramipexole or placebo in addition to mood stabilisers.

Randomisation system URL:

https://www.sealedenvelope.com/access/

This system is available 24 hours a day, seven days a week.

In the event that the online system is not accessible at site, NCTU can liaise with Sealed Envelope Support to investigate the cause. Site staff should contact NCTU Database Support during normal working hours:

Email: nctu.database.support@newcastle.ac.uk

Telephone: 0191 208 8211

Treatment Allocation

A non-deterministic minimisation algorithm will be used to produce treatment groups balanced for important prognostic factors. The first 10 patients will be allocated randomly without minimisation to avoid predictability. Subsequently, the minimisation algorithm will be applied with an allocation ratio that is not fully deterministic: there will be an 80% bias in favour of allocations that minimise the imbalance. The randomisation algorithm will minimise for 9 variables related to prognosis at baseline:

- bipolar I or bipolar II (based on DSM-5 criteria)
- severity of depression at randomisation (QIDS-SR) — 3 categories: moderate 11 – 15, severe 16 – 20 and very severe > 20
- age – 2 categories: 18-50 and > 50
- biological sex – 2 categories: male and female
- site region – 8 categories: North, Midlands and East, London, South East, South West, Scotland, Wales, Northern Ireland
- concurrent mood stabiliser – 5 categories: lithium, valproate, lamotrigine, carbamazepine and multiple mood stabilisers
- concurrent antidepressant (Y/N)
- Withdrawn from an antipsychotic during the pre-randomisation phase (Y/N)
- number of mood episodes in the past year – 2 categories: < 4 and ≥ 4

7.6. Baseline Assessments/ Tests

7.6.1. Trial RA Telephone Call

Trial RAs will contact participants via telephone within approximately two working days after the randomisation. The RA will:

- Confirm with eligible participants they have been randomised to the main phase
- Outline trial procedures and contacts
- Explain the medication dispensing procedure
- Administer baseline assessments (YMRS and MADRS & QUID-C)

7.6.2. Participant Completion of True Colours Assessments

If confirmed as eligible and randomised, participants will continue to use True Colours to complete the pre-randomisation phase measures (QIDS-SR, GAD-7 and ASRM) on a weekly basis.

At the first weekly True Colours assessments following randomisation, participants will also be asked to complete the following baseline assessments: QUIP-RS, WSAS, SHAPS, HEQ, EQ-5D-5L, ICECAP-A and OxCAP-MH. Participants will be asked to complete these assessments prior to starting to take trial medication.

7.7. Post-randomisation Phase (Weeks 1-52)

The post-randomisation period will include 4 phases pertaining to trial medication as described in protocol section 8.4 Dosage Schedule & Modifications:

- Phase 1: Titration phase (Weeks 1-4)
- Phase 2: Fixed dose phase (Weeks 5-12)
- Phase 3: Flexible dose follow-up phase (Weeks 13-48)
- Phase 4: Tapering of IMP (Weeks 48-52)

There are 7 set periods for prescribing and dispensing trial medication. The local PI or delegate should prescribe trial medication during the post-randomisation phase as per section 8.5 Provision of Trial Medication. The PI/delegate will issue participants with a patient alert card.

Week 1 of the post-randomisation phase starts for a participant on the day they start taking the trial medication.

Following randomisation and receipt of a prescription at CNTW pharmacy, participants will be sent bottles of prescribed trial medication with a titration schedule, by post. Participants should receive and start taking trial medication within 7 calendar days, and no more than 10 calendar days, of the baseline assessments. Adherence to the schedule and number of tablets taken will be verbally checked with the participant during the RA telephone calls. Participants who are subsequently advised to follow a different dosing schedule due to adverse effects will be sent a revised schedule and discussed accordingly. Bottles of medication will be sent in the post to participants throughout the trial.

7.7.1. Trial RA Telephone Calls

The trial RAs will telephone participants **within 1 week of trial medication being dispensed, then weekly during the first 12 weeks of treatment, 4 weekly to week 48.** During the end of trial tapering period (weeks 49 to 52 + up to 2 weeks), or if a participant tapers and stops medication at any point during the post-randomisation phase, RAs will telephone participants weekly. Telephone calls will be made to participants to coincide with the end of dispensing periods. The RA will:

- If applicable, confirm the participant has received their medication (and record the start date).
- IMP Compliance - query the dose taken and any missed doses. RAs will check that participant reports correspond to a chart detailing the number and type of tablets a participant should have taken at each time point, and any discrepancies will be reported immediately to the participant's relevant treatment team and PI for intervention.

- Administering Safety and Tolerability SOP, including Adverse Event check and recording, symptomatic monitoring for low BP* and, during tapering, dopamine agonist withdrawal syndrome (DAWS) screening.
- Concomitant medication check and recording, including mood stabilising medication.
- Administering the YMRS and MADRS & QUID-C at time points as outline in section 7.1. Schedule of Events (and consulting with the CI, medical delegates and local clinical team as appropriate) and reviewing weekly ASRM on True Colours.
- Administering PAX-BD Suicide, Mania and Psychosis or Impulse Control SOPs if indicated by QIDS-SR item 12, ASRM or Adverse Event screening questions.
- Monitor and address any issues or missing data on True Colours with the participant.
- Guide the participant through completion of forms/missing data if required.
- Ask for participant opinion on if they are receiving active or placebo medication (week 48 only).
- Participants will receive a final 'thank you' RA phone call on trial completion.

The RAs will be vigilant of any significant changes or cause for concern, such as increasing suicidality or the possible development of an impulse control disorder.

* If the participant reports any symptoms suggestive of possible hypotension this will be reported by the RAs to the site team (outside of the usual adverse events reports sent to site – see section 9.3). The clinical team can then follow this up with the participant as per local clinical practice.

7.7.2. CSO Contacts (or local equivalent)

Wherever possible the following tasks can still be completed via arrangement with the participant for door stop collection (without going in to the patients' house to observe social distancing guidelines)

- At weeks 2, 6, 12, 24, 36, 48 and final study assessment - collect unused medication and empty bottles. CSO or delegate to complete accountability log and return a copy of this along with the unused medication and empty bottles to CNTW pharmacy using the pre-paid envelopes provided.
- Provision of Record Sheet/Diaries at the relevant time points. Collection of completed Record Sheet/Diaries from participants for filing in the ISF.
- Urine pregnancy test for women of child-bearing potential will be administered at end of exposure (usually final study assessment at week 52 + up to 2 weeks) – please see 'Urine Sample Collection' within section 7.3.3 for options regarding this.

7.7.3. Participant Completion of True Colours Assessments

The post-randomisation phase requires participants to continue to use the True Colours system (or paper versions) to complete the questionnaires at the time points outlined in section 7.1. Schedule of Events using the True Colours system.

If participants miss any consecutive weeks of completing the measures, the RAs will follow them up by telephone. If the participant is not responding to phone contacts, the RA will ask the CSO or local PI to discuss if the participant should continue in the study.

7.7.4. Participant Diary

Sites will provide eligible patients with a Stage 1 Record Sheet at or following the Pre-Randomisation screening/consent contact and with a participant diary at or following the screening/randomisation contact . Participants will be required to complete these daily throughout the pre and post-randomisation phases to record, adverse events and concomitant medications and during the post-randomisation phase to record dose of trial medication taken each day. This will act as an aide memoire for participants during RA phone calls.

As the post-randomisation stage can last for up to 52 weeks, the diary has been split into two versions for the ease of the participant – the first covering weeks 1-12 and the second covering weeks 13 onwards.

These documents can be provided to the participant either at a standard clinic visit, via a CSO Contact/door stop collection or via post. Completed copies will need to be returned by the participant, again this can be done either by returning while attending site for a standard clinic visit, via a CSO Contact/door stop collection or via post (stamped, addressed envelopes will be provided for this).

7.7.5. Return of unused medication and empty bottles

There are 3 options regarding return of unused IMP and empty bottles

a) Collected from the patients door by member of the site team (for example the CSO) - without going in the patients' house to observe social distancing guidelines - the study team can then return the medication to CNTW pharmacy following guidance in section 7.7.2.

b) Delivered in person by the participant to site (for example if they are attending for a standard clinic visit) – the study team can then return the medication to CNTW pharmacy following guidance in section 7.7.2.

c) Participants can return the unused medication/empty bottles directly to CNTW themselves using the pre-paid envelope provided.

Ideally options A or B should be used wherever possible in order to allow thorough IMP accountability checks to be carried out by the central study team.

Where neither of these are possible, as a last resort option C may be used.

When medication is posted to participants by CNTW pharmacy, a pre-paid addressed envelope will be provided as part of this parcel, for returning any unused medication/empty bottles from the last prescription.

When the RAs contact a participant to check they have received the next dispensing of trial medication, they will also check that provisions have been made for the return of any unused medication from the previous dispensing.

7.7.6. End of Treatment Phase (Weeks 48-52)

Week 46 Participants will be asked by their local clinical team to consider if they would wish to continue on the trial IMP after 48 weeks, if they were found to be receiving pramipexole. The local clinical team will discuss this with the local PI.

The End of Study Information Sheet relating to trial completion needs to be provided to the participant at this time point to allow the participant time to consider the document before the week 48 contact. This can be provided either via a visit to site (for example at the same time as a standard clinic appointment), via post or via email.

Week 48 All participants will be asked at the week 48 RA phone call for their opinion on whether they have received active or placebo medication. Participants will not be routinely unblinded unless they have indicated that they would wish to continue taking pramipexole after the end of the trial, if they were found to be receiving the active drug.

The study medication will be tapered over weeks 48-52 by the PI/medical delegate as per section 8.4.2 Tapering and Stopping and the guidance in the PAX-BD Clinician Manual. Safety monitoring will continue until week 52 or until participants have been off-drug for 2 weeks (whichever is later), with a final participant safety assessment completed by the RA at the end or this time (expected at week 52 + up to 2 weeks).

Participants who have indicated they would wish to continue taking pramipexole after the end of the trial will be unblinded by the local PI or delegate using the randomisation system, as soon as possible after the 48 week assessment has been completed. The participant is informed as soon as possible whether they are receiving IMP or placebo. The clinical team are unblinded to the treatment arm for this participant to enable local clinical discussions and decisions to take place, including around continuation of IMP after the end of trial. The RAs and CSOs are also unblinded to treatment arm at this stage.

A final urine pregnancy test for women of child-bearing potential will be administered at the end of study medication exposure (usually week 52 + up to 2 weeks but could be earlier if a participant withdraws from study medication earlier). This final test is however not applicable for participants who have been unblinded and are found to be taking placebo.

Regarding options for collection of the urine sample please see 'Urine Sample Collection' within section 7.3.3.

Continuing IMP: if the participant wishes to continue receiving IMP with agreement from their clinical team, after seeking their own organisational approval, the treating clinician will arrange dispensing of open-label pramipexole from local pharmacy after the trial ends (>52 weeks). The participant will continue with their tolerated dose of IMP until week 52, and then move to open-label pramipexole. Safety monitoring will continue until week 52, with a final participant safety assessment (RA and CSO) done at week 52. The PAX-BD team will be unable to provide any trial medication for patients after week 52.

Placebo: if the participant is receiving placebo, care transfers to the local clinical team at week 48. The final study assessments for these participants are performed at week 48. Any unused trial medication and empty bottles will be returned to the central CNTW Pharmacy team (see section 7.7.5)

If a participant is unblinded and found to be receiving pramipexole, but then decides at this stage that they do not wish to continue taking pramipexole after the end of the trial, they will follow the week 48-52 tapering and safety assessment schedule as described above. Participants who have been receiving placebo but would like to try taking pramipexole outside of the trial will be able to discuss this option with their clinician as part of their ongoing clinical care.

7.8. Blinding

IMP (pramipexole, 1 mg and 0.25mg – *NOTE: these weights are salt weights and equivalent to 0.7mg and 0.18mg of the base weight. All weights described in this protocol are SALT WEIGHTS)* and matching placebo will be delivered blinded (pre-packaged and labelled) by MODEPHARMA to Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust. Trial medication will be prescribed and dispensed at St Nicholas Hospital (GPhC registration number 1109789), then distributed directly to patients in batches via secure post.

The Trial Management Team, including the Trial Senior Statistician, will be blinded to the treatment allocations, with the exception of the Data Manager and Trial Statistician. The Trial Statistician will prepare reports and perform the data analysis for Data Monitoring Committee (DMC) reports. For the DMC closed report, the unblinded Data Manager will provide the Trial Statistician with data with the treatment allocation identified by codes, so that the Trial Statistician remains partially blinded. In emergency situations, some clinical TMG members may be unblinded to individual patients under their care.

7.8.1. Emergency Unblinding

Participants may need to be unblinded as the result of a clinical emergency. The randomisation system provides a 24-hours-a-day, 7-days-a-week online service for emergency unblinding. Unblinding will be carried out by the PI or medical delegate on the delegation log using Sealed Envelope.

If a participant should need to be unblinded for any other reason, the PI or medical delegate should first consult with the CI or delegated co-applicant for further discussion prior to performing the unblinding. Patients should only be unblinded if there is a clinical need, or at 48 weeks for participants who have indicated they wish to continue taking pramipexole after the end of the trial.

The CI and delegated psychiatrists will be available via the out-of-hours on call system “Out of Hours Research Mental Health”, as defined by the PAX-BD Out of Hours Cover SOP, via the Sunderland Initial Response Service on telephone +44(0) 303 123 1145. The on call psychiatrists will have access to a trial-specific unblinding SOP. An audit trail of any unblinding performed on the Sealed Envelope system will be recorded; this includes Participant ID number of the unblinded participant, date and time of unblinding, name of person performing unblinding and reasons for this. Reasons for unblinding any participant will also be recorded thoroughly in the Trial Master File (TMF), ISF and patient medical notes.

7.9. Withdrawal Criteria

Participants have the right to withdraw from the trial at any time without having to give a reason. Investigator sites should try to ascertain the reason for withdrawal and document this on the Withdrawal Form and patient medical notes. The withdrawal form can be completed at a visit to site (for example at the same time as a standard clinic appointment), via telephone or via videoconference. The Participant will also need to be provided with the End of Study Information Sheet relating to withdrawal or early completion of trial medication. This can be provided either at a visit to site (for example at the same time as a standard clinic appointment), via post or via email.

The Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason, including:

- Pregnancy
- Symptomatic deterioration
- Unacceptable toxicity
- Significant protocol deviation or non-compliance
- Investigator's discretion that it is in the best interest of the participant to withdraw
- An adverse event that requires discontinuation of the trial medication or renders the participant unable to continue in the trial
- Termination of the clinical trial by the sponsor
- Where a participant has lost Mental Capacity
- Where a participant has been the subject of a Deprivation of Liberty Safeguard subject to the clinical decision of the PI

Participants who withdraw from the trial will not be replaced. Participants will be classed as enrolled once randomised. Where a participant no longer wishes to take trial medication, and gives consent for continued participation in the trial, s/he will be followed up to 48 weeks. A pregnancy test will be administered for women of child-bearing potential once the participant has been drug-free for 2 weeks (see 'Urine Sample Collection' within Section 7.3.3 for full details regarding options for collection of this sample)f.

If a participant withdraws, the PI/medical delegate should advise on how to taper medication safely as per section 8.4.2 Tapering and Stopping and guidance in the PAX-BD Clinician Guide. A taper and stop prescription may be required to ensure the participant has sufficient quantities of both strengths of medication to taper dose gradually. Investigators should not unblind participants who withdraw unless there is a clinical need.

Participants who withdraw consent will be asked to complete safety assessments during the tapering phase. All trial data collection will be stopped once tapering safety assessments, including pregnancy test for women of child-bearing potential are complete. Data collected prior to that withdrawal will be retained. Where appropriate, the participant will be advised on ongoing treatment.

7.10. Study Samples

Female participants of child-bearing potential will be asked to provide three urine samples for pregnancy testing (before they can be confirmed as eligible for the pre-randomisation phase, before

they can be confirmed as eligible to be randomised and at the end of exposure). The samples will be destroyed once the testing has been complete.

7.11. End of Trial

The definition of the end of trial is the last patient, last visit (LPLV) date.

8. TRIAL MEDICATION

8.1. Name and Description of IMP

For the purposes of this trial pramipexole will be classed as IMP. Pramipexole is currently licenced for the treatment of idiopathic Parkinson's disease and restless legs syndrome.

IMP:
Pramipexole (pramipexole dihydrochloride monohydrate) 0.25 mg tablet (SALT WEIGHT); equivalent to 0.18 mg pramipexole (POM) (BASE WEIGHT)

Pramipexole (pramipexole dihydrochloride monohydrate) 1 mg tablet (SALT WEIGHT); equivalent to 0.7 mg pramipexole (POM) (BASE WEIGHT)

NOTE: All weights subsequently described in this protocol are SALT WEIGHT, unless otherwise specified.

Placebo:
Matching placebo tablet for pramipexole 0.25 mg tablet
Matching placebo for pramipexole 1 mg tablet

8.1.1. Reference Safety Information

Section 4.8 of the MHRA approved version of the SmPC for pramipexole 0.7mg (Aurobindo Pharma – Milpharm Ltd) will be used as RSI for this trial. The manufacturer may make updates to the SmPC for this IMP. The CI/Sponsor/NCTU will monitor and review the changes to the SmPC, considering the impact on the trial and will revise relevant documentation as required.

Note: Weight above is the base weight.

Serious Adverse Events (SAEs) that are thought to have a causal relationship with pramipexole must be assessed for expectedness against the RSI outlined above only.

8.2. Preparation and Labelling of IMP

Placebo tablets will be manufactured by Custom Pharmaceuticals Limited MIA(IMP).

Pramipexole tablets will be procured by MODEPHARMA.

Pramipexole tablets and placebo tablets will be bottled, packaged and labelled (Annex 13-compliant) and QP released by Wasdell Packaging Limited MIA(IMP).

Pramipexole and placebo will be distributed, as blinded trial medication, by MODEPHARMA (MHRA-licensed wholesale distributor) to the Sponsor Pharmacy (CNTW).

Please refer to the SmPC and Investigational Medicinal Product Dossier (IMPD) for more details about the active and placebo IMPs.

8.3. Drug Storage and Supply

There are no specific storage requirements for the trial medication.

IMP will be supplied as tablets of either 0.25mg pramipexole dihydrochloride monohydrate (salt form, equivalent to 0.18 mg pramipexole) or 1.0mg pramipexole dihydrochloride monohydrate (salt form, equivalent to 0.7 mg pramipexole). Placebo will be supplied as tablets matched to both doses of IMP.

8.4. Dosage Schedule & Modifications

8.4.1. Medication dosages

For all participants, initiation of trial treatment will follow a 4-week titration schedule starting at 0.25mg/day in a single dose usually at night for 3 days. Thereafter the dose will be increased by 0.25mg/day every 3 days. The target dose will be 2.5mg/day but titration will be based on tolerability and response.

Dose of mood stabilisers should ideally be kept stable throughout the titration and fixed dose phases unless clinical need dictates otherwise as judged by the participant's local clinician. Mood stabilisers can be adjusted by the local clinician in the flexible dose phase but if the participant remains on study medication then it is recommended that they remain on at least one of the four recommended mood stabilisers (lithium valproate, carbamazepine or lamotrigine).

Antipsychotics should ideally be avoided through the entire trial whilst the patient is on study medication. However, an antipsychotic may be clinically indicated if the patient experiences manic or psychotic symptoms, determined by the participant's treating clinician. In such circumstances, study medication may need to be cut or discontinued. This is a clinical decision made by the treating clinical team.

Titration phase: Weeks 1-4.

Participants will start at a dose of 0.25mg daily which will increase by 0.25mg every 3 days to a maximum dosage of 2.5mg if tolerated by end of Week 4.

If participants experience mild side effects and do not feel able to increase the dose at any point, they should wait a further 3 days before considering further up-titration. If the patient still feels unable to increase the dose, then this remains at the existing level.

If the participant experiences significant side effects and is not able to tolerate the drug, they step down to the last tolerated dose and do not attempt to increase again.

Fixed dose phase: Weeks 5-12

The dose attained at the end of Week 4 is continued. If participants are still continuing to increase their daily dose by the end of week 4 (due up-titration being delayed due to missed doses or side effects), up-titration can continue for up to a further 2 weeks (i.e. to the end of week 6).

Flexible dosing phase: Weeks 13- 48

Beyond 12 weeks, pramipexole will be flexibly dosed between 0.25 and 2.5mg/day, determined by response and tolerability and guided by the algorithm below.

During the flexible dosing stage of the study, decisions around medication dose alterations will be based on weekly mood scores (QIDS-SR and ASRM) and scores from the side effect items of the TSQM (Version II: Question 4, 5 and 6) administered 4-weekly. Patient's mood and response, and tolerability, will be categorised every 4 weeks.

With regards to mood and response, using the Participant Schedule spreadsheet with built-in formulas, participants will be categorised by the RAs:

1. Degree of response, judged from the most recent QIDS-SR scores as follows:

- If Score > Randomisation Score (RS)-2 = **no response**
- If Score ≤ RS-2 AND Score > RS/2 = **partial response**
- If Score ≤ RS/2 AND Score > 5 = **response**
- If Score ≤ 5 = **remission**

2. Trajectory of change, based on the QIDS-SR scores over the last 4 weeks:

- **Generally improving**. Overall decrease in QIDS score over the 4 weeks of ≥3 points AND latest score < preceding score +2.
- **Generally deteriorating**. Overall increase in QIDS score over the 4 weeks of ≥3 points AND latest score > preceding score -2.
- **No clear pattern of change**. Not meeting the criteria of either generally improving or deteriorating.

3. Risk of manic switch, judged from ASRM:

- If Current score ≥6, **probable manic/hypomanic episode**
- If ASRM score has increased by >2 over the preceding 4 weeks and 3 ≤ score < 6, then **possible manic/hypomanic episode.**
- If neither of the above then **not in hypomanic/manic episode.**

With regards to tolerability, using the Safety and Tolerability SOP administered by the RAs, participants will be categorised as follows:

1. If the participant scores 1 or 2 on any of the TSQM questions 4-6 = **intolerant**.
2. If the participant scores 3 on at least one of the TSQM questions 4-6 but no score of 1-2 on any of the questions 4-6 = **partially tolerant**
3. If participant scores 4 or 5 on all three TSQM question 4-6 = **tolerant**.

The above categorisations will be used by RAs to provide advice to the local PI regarding the dose of study medication to prescribe the patient as indicated in the table below. The clinical team together with the patient can agree to over-ride these recommendations and this will be clearly documented with the alternative dose recorded.

This advice will be provided in the form of a Flexible Dosing Report sent to the site team at various time points throughout this stage of the study. As part of their telephone contacts with participants the central Research Assistants will check that the participant is taking the correct amount of medication. To facilitate this sites must advise as to whether these recommendations were implemented or not by completing and returning the appendix attached to the flexible dosing report.

Category	**Action Required**
Remission (regardless of the trajectory of change) OR a **response with a pattern of general improvement** AND **Tolerant** OR **partially tolerant and patient happy to continue on current dose**	A change in dose of medication is not recommended.
No response OR a **partial response** OR a **response without a current pattern of general improvement** AND **Tolerant** OR **partially tolerant and patient happy to increase dose**	It is recommended trial medication be increased by **0.25mg every 3 days** to a maximum of 2.5mg daily. If participants experience mild side effects and do not feel able to increase the dose at any point, it is recommended they wait a further 3 days before considering further up-titration. If the patient still feels unable to increase the dose, then it is recommended this remains at the existing level.
Intolerant OR **partially tolerant and/or patient not agreeing to maintain or increase dose**	It is recommended the dose of trial medication be decreased by **0.25mg every week** until reaching a dose at which the participant feels able to continue on this until the next 4 weekly assessment/is not changed
Possible or probable hypomanic/manic episode	If probable mania, the RA must discuss this with the CI, local PI or clinical team with regards to whether there is a safety issue that necessitates urgent dose reduction or discontinuation. If it is deemed that there is no urgent safety issue, then the RA should provide the participant's clinical team with all the current rating scale scores and any other relevant information. If the clinical team deem that the participant is indeed suffering from a hypomanic or manic episode, then the recommendation is that the dose of study medication be cut or discontinued.

8.4.2. Tapering and Stopping

At the end of the trial or if a patient needs to stop medication for any reason, medication will be tapered. Trial medication must never be stopped suddenly. Dose reductions during tapering will be made at a rate of 0.25mg every 3 days. This will reduce the risk of developing dopamine withdrawal

syndrome which may be caused by abrupt withdrawal of dopaminergic therapy. Clinicians will receive further guidance for tapering as part of the Clinician Manual.

If a participant stops taking medication for any reason during the trial, week 49-52 schedule of assessments for tapering will be followed, with final safety assessment, including pregnancy test for women of child-bearing potential, when participant has been drug-free for 2 weeks.

8.5. Provision of Trial Medication

Supplies of medication in bottles of 56 tablets will be securely posted to participants' nominated addresses (which will usually be their home address) from the Sponsor (Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust) Pharmacy on receipt of a prescription, allowing approximately 5 working days to send each dispensing to the participant. Each supply will be posted via 'Signed For' delivery. The pharmacy will email the trial RAs to inform them the trial medication has been posted and provide tracking number for follow up. An RA will tell the participant by phone that the medication is in transit. Undelivered/uncollected prescriptions will be returned to the Sponsor Pharmacy via usual returns systems.

With each batch of trial medication, the participant will also receive a titration/dosage schedule. The schedule will indicate how many tablets to take each day.

The schedule will be explained to patients during the screening and randomisation contact, and by the RAs over the telephone. If subsequent dose changes need to be made, the participant will be provided with a revised schedule.

8.5.1. Prescriptions

Prescriptions for trial medication should be written by a member of staff delegated to do so on the site delegation log. Prescriptions should be written and sent to Sponsor Pharmacy by secure email to Ntawnt.paxbdprescriptions@nhs.net email address.

To maintain blinding of treatment allocation, trial medication is pre-labelled by ModePharma with a kit number. On randomisation of a participant, medication kit numbers for that participant will be provided on the Sealed Envelope system. These kit numbers must be included on trial prescriptions. For future prescriptions, the randomisation system must be used to assign new kit numbers to a participant for every dispensing.

Prescriptions should be sent to Sponsor Pharmacy as soon as possible following randomisation and then for future dispensings a minimum of 2 weeks before the participant requires the medication to allow adequate time for unforeseen circumstances, such as if medication is not delivered. For example, for medication that is required at the start of week 6, a prescription should be sent to Sponsor Pharmacy by the end of week 3.

At the end of week 3, some participants who have tolerated the higher doses may still be in the titration phase. The RA will feedback to local site staff on participant dose following the week 3 RA phone call. In the case that a participant is still in the titration phase at this point, dispensing 2 will

provide enough medication for the maximum dose of 2.5mg daily to be reached for those participants. For all other dispensings a dose will be specified on the prescription.

Prescription/Dispensing Schedule

<table>
<tr><th>Dispensing Number</th><th>Medication for Weeks:</th><th>Prescription to be written:</th><th>Medication Amount</th></tr>
<tr><td>1</td><td>Week 1- week 5 (5 weeks)</td><td>As soon as possible after randomisation</td><td>All participants will be prescribed and dispensed sufficient medication to cover the titration phase (weeks 1 – 4) and week 5, to reach any tolerated dose, up to a maximum dose of 2.5mg daily:

• 2 x 56 bottle of pramipexole/placebo 0.25 mg tablets
• 1 x 56 bottle of pramipexole/placebo 1 mg tablet</td></tr>
<tr><td>2</td><td>Week 6 – week 12 (7 weeks)</td><td>By end of week 3</td><td>Participants will either be:
a. Still titrating dose – Medication will be sent out to cover for up to the maximum dose of 2.5mg daily and the following medication will be prescribed:

• 3 x 56 bottle of pramipexole/placebo 0.25 mg tablets
• 2 x 56 bottle of pramipexole/placebo 1 mg tablet

b. Have reached their maximum tolerated dose. In this case the maximum tolerated dose will be entered into randomisation system and number of packs required will be calculated.</td></tr>
<tr><td>3</td><td>Week 13 – week 20 (8 weeks)</td><td>By end of week 10</td><td rowspan="4">Participants will be prescribed and dispensed a personalised amount of medication according to their personal dose, as determined by response and tolerability. The required dose will be entered into the randomisation system and number of bottles required will be calculated.</td></tr>
<tr><td>4</td><td>Week 21 – week 28 (8 weeks)</td><td>By end of week 18</td></tr>
<tr><td>5</td><td>Week 29 – week 36 (8 weeks)</td><td>By end of week 26</td></tr>
<tr><td>6</td><td>Week 37 – week 44 (8 weeks)</td><td>By end of week 34</td></tr>
<tr><td>7</td><td>Week 45 – week 52 (8 weeks)</td><td>By end of week 42</td><td>Participants will be prescribed and dispensed a personalised amount (rounded up to nearest bottle of 56 tablet) of medication according to their personal dose, as determined by response and tolerability, including sufficient medication for continuing or tapering in weeks 49-52. The required dose will be entered into the randomisation system and number of bottles required will be calculated.</td></tr>
<tr><td>Emergency/ extra dispensing</td><td colspan="3">Patients should not routinely require extra dispensings. Dose changes should be considered at the time of dispensing and this will then be reflected in their next prescription. If a participant requires extra medication for any reason throughout the trial (due to emergency tapering or lost medication) an extra prescription may be required. In this case, the PI should determine the minimum number of bottles of medication that are required and enter this into the randomisation system.</td></tr>
</table>

Taper and stop prescription and replacement medication

If a participant needs to discontinue medication for any reason throughout the trial or at the end of the trial, the PI/delegated clinician must ascertain if they have sufficient quantities of both strengths of medication to taper dose gradually as per section 8.4.2 Tapering and Stopping. If they do not this will need to be prescribed, kit codes generated using the randomisation system and a prescription (including kit numbers) sent to CNTW pharmacy as soon as possible indicating that it is a taper and stop prescription.

If medication needs to be replaced for any reason throughout the trial (e.g. lost medication), this will need to be prescribed, kit codes generated using the randomisation system and a prescription (including kit numbers) sent to CNTW pharmacy as soon as possible indicating that it is a replacement prescription.

8.6. Known Drug Reactions and Interactions

Plasma protein binding

Pramipexole is bound to plasma proteins to a very low (< 20%) extent, and little biotransformation is seen in man. Therefore, interactions with other medicinal products affecting plasma protein binding or elimination by biotransformation are unlikely. As anticholinergics are mainly eliminated by biotransformation, the potential for an interaction is limited, although an interaction with anticholinergics has not been investigated. There is no pharmacokinetic interaction with selegiline and levodopa.

Inhibitors/competitors of active renal elimination pathway

Cimetidine reduced the renal clearance of pramipexole by approximately 34%, presumably by inhibition of the cationic secretory transport system of the renal tubules. Therefore, medicinal products that are inhibitors of this active renal elimination pathway or are eliminated by this pathway, such as cimetidine, amantadine, mexiletine, zidovudine, cisplatin, quinine, and procainamide, may interact with pramipexole resulting in reduced clearance of pramipexole. Reduction of the pramipexole dose should be considered when these medicinal products are administered concomitantly with pramipexole.

Combination with levodopa

When pramipexole is given in combination with levodopa, it is recommended that the dose of levodopa is reduced and the dose of other anti-parkinsonian medicinal products is kept constant while increasing the dose of pramipexole .

Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with pramipexole (see SmPC section 4.4, 4.7 and 4.8).

Antipsychotic medicinal products

Coadministration of antipsychotic medicinal products with pramipexole should be avoided (see SmPC section 4.4), e.g. if antagonistic effects can be expected.

8.7. Concomitant Medications

Contraindications: Hypersensitivity to the active substance or to:

Mannitol (E421)
Maize starch
Silica, colloidal anhydrous
Povidone K30
Povidone K90
Magnesium stearate

8.8. Tolerability and Safety

Adverse effects: Participants will be provided with information about key (common and serious) adverse effects of pramipexole and given advice on when to seek medical attention. Common adverse effects include nausea, sedation and dyskinesias (unusual, involuntary movements). More serious effects include somnolence, sudden sleep onset and impulse control disorders.

Specific risk of impulse control symptoms associated with pramipexole:
Pramipexole, in common with other dopaminergic drugs, can induce impulse control symptoms (e.g. increased gambling, self-initiated escalation of dosage) in a sub-group of patients. The risks associated with this side effect will be mitigated in 4 key ways:

a) A history of impulse control problems is a strong predictor of the development of such symptoms with dopaminergic drugs. This is therefore an exclusion criterion and the Participant Information Sheet will clearly describe the potential for the medication to induce impulse control difficulties and state that potential participants who have experienced these problems in the past should not take part in the trial.

b) At screening, symptoms suggestive of previous impulse control disorders (including harmful alcohol or drug use, binge eating, gambling or sexual behaviours) will be assessed and potential participants with such symptoms will not be enrolled.

c) The QUIP-RS questionnaire will be completed regularly by participants and the scores will be reviewed by the trial RAs. This questionnaire is specifically designed to test for the presence of symptoms of impulse control difficulties (including increase in medication use). Participants showing an increase in this score (of 2 or more points from baseline) will trigger a clinical assessment by the local trial team. Where necessary these trial assessments will be supplemented by additional contacts as deemed necessary by the treating clinical team.

d) Excessive use of the trial medication will be monitored by RAs recording dose taken during the regular telephone contacts. Participants who are identified as inappropriately escalating the dose of the medication will (as for other impulse control disorders) be referred to the local clinical team for management of a monitored dose reduction

Tolerability: This will be judged by the clinical team, with guidance from the RAs providing details of rating scale scores (measured using the TSQM and QUIP-RS on True Colours, and supplemented by RA phone calls using further questions about psychosis and suicidality as needed) and reports of adverse effects. In addition, participants will be provided with the contact number for their Trial Site and asked to make contact should they develop any other side effects. Participants who are unable to tolerate an increased dose of pramipexole will be advised to reduce the dose to the highest tolerated.

Effects on ability to drive and use machines:
Participants will be informed in the Participant Information sheet that pramipexole can have a major influence on the ability to drive and use machines. Hallucinations or somnolence can occur.

Participants presenting with somnolence and/or sudden sleep episodes will be told to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved.

8.9. Assessment of Compliance

Participants will be taking trial IMP or placebo as part of the trial for up to a maximum of 52 weeks. IMP compliance will be checked via RA telephone calls. IMP compliance will be recorded centrally on eCRFs by the RAs in order to allow for ongoing accountability monitoring.

Unused medication will be returned by the study team (local CSO or equivalent) to CNTW pharmacy, or where this is not possible by the participant (see section 7.7.2 and 7.7.5). This should be returned using the prepaid envelope provided. The CNTW site can return unused trial medication by hand as they are based at the same site as CNTW pharmacy. All returned medication will be monitored by the NCTU Trial Managers and compared against the accountability records. If satisfied (with sponsor delegation) approval for secure destruction will be confirmed and documented by CNTW pharmacy. Trial technicians will complete paperwork to document details of the IMP/placebo returned, document when it has been destroyed, and retain copies of these records. The Trial Managers will perform and monitor IMP accountability for all sites.

8.10. Missed Doses

Participants will be provided with guidance regarding the management of their medication and what action to take if doses are missed in the form of the Participant Diary (the diary will include the titration schedules and additional guidance).

Participants will be advised that if they forget to take a dose, but remember within 12 hours of the usual time, they should take the dose straightaway, and then take the next dose at the usual time. If they forget for more than 12 hours, they should only take the next single dose at the usual time. Participants should not take a double dose to make up for a forgotten tablet dose.

If a participant misses any doses, up titration decisions will require a participant to have demonstrated at least three consecutive days of 100% patient compliance immediately prior to up titration. If necessary, the treating clinician may instruct participants to remain at their current dose level for an

appropriate amount of extra days before up titrating to the next dose level if compliance is below this level to ensure compliance is met. Participants will be instructed to consult the PI and /or local treating team for advice before up titrating under these circumstances if side effects/adverse events are experienced during the extra days.

8.11. **NIMPs**

The mood stabilisers used in the trial (lithium, lamotrigine, valproate, carbamazepine) are classified as non-Investigational Medicinal Products (nIMPs). These are licenced products, so section 4.8 of the SmPCs serve as their Reference Safety Information. The mood stabilisers in this trial will be dispensed to participants in accordance with a prescription given by an authorised healthcare professional and labelled with a standard dispensing label. Clinical trial labelling is not required, in this case.

9. PHARMACOVIGILANCE

9.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward or unintended response in a participant to an Investigational Medicinal Product (IMP) that is related to any dose administered to that participant. The phrase "response to an IMP" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions
Reference Safety Information (RSI)	The RSI is a list of medical terms detailing the ARs that are expected for an IMP and must be referred to when assessing a SAR for expectedness.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening* • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences * Life threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based upon the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the approved Reference Safety Information.

9.2. Adverse Events (AEs)

Adverse events will be recorded by trial RAs for all participants from the date of consent to the pre-randomisation phase until the participant's final trial assessment (at week 48 (placebo only) or week 52 + up to 2 weeks (IMP or placebo)), or until participant withdraws. Participants will be asked about AEs at each scheduled telephone call from RAs. During the post-randomisation phase, this will include an open ended question "Have you experienced any effects which may be side-effects of the trial drug" and specifically asked about:

- blurred, double or compromised vision
- features of postural hypotension, i.e. dizziness on standing, weakness, fainting and nausea.

Participants will also be asked if they have had any hospitalisations as a result of any adverse events.

Participants will be reminded during RA phone calls to discuss any symptoms with their clinical care team.

Eye symptoms during the post-randomisation phase should prompt review of the patient by the local clinical care team, including a review of drug dosage by the site PI or medical delegate, in consultation with the CI, if required.

Adverse event line listings will be reviewed by the trial DMC, with pre-randomisation phase and randomisation phase data reported separately.

9.3. Recording and Reporting Adverse Events (AEs)

AEs will be recorded on the trial's MACRO™ system by the trial RAs. Line listings of all AEs for a participant will be sent to the site PI/delegated clinician for assessment 4 weekly during the pre-randomisation phase, then at weeks 2, 8 and 12, and then 4 weekly until the participant's final trial assessment. Sites will be asked to include line listings of AEs including the assessment in patient medical records.

9.4. Assessment of Adverse Events (AEs)

The trial RAs are responsible for the identification of any AE as defined in the protocol. Each AE must be assessed for **severity (9.3.1), seriousness (9.3.2).** AEs occurring after the participant starts taking trial medication must also be assessed for causality (9.3.3).

9.4.1. Assessment of Severity

Each AE must be assessed for severity by PI/delegated clinician. The following definitions should be used:

- Mild
- Moderate
- Severe

9.4.2. Assessment of Seriousness

The PI/delegated clinician must make an assessment against the standard definition in the Safety Reporting Definitions section 9.1.

The RA may make an initial assessment of seriousness following the phone calls with participants in the interests of timely reporting of SAEs but this assessment must ultimately be confirmed by the PI/delegated clinician.

9.4.3. Assessment of Causality

All AEs occurring from the date the participant starts taking trial medication until the participant's final trial assessment (week 48 (placebo only) or week 52 + up to 2 weeks (IMP or placebo)), or participant withdraws, must be assessed for the relationship to pramipexole by the PI/delegated clinician. If there is any doubt, the CI may be consulted. The following definitions should be used:

Yes (related)	The event is considered related to pramipexole
No (unrelated)	The event is not considered related to pramipexole
Unable to Determine	After review of the information the PI/delegated clinician is unable to determine if the event is related to pramipexole or not

9.5. Reporting of SAEs

SAEs occurring before the date the participant starts taking trial medication will be recorded on trial's MACRO™ system.

All **SAEs** occurring from the date the participant starts taking trial medication until the participant's final trial assessment (week 48 (placebo only) or week 52 + up to 2 weeks (IMP or placebo)), or participant withdraws, must be reported to the NCTU on an SAE Form, and recorded in the patient medical records. All corresponding AEs will be recorded by trial RAs in the trial's MACRO™ database and marked as serious.

If participant withdraws from the study due to an SAE, the site team will continue to follow up the event until the SAE has resolved or stabilised.

For **SARs**, investigators are still required to report any SARs for trial participants they become aware of for the duration of the study (i.e. LPLV).

SAEs/SARs occurring from the date the participant starts taking trial medication until the participant's final trial assessment (week 48 (placebo only) or week 52 + up to 2 weeks (IMP or placebo)), or participant withdraws, must be reported to the Newcastle Clinical Trials Unit immediately but **no later than 24 hours** after the RA/site learn of its occurrence using the SAE Report Form.

Initial Report: if necessary can be made by telephone or email to Newcastle Clinical Trials Unit. The RA/PI or designee must then complete the agreed initial Report Form and send via secure system to Newcastle Clinical Trials Unit / CI / nominated Sponsor contact.

Follow Up Report: In the case of incomplete information at the time of initial reporting, or follow up information, a follow up Report Form must be completed and sent via the secure system as soon as possible. All SAEs will be tracked until they are resolved.

Please send the completed and signed SAE report form(s) using the PAX-BD secure email address:

FAO PAX-BD TRIAL MANAGER to: nctu.PAXBD.SAE@nhs.net

For each SAE the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Severity
- Action taken
- Outcome
- Seriousness criteria
- Causality in the opinion of the investigator
- Whether the event is considered expected or unexpected in accordance with the approved Reference Safety Information (RSI) if a causal relationship is suspected.

Any change of condition or other follow-up information should be submitted securely as soon as it is available. Events will be followed up until resolution or a final outcome has been reached, or until the end of the study.

9.5.1. Assessment of Expectedness

All SARs (SAEs determined as having a reasonable suspected causal relationship to pramipexole) must be assessed for expectedness.

The assessment of expectedness will be initially performed by the PI/delegated clinician using the MHRA approved RSI for the trial (see section 8.1.1 Reference Safety Information) and reviewed by the CI.

In the event of a SAR, which is thought to have occurred due to a reaction of another medicinal product with the IMP, please also ensure to check section 4.5 'interaction with other medicinal products and other forms of interaction', of the SmPC detailed in section 8.1.1.

9.6. Recording and Reporting SUSARs

All SARs assessed as unexpected by the CI must be reported to the MHRA and REC as SUSARs. In the UK, the trial Sponsor is responsible for reporting SUSARs to the MHRA and REC.

To ensure adherence with the required reporting timeframes, sites must notify NCTU of SARs immediately but no later than 24 hours after becoming aware. Information should be submitted via secure e-mail to nctu.PAXBD.SAE@nhs.net or via secure transfer methods. NCTU will be responsible for ensuring that the CI reviews the expectedness assessment to determine if a SAR is unexpected and requires reporting as a SUSAR. The reporting timeframe starts at day 0 when the Sponsor is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (sponsor reference)

- EudraCT number
- Patient trial number and date of birth
- Name of IMP(s)
- Date of notification of the event
- Medical description of the event
- Date and time of the onset of the event (including event end date if applicable)
- Causality assessment
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g. Principal Investigator)

The site is expected to co-operate fully with NCTU and sponsor staff, to ensure that a full and detailed report is submitted to the MHRA and REC within the required timelines.

SUSARs which are determined as fatal and life-threatening must be sent to the MHRA within 7 calendar days of notification (with a further 8 days for follow up information).

Non-life threatening SUSARs must be reported no later than 15 calendar days with any relevant follow-up information sought and reported as soon as possible after the initial report.

SUSARs are reported directly to the MHRA by the sponsor using the electronic SUSAR form via the eSUSAR website. A copy of the electronic form and the CTIMP safety report will be sent to the REC in line with sponsor standard operating procedures.

9.7. Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, the NCTU must be notified immediately (and within 24 hours of becoming aware) and details of the USM given. In the UK, the CI and NCTU must inform the MHRA and the NHS REC in accordance with the Sponsor's standard operating procedures.

9.8. Development Safety Update Report

In the UK, a Development Safety Update Report (DSUR) will be submitted to the MHRA and NHS REC once a year on the anniversary of the Clinical Trial Authorisation date. NCTU must ensure that the report is submitted within 60 days of the end of the reporting period. The Trial Management Group must contribute to the compilation of the DSUR and the CI must review and authorise the final report before it is ready for submission. The DSUR should also be reviewed by the NCTU QA Manager and sponsor Representative prior to submission. NCTU staff will prepare and submit Development Safety Update Reports (DSURs) for the trial, in accordance with NCTU SOPs.

Submission of relevant safety reports equivalent to the DSUR for all non-UK competent authorities will be delegated to the trial site as per local reporting procedures, with oversight from NCTU and Sponsor.

9.9. Responsibilities

9.9.1. Chief Investigator

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit
- Period review of line listings of AEs (including SAEs) for all study participants
- Using medical judgement in assigning seriousness and causality of SAEs where it has not been possible to obtain local medical assessment
- Using medical judgement in assigning expectedness to SARs in line with the RSI
- Immediate review of all SUSARs
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol
- Review/assignment of Medical Dictionary for Regulatory Activities (MedDRA) or body system coding for all SAEs and SARs
- Preparing the clinical sections and final sign off of the DSUR.

9.9.2. Principal Investigators

- Checking for AEs and ARs (delegated to RAs)
- Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness of events using the RSI approved for the trial
- Ensuring that all SAEs and SARs, including SUSARs, which occur after the date the participant has started study medication, are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol
- Ensuring that a record of all AEs/SAEs is maintained in participant medical notes

9.9.3. RAs

- Checking for new AEs and following up on ongoing AEs during phone calls to participants
- Documenting reported AEs in the trial's MACRO™ database
- Sending line listings of AEs to site PIs/delegate for assessment
- Completing initial report form within 24 hours of becoming aware of SAEs identified during phone calls to participants, which have occurred after the date the participant started taking study medication

9.9.4. Sponsor

- Data collection and verification of AEs, ARs, SAEs, SARs and SUSARs onto a database (may be delegated to NCTU)
- Reporting safety information to the independent oversight committees for the ongoing assessment of the risk/benefit ratio throughout the life of the trial (may be delegated to NCTU*).*
- Assessment of expectedness of any SUSARs (may be delegated to the CI)
- Expedited reporting of SUSARs to the CA and REC within required timelines

- Notification of all investigator sites of any SUSAR that occurs (may be delegated to NCTU)
- Reviewing RSI at least annually and notification of PIs of any required updates. (may be delegated to NCTU)
- Preparing tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC. (may be delegated to NCTU)

9.9.5. DMC/TSC

- Review of safety data collected to date to identify any trends

9.10. Notification of Deaths

Should a site staff member/RA become aware of the death of a participant, this should be notified to the NCTU as an SAE immediately. This will form the notification of death to the Sponsor.

9.11. Pregnancy Reporting

In the event of a trial participant becoming pregnant while in the trial, site staff must notify the NCTU, CI and Sponsor representative within 24 hours of becoming aware of the pregnancy using the pregnancy reporting form. Initial notification can be by telephone to the Trial Manager. If RAs become aware of a trial participant becoming pregnant while in the trial, they will alert the site PI and patient's local clinical team.

Female participants of child-bearing potential will be asked at the start of the trial to provide consent to follow the pregnancy to completion, should they become pregnant during the trial. This will comprise regular telephone calls to the participant, and documentation of the outcome of the pregnancy, and any AEs, in the ISF and patient medical notes.

9.12. Contraception and Pregnancy

The effect of pramipexole on pregnancy has not been investigated in humans but the advice in SmPC for several brands of the medication is that it should not be used during pregnancy unless clearly necessary. Pregnancy, lack of agreement by females to use effective contraception and lactation are all exclusion criteria and the Participant Information Sheet will advise females to contact the local trial team immediately should they become pregnant during the trial. Advice on tapering pramipexole will be given and alternative treatment provided if indicated. Participants who become pregnant will be followed up until the end of the pregnancy and any complications or other adverse events experienced by mother and/or baby reported as required.

9.13. Overdose

Standard NHS procedures at trial sites will be followed to identify, notify and follow up any overdose.

There is no clinical experience with massive overdose. The expected ARs would be those related to the pharmacodynamic profile of a dopamine agonist, including nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. If signs of central nervous system stimulation are present,

an antipsychotic agent may be indicated. Ideally use one that has high affinity for dopamine D3 receptors as well as D2, such as haloperidol or amisulpride, or one with moderate D3 affinity such as chlorpromazine, olanzapine or risperidone. Management of the overdose may require general supportive measures, along with gastric lavage, intravenous fluids, administration of activated charcoal and electrocardiogram monitoring.

Any instance of a trial participant taking more medication than listed on the dose schedule should be reported as a protocol deviation and the PI/delegate should assess whether participant is suitable to stay in the study. Multiple overdoses would be assessed by the trial Sponsor as to whether they constituted a serious breach.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size

Due to the high proportion of people with BD currently taking antipsychotics(11), PAX-BD requires a pre-randomisation phase to allow for tapered discontinuation of antipsychotics, as a well as commencement of non-antipsychotic mood stabiliser medication (lithium, lamotrigine, valproate, carbamazepine), where necessary. We anticipate a 30% drop out during this pre-randomisation phase based on the experience in the BALANCE study in BD run primarily in the UK (63). This study required patients to be switched onto lithium and valproate over a 4-8 week period and then be randomised to have one or other or neither.

We have estimated dropout rates during the randomised phase on the basis of the CEQUEL study (54) which is the closest in nature to the proposed PAX-BD study on the basis of the nature of the patients (suffering from a depressive episode in the context of BD and with a clinical decision that a change in medication was required), the remote collection of data and the timings of the primary and final data collection points (12 and 52 weeks respectively). Dropout rates in CEQUEL were 20% at 12 weeks and 50% at 52 weeks (54).

Our power calculation has been conducted based on a 2-sample t-test at 12 weeks detecting a 3 point difference in QIDS-SR between drug and placebo (at $p < 0.05$) with a QIDS-SR standard deviation of 7 based on QIDS-SR data at the 12 week time point in CEQUEL (54). 3 QIDS-SR points equates to Cohen's $d=0.4$ (considered clinically meaningful (40). We require 232 (116 per arm) patients to complete the study meaning **a sample size of 290 at randomisation gives a power of 90%**, assuming a 20% dropout rate at 12 weeks as described above. It also provides an 80% power of detecting a 3.3 point QIDS-SR difference between drug and placebo at 48 weeks assuming the 50% dropout rate seen at 52 weeks in CEQUEL (54) is representative, and using the above standard deviation estimate as the most appropriate available

The minimum possible number of participants will be recruited to the pre-randomisation phase to enable randomisation of a minimum of 290 participants. Given our estimate of a 30% drop out during the pre-randomisation phase, we estimate that an initial population of 414 patients will be required for the pre-randomisation phase. Recruitment to the pre-randomisation phase will stop when 290 participants have been randomised. When the trial closes to recruitment, participants in the pre-randomisation phase will continue to be randomised, if confirmed as eligible for the post-randomisation stage. Randomisation will close 3 months after the trial closes to recruitment.

10.2. Analysis Population

Analysis will be undertaken when all 48 week data is available and will be carried out initially on an intention to treat (ITT) population but consideration will be given to per protocol analyses in addition should a population defined in this way deviate sufficiently from the ITT population; for example should the study drug be discontinued post 12 weeks.

10.3. Statistical Analyses

10.3.1. Analysis of the Primary Outcome Measure

Analysis of the primary outcome measure of QIDS-SR at week 12 will use analysis of covariance (ANCOVA) to examine the difference between the trial arms with adjustment for baseline covariates including initial QIDS-SR score, other minimisation factors and anxiety (GAD-7) score. Other baseline covariates will be examined for potential inclusion during the modelling process. A two sided significance level of $p<0.05$ will be used throughout.

Other unadjusted analyses, such as the t-test for the difference in mean QIDS-SR between the arms, will also be undertaken and reported.

10.3.2. Analysis of Secondary Outcome Measures

Secondary outcomes include the QIDS-SR scores at weeks 6, 24 and 48.
Additionally, weekly repeated measures scores for QIDS-SR will be examined to ascertain patient compliance in completion. Should this be judged sufficient, a mixed effects linear regression model will be used to account for the repeated measures over time in comparing this outcome between the randomised groups.

Other secondary outcome measures include:

- The proportion of participants in remission at 12 and 48 weeks (defined as a QIDS-SR score of ≤ 5)
- The proportion of participants who have achieved a response at 12 and 48 weeks (defined as QIDS-SR score reduction of ≥50% from the Baseline measure at week 0.
- Proportion of time over 48 weeks that participants are free of depressive symptoms (QIDS-SR ≤ 5)
- Proportion of time over 48 weeks that participants are free of manic symptoms (ASRM ≤ 5)
- Changes in psychosocial function (WSAS)

Secondary outcomes, other than those collected specifically for the health economic analysis, will be analysed in a similar manner to the primary outcome as described above with the use of appropriate ANCOVA or regression techniques. The ASRM and GAD-7 scores will also be examined on a weekly basis as described for the QIDS-SR previously with the use of YMRS, SHAPS, MADRS and QIDS-C between 0 and 12 weeks will be examined in a manner analogous to the primary analysis of the primary outcome.

Safety and tolerability assessments will include ANCOVA of TSQM and QUIP-RS scores, co-varying for baseline score and GAD-7 anxiety scores given the impact of anxiety on tolerability and reported side effects with medication. Additionally, tolerability will be assessed through an examination of AEs, SAEs and SUSARs, including those related to expected side effects of pramipexole such as symptoms of low blood pressure symptoms.. Safety data collected after 48 weeks will be reported as unblinded, uncontrolled data only.

Levels of missing data will be described and baseline values tabulated for those for whom the primary end point can and cannot be calculated in order to summarise any characteristics related to missingness. Data with missing observations due to participant withdrawal or loss to follow-up will be examined to determine both its extent and whether it is missing at random. It is likely that missingness will be related to the outcome itself with depressed patients less likely to complete assessments. However it has been suggested that even when non-random, a valid approach is to assume

randomness since results tend to remain stable when randomness is violated. The primary analysis will utilise complete case analysis with covariate adjustment. This yields similar results to multiple imputation in data that are missing randomly, as long as predictors of missingness are included. If data are missing to a sufficient extent (e.g. between approximately 10% and 20%), the use of appropriate multiple imputation techniques will be considered. The QIDS-SR is assessed weekly. For the primary analysis, the assessment closest to 12 weeks in the range 10-14 weeks will be employed. Missing items from a partially completed TQSM questionnaire will be handled as described in the scoring manual.

Full details of all statistical analyses will be specified in a pre-defined statistical analysis plan (SAP) finalised prior to data lock and analysis commencing.

10.3.3. **Interim Analyses and Criteria for the Premature Termination of the Trial**

There are no formal interim analyses planned except for snapshots reported to DMC. There are no formal statistical stopping rules.

11. HEALTH ECONOMIC ANALYSIS

The main health economic analysis will include: (i) a detailed patient-level cost analysis of health, social care and other broader societal costs for both the pramipexole and placebo arms of the study and (ii) an incremental within-trial economic evaluation comparing the pramipexole and placebo arms of the trial in terms of their costs and outcomes over the 48 weeks trial follow-up period.

The cost analysis will be based on resource use data collected as part of a bespoke Health Economics Questionnaire (HEQ) whose development was based on previous versions of the Client Service Receipt Inventory (CSRI) instrument (59;60), a widely-used and validated instrument for collection of resource use data in mental health. Collected data will include all hospital and community health and social services, medication, productivity losses, informal care and patient's travel expenses. Costing will be conducted using national-level unit costs from the UK for a common year, e.g. PSSRU Unit Costs Database (64) and BNF (65). Lost productivity costs due to absenteeism or presenteeism will be estimated using the human capital approach where time off work is multiplied by the average daily national salary for participants who are employed or self-employed (66, 67).

The primary health economic analysis will be a cost-utility analysis from a health and social care perspective where quality-adjusted life years (QALYs) will be calculated using utility values from the EQ-5D-5L health-related quality of life questionnaire as recommended by most health technology assessment agencies (68, 69, 70). Health states will be valued by using the common tariff set from the UK and results will be expressed in an incremental cost-effectiveness ratio (ICER). Secondary economic analyses using the ICECAP-A (61) and the OxCAP-MH (50) capability indices as outcome measures will be also carried out. The capability states measured by the ICECAP-A will be valued by the tariff set for the UK (71). A similar tariff weighting score concept will be developed for the OxCAP-MH alongside this trial and will subsequently be applied in the valuation of the dataset. Further analyses will estimate cost-effectiveness from a societal perspective.

All economic analyses will be on an intention-to-treat basis. Relevant outcome and resource use data will be collected electronically from participating patients at pre-defined time points throughout the trial (pre-randomisation and weeks 0, 12, 24, 36, 48). Data on HEQ, EQ-5D-5L, ICECAP-A and OxCAP-MH will be collected on six occasions via the True Colours clinical platform, and can be completed using any internet-enabled device (computer, tablet or smartphone) in the clinic or remotely. The questionnaires will be filled out by the estimated 414 patients at the pre-randomisation phase, i.e. four weeks prior to randomisation. Participants will subsequently complete the Health Economic questionnaires at randomisation and then at 12 weekly intervals, as per trial protocol.

Missing data will be reported and their potential impact on the results in contrast to the complete cases dataset will be investigated in a sensitivity analysis using multiple imputation based on the missing at random assumption (72, 73). Further sensitivity analyses will address the potential impact of uncertainties in unit costs and outcomes.

Results will be reported as means with standard deviations or as mean differences with 95% confidence intervals. Differences in mean costs and effects will be compared in a regression framework with a p-value less than 5% considered as statistically significant. Non-parametric

bootstrapping (74) from the cost and effectiveness data will be used to generate a joint distribution of the mean incremental costs and effects for the options under comparison and to calculate the 95% confidence intervals of the incremental cost-effectiveness ratios (ICERs). Uncertainty around the main cost-effectiveness estimates will be represented by cost-effectiveness acceptability curves (CEACs) using the net benefit approach (75; 76). CEACs show the probability that each option is cost-effective to a range of maximum values (ceiling ratio) that a decision maker might be willing to pay for an additional unit of improvement in outcomes. All analyses will be carried out in Excel (Microsoft Office 2013) and STATA (StataCorp, College Station, Tex., USA).

12. QUALITATIVE ANALYSIS

The qualitative analysis will be based on interviews with patients and PIs and will be used to assess barriers and facilitators to recruitment and acceptability of study procedures. Analysis of barriers and facilitators will specifically draw on a meta-analysis of studies in depression, providing a framework for the qualitative interview. Specifically, the framework is as follows:

Barriers to recruitment of patients

1. Expression of depression symptoms
   Presentation, endorsement and impact of depression symptoms.
2. Risk of trial to mental health
   Participation would be depressing or anxiety provoking.
3. Stigma
   Perceived stigma, self-stigma – weakness or vulnerability associated with mental illness, moral judgement e.g. not ill just lazy, craziness.
4. Protecting the vulnerable patient
   Clinician concerns about the capacity of depressed patients to provide valid informed consent, concerns of clinicians about the welfare of patients being experimented on, patients perceived to be “too depressed” to take part in a research trial.
5. Presenting depression trials to patients.
   Particular difficulties introducing research in a depression consultation, clinician skills, confidence and experience in introducing the trial to patients.
6. Treatment preferences.
   Strong patient or clinician preferences for particular trial treatments, negative views about one or more treatment options in the trial, objections to randomisation.
7. Views of trial processes and procedures.
   Inconvenience faced by participants, especially when patients have low motivation, poor concentration, planning and memory, high levels fatigue or high social anxiety.

Facilitators of recruitment of patients

1. Access to services to meet mental health need.
   Gaining additional resources and trial being perceived as offering a service.
2. Altruism
3. Marketing.
   Active promotion of trial to patients and gatekeepers.
4. Trust
   In research teams and referrers, endorsement by valued individuals and organisations.

13. DATA HANDLING

13.1. Data Collection Tools and Source Document Identification

Clinical and safety data for the trial participants will be collected by local site staff, trial RAs and CSOs/equivalent and recorded in the electronic case report form (eCRF) of the clinical data management system MACRO™ of the trial and on the trial Participant Schedule spreadsheet. Participant identification on the eCRFs and Participant Schedule Spreadsheet will be through a unique trial identifier number.

Primary outcome data, in the form of answers to all trial questionnaires (Health Economic and otherwise) will be entered directly by the trial participants into the University of Oxford True Colours online platform. Participants will receive login details in the form of a username and password at the start of the trial, and will change their password to something that only they know. Participants will also receive reminders to complete the questionnaires, throughout the trial.

Medication compliance, safety data and concomitant medication data will be recorded in Participant Diaries, which will be held by participants for the duration of the trial and collected in at the end of the trial for archiving with the ISF at trial sites.

Data Handling and Record Keeping

Overall responsibility for data collection lies with the Chief Investigator. Data will be handled, computerised and stored in accordance with the Data Protection Act 2018. Paper copies of trial related documentation will be annotated, signed and dated, and filed in the medical notes. The overall quality and retention of trial data is the responsibility of the Chief Investigator. All trial data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

13.2. Data Integrity

Participants will not be routinely unblinded at the end of the trial to ensure scientific integrity of trial data. If desired, site PIs/ delegated clinicians can contact the trial management team after study data lock to unblind participants at this point.

It is recognised that participants who wish to continue taking pramipexole after the end of the study, should they be found to be receiving it, are required to be unblinded prior to study data lock. The following points ensure as far as possible that the data is not changed or influenced following unblinding for these participants.

- Unblinding will take place after week 48 assessments.
- Primary outcome data is participant reported through True Colours and cannot be edited after questionnaire submission. Similarly, all secondary outcome data and health economics data is participant reported through True Colours.
- Secondary outcome safety and acceptability data is partially participant reported through True Colours. Non-participant recorded outcomes of reported dose taken, are collected up to 48 weeks and due to the short timeframe in which unblinding must take place, cannot practically be frozen prior to unblinding. However, these are objective measures that will not

be affected by unblinding. It is also accepted that it will not be possible to freeze all adverse event data prior to unblinding due to this short timeframe. SAEs will be reconciled on an ongoing basis from the start of the study.

- Any changes to study data in the MACRO database (e.g. to correct errors in data entry) will be fully documented and justified with an audit trail being available.
- Comparison Analysis data collected by phone at week 12 (YMRS, MADRS and QID-C) will be frozen prior to week 48.

13.3. **Access to Data**

Staff involved in the conduct of the trial, including the PI, trial management team and NHS staff involved in screening and intervention will have access to the Investigator Site File.

The trial data and patient medical records may be looked at by monitoring or auditing personnel from Research Ethics Committee (REC) or Medicines and Healthcare products Regulatory Agency (MHRA), or the Sponsor.

Password limited access, restricted to own particular role and site, to the trial's MACRO™ database will be granted to site's PIs and their delegated data entry personnel at these sites. Central trial RAs will have access to the trial's MACRO™ database for all sites for data entry purposes. NCTU trial management team will also have access to the trial's MACRO™ database for all sites for monitoring purposes. Trial RAs will have access to the Participant Schedule spreadsheet.

Clinical information shall not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, the DMC or the REC. Secure anonymised electronic data will be released to the trial statistician for statistical analyses. The PI and trial site staff involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial.

Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

Access and management of the systems True Colours will be controlled and monitored by the online platforms providers. Trial RAs and data manager will have administrative access to True Colours system.

13.4. **Archiving**

Data will be archived in accordance with the NCTU SOP and European Commission Directive 2005/28/EC Article 17. Essential data will be retained for a period of at least 5 years following close of trial in line with sponsor policy and the latest Directive on GCP (2005/28/EC). Archiving will be authorised by the Sponsor following submission of the end of trial report. Authorisation will be requested from the Sponsor to destroy the documentation at the end of the archiving period.

14. MONITORING, AUDIT & INSPECTION

The trial may be subject to audit by Sponsor representatives or inspection by the MHRA or NIHR HTA. Each investigator site will permit trial-related monitoring, audits and regulatory inspection including access to all essential and source data relating to the trial.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Research Ethics Committee Review and Reports

NCTU staff will obtain a favourable ethical opinion from an NRES Committee (REC) prior to the start of the trial. All parties will conduct the trial in accordance with this ethical opinion.

NCTU staff will notify the REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or Participant Information Sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. NCTU staff will notify the REC of any serious breaches of GCP or the protocol, USMs or SUSARs that occur during the trial.

An annual progress report will be submitted each year to the REC by NCTU staff until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

NCTU staff will notify the REC of the early termination or end of trial in accordance with the required timelines.

15.2. Peer Review

The trial has undergone Peer review through the process of grant application and funding award by the NIHR HTA Panel.

15.3. Public and Patient Involvement

Patients and carers, including from a Bipolar Support Group, contributed to the selection of the outcome measures used in the trial and to the trial planning. Feedback from the PPI group on ethical issues contributed to the grant application; in particular, to the lay summary. PPI representatives will be invited to join the TMG, TSC and DMC. A trial PPI group has been set-up and has inputted to the trial protocol and commented on the trial documents, e.g. Participant Information Sheets. The PPI group will meet throughout the trial, including to review both the quantitative and qualitative data from the internal pilot trial. This group will provide an opinion and recommendations to the TSC and DMC. Lay representatives are also keen to be involved in the dissemination of findings from the trial to patient and lay groups, including via Northern Centre for Mood Disorders (NCMD) events.

Trial participants will receive a £25 gift voucher at 12 weeks, 36 weeks and 52 weeks as a gesture of thanks for participating in the study.

15.4. Regulatory Compliance

The trial will be conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. All parties must abide by these regulations and the ICH GCP guidelines.

NCTU staff will obtain a Clinical Trial Authorisation (CTA) from the MHRA prior to the start of the trial and will notify the MHRA of any substantial amendments that require review by the competent authority. These substantial amendments will not be implemented until the MHRA has issued an acceptance of the amendment.

The sponsor will notify the MHRA of any serious breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial.

The Development Safety Update Report will be submitted each year to the MHRA by NCTU staff, until the end of the trial.

NCTU staff will notify the MHRA of the early termination or end of trial in accordance with the required timelines.

15.5. Protocol Compliance

It is the responsibility of the CI to ensure that the clinical investigation is run in accordance with GCP and the protocol. Study tasks may be delegated to a suitably qualified or experienced member of the research team but the CI and PI will retain overall responsibility for adherence to protocol and GCP. The trial will be monitored by NCTU staff, to measure protocol compliance and manage deviations. Site staff and RAs are responsible for compliance with the protocol in their everyday trial activities, and must report anything that they feel constitutes an AE, SAE, SUSAR, protocol deviation, serious breach, anything that requires an USM, or anything else that should be reported and documented between monitoring visits.

Protocol deviations, non-compliances or breaches are departures from the approved protocol. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

Deviations from the protocol and GCP occur in clinical trials and the majority of these events are technical deviations that are not serious breaches. These events must be documented on the protocol deviation log, including the relevant Corrective and Preventive Actions (CAPA) required.

Deviations that are found to frequently recur at a site are not acceptable and could be classified as a serious breach.

15.6. Notification of Serious Breaches to GCP and/or the Protocol

Any violations must be reported to NCTU within 3 days of awareness. The trial manager will notify the sponsor of all violations as soon as they become aware of them. Violations will be reviewed to determine if they meet the criteria for a serious breach. Where a serious breach has been identified,

it is the responsibility of the Sponsor to notify the REC and MHRA within **7 calendar days** of determining that a serious breach has occurred.

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial, or
(b) the scientific value of the trial

15.7. Data Protection and Patient Confidentiality

The trial will be run in accordance with the Data Protection Act 2018, to maintain the confidentiality of trial participants and trial data integrity.

15.8. Indemnity

NHS indemnity for clinical trials conducted with NHS permission will apply for clinical negligence that harms individuals towards whom the NHS has a duty of care. Indemnity in respect of protocol authorship will be provided through a combination of NHS schemes (for those protocol authors who have substantive NHS employment contracts) and through Newcastle University's public liability insurance (for those who have their substantive contracts of employment with the University). There is no provision for indemnity in respect of non-negligent harm.

15.9. Amendments

It is the responsibility of the Sponsor to determine whether an amendment is substantial or not and trial procedures must not be changed without the mutual agreement of the CI, Sponsor and Trial Steering Committee.

Substantial amendments will be submitted to the REC and/or MHRA (as appropriate) and will not be implemented until this approval is in place. It is the responsibility of NCTU staff to submit substantial amendments.

Non-substantial amendments will be submitted to the Health Research Authority (HRA) and will not be implemented until authorisation is received.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS R&D Departments for notification, to determine whether the amendment affects the NHS permission for that site. Amendment documentation will be provided to sites by NCTU staff.

15.10. Access to the Final Trial Dataset

In accordance with Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, Government and NIHR policies, non-identifiable research data may be shared with researchers in other Universities and organisations (including those in other countries), for research in health and social care. If there is a need to share identifiable information, explicit consent will be sought from participants. Appropriate safeguards will be in place where any identifiable information is

transferred to other countries, in particular those countries with different data protection laws to the UK.

We are committed to sharing de-identified individual level data, where a rigorous research question may be answered by those data. The research team, including NCTU staff and the CI, will consider proposals from researchers as long as there is no constraint due to:

- Ethical approval and informed consent
- The NIHR contract
- The request does not require the data prior to publication of the main trial findings
- The request for data does not extend beyond that which is needed to answer the specific research question.

The CI is nominated by the sponsor to take responsibility, as custodian of the data.

16. DISSEMINATION POLICY

Dissemination to the academic community will include a final report for the funders, as well as findings presented at international scientific meetings and submitted for publication in high-impact open-access peer-reviewed journals.

Dissemination to clinicians will include web-based information on the Northern Centre for Mood Disorders (NCMD) web site (http:\\mood-disorders.co.uk\PAX-BD), with links to this from all Universities and Trusts involved in the trial and verbal presentations at meetings such as those organised by the British Association of Psychopharmacology (BAP) and the Royal College of Psychiatrists (RCPsych).

The research findings will be disseminated to Clinical Commissioning Groups via the CI and PI links as clinicians within regionally facing specialist mood disorders services.

The findings will be supplied to the two main pharmacological treatment guidelines used by clinicians in the UK: those produced by NICE and the BAP.

The trial results will be disseminated to patients and carers in partnership with our patient advisory group. We will produce a leaflet explaining the findings of the trial and their implications. We will utilise both the NCMD website and the regular two-monthly NCMD public engagement events to promote and disseminate this leaflet. Dissemination will also be via the patient organisation Bipolar UK and Bipolar Scotland and to the general public e.g. via the Science Media Centre. The results will also be disseminated to the Drug and Therapeutics (or equivalent) Committee of each participating Trust via the local PIs. Trial results may also be disseminated using social media to access a wider audience.

17. REFERENCES

1 Clemente AS, Diniz BS, Nicolato R, Kapczinski FP, Soares JC, Firmo JO, et al. Bipolar disorder prevalence: a systematic review and meta-analysis of the literature. Rev Bras Psiquiatr 2015 Apr;37(2):155-61.

2 Kessing LV, Vradi E, Andersen PK. Life expectancy in bipolar disorder. Bipolar Disord 2015 Aug;17(5):543-8.

3 National Institute for Health and Care Excellence. Bipolar disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. 2006. https://www.nice.org.uk/guidance/cg185

4 Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002 Jun;59(6):530-7.

5 Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003 Mar;60(3):261-9.

6 National Institute for Health and Care Excellence. Bipolar disorder: Assessment and management. NICE Guidelines 2014;CG185.

7 Calabrese JR, Keck PE, Jr., Macfadden W, Minkwitz M, Ketter TA, Weisler RH, et al. A Randomized, Double-Blind, Placebo-Controlled Trial of Quetiapine in the Treatment of Bipolar I or II Depression. Am J Psychiatry 2005 Jul;162(7):1351-60.

8 Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 2003 Nov;60(11):1079-88.

9 Prescribing Observatory for Mental Health (2016). Topic 15a baseline audit report. Prescribing valproate for bipolar disorder. Prescribing Observatory for Mental Health, CCQI222 (data on file)

10 Kupfer DJ, Frank E, Grochocinski VJ, Luther JF, Houck PR, Swartz HA, et al. Stabilization in the treatment of mania, depression and mixed states. Acta Neuropsychiatr 2000 Sep;12(3):110-4

11 Willner P, Lappas S, Cheeta S, Muscat R. Reversal of stress-induced anhedonia by the dopamine receptor agonist, pramipexole. Psychopharmacology (Berl) 1994 Aug;115(4):454-62

12 Kitagawa K, Kitamura Y, Miyazaki T, Miyaoka J, Kawasaki H, Asanuma M, et al. Effects of pramipexole on the duration of immobility during the forced swim test in normal and ACTHtreated rats. Naunyn Schmiedebergs Arch Pharmacol 2009 Jul;380(1):59-66.

13 Chiu WH, Depboylu C, Hermanns G, Maurer L, Windolph A, Oertel WH, et al. Long-term treatment with L-DOPA or pramipexole affects adult neurogenesis and corresponding nonmotor behavior in a mouse model of Parkinson's disease. Neuropharm 2015 Aug;95:367-76.

14 Breuer ME, Groenink L, Oosting RS, Buerger E, Korte M, Ferger B, et al. Antidepressant effects of pramipexole, a dopamine D3/D2 receptor agonist, and 7-OH-DPAT, a dopamine D3 receptor agonist, in olfactory bulbectomized rats. Eur J Pharmacol 2009 Aug 15;616(1-3):134-40.

15 Duman RS, Nakagawa S, Malberg J. Regulation of adult neurogenesis by antidepressant treatment. Neuropsychopharm 2001 Dec;25(6):836-44.

16 Serafini G, Hayley S, Pompili M, Dwivedi Y, Brahmachari G, Girardi P, et al. Hippocampal neurogenesis, neurotrophic factors and depression: possible therapeutic targets? CNS Neurol Disord Drug Targets 2014;13(10):1708-21.

17 Shen T, Ye R, Zhang B. Efficacy and safety of pramipexole extended-release in Parkinson's disease: a review based on meta-analysis of randomized controlled trials. Eur J Neurol 2017 Jun;24(6):835-43.

18 Leentjens AF, Koester J, Fruh B, Shephard DT, Barone P, Houben JJ. The effect of pramipexole on mood and motivational symptoms in Parkinson's disease: a meta-analysis of placebo-controlled studies. Clin Ther 2009 Jan;31(1):89-98.

19 Barone P, Poewe W, Albrecht S, Debieuvre C, Massey D, Rascol O, et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2010 Jun;9(6):573-80.

20 Ashok AH, Marques TR, Jauhar S, Nour MM, Goodwin GM, Young AH, et al. The dopamine hypothesis of bipolar affective disorder: the state of the art and implications for treatment. Mol Psychiatry 2017 May;22(5):666-79.

21 Sporn J, Ghaemi SN, Sambur MR, Rankin MA, Recht J, Sachs GS, et al. Pramipexole augmentation in the treatment of unipolar and bipolar depression: a retrospective chart review. Ann Clin Psychiatry 2000 Sep;12(3):137-40.

22 Perugi G, Toni C, Ruffolo G, Frare F, Akiskal H. Adjunctive dopamine agonists in treatment resistant bipolar II depression: an open case series. Pharmacopsychiat 2001 Jul;34(4):137-41.

23 Lattanzi L, Dell'Osso L, Cassano P, Pini S, Rucci P, Houck PR, et al. Pramipexole in treatment resistant depression: a 16-week naturalistic study. Bipolar Disord 2002 Oct;4(5):307-14.

24 El-Mallakh RS, Penagaluri P, Kantamneni A, Gao Y, Roberts RJ. Long-term use of pramipexole in bipolar depression: a naturalistic retrospective chart review. Psychiatr Q 2010 Sep;81(3):207-13.

25 Hori H, Kunugi H. The efficacy of pramipexole, a dopamine receptor agonist, as an adjunctive treatment in treatment-resistant depression: an open-label trial. Scientific World Journal 2012; 2012:372-474.

26 Dell'Osso B, Timtim S, Hooshmand F, Miller S, Wang PW, Hill SJ, et al. Superior chronic tolerability of adjunctive modafinil compared to pramipexole in treatment-resistant bipolar disorder. J Affect Disord 2013 Aug 15;150(1):130-5.

27 Fawcett J, Rush AJ, Vukelich J, Diaz SH, Dunklee L, Romo P, et al. Clinical Experience With High-Dosage Pramipexole in Patients With Treatment-Resistant Depressive Episodes in Unipolar and Bipolar Depression. Am J Psychiatry 2016 Feb 1;173(2):107-11.

28 Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. Am J Psychiatry 2004 Mar;161(3):564-6.

29 Zarate CA, Jr., Payne JL, Singh J, Quiroz JA, Luckenbaugh DA, Denicoff KD, et al. Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. Biol Psychiatry 2004 Jul 1;56(1):54-60.

30 Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry 2007 May;64(5):543-52.

31 McCrone PR. Paying the price : the cost of mental health care in England to 2026. The King's Fund, London, UK; 2008.

32 Young AH, Rigney U, Shaw S, Emmas C, Thompson JM. Annual cost of managing bipolar disorder to the UK healthcare system. J Affect Disord 2011 Oct;133(3):450-6.

33 Loebel A, Cucchiaro J, Silva R, Kroger H, Sarma K, Xu J, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, doubleblind, placebo-controlled study. Am J Psychiatry 2014 Feb;171(2):169-77.

34 Loebel A, Cucchiaro J, Silva R, Kroger H, Hsu J, Sarma K, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am J Psychiatry 2014 Feb;171(2):160-8.

35 Bernstein IH, Rush AJ, Stegman D, Macleod L, Witte B, Trivedi MH. A Comparison of the QIDS-C16, QIDS-SR16, and the MADRS in an Adult Outpatient Clinical Sample. CNS Spectr 2010 Jul;15(7):458-68.

36 Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006 Nov;163(11):1905-17.

37 Rush AJ, Trivedi MH, Stewart JW, Nierenberg AA, Fava M, Kurian BT, et al. Combining medications to enhance depression outcomes (CO-MED): acute and long-term outcomes of a single-blind randomized study. Am J Psychiatry 2011 Jul;168(7):689-701.

38 Martinez JM, Katon W, Greist JH, Kroenke K, Thase ME, Meyers AL, et al. A pragmatic 12-week, randomized trial of duloxetine versus generic selective serotonin-reuptake inhibitors in the treatment of adult outpatients in a moderate-to-severe depressive episode. Int Clin Psychopharmacol 2012 Jan;27(1):17-26.

39 Schatzberg AF, DeBattista C, Lazzeroni LC, Etkin A, Murphy GM, Jr., Williams LM. Genetic Effects on Antidepressant Outcomes: A Report From the iSPOT-D Trial. Am J Psychiatry 2015 Aug 1;172(8):751-9.

40 Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB. "The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression" Biol Psychiatry. 2003 Sep 1;54(5):573-83

41 Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. Arch Intern Med. 2006; 166(10):1092–1097. doi:10.1001/archinte.166.10.1092

42 Snaith, R. P., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., & Trigwell, P. (1995). A scale for the assessment of hedonic tone the Snaith–Hamilton Pleasure Scale. The British Journal of Psychiatry, 167(1), 99-103.

43 Mundt, J., Marks, I., Shear, M., & Greist, J. (2002). The Work and Social Adjustment Scale: A simple measure of impairment in functioning. British Journal of Psychiatry, 180(5), 461-464. doi:10.1192/bjp.180.5.461

44 Altman EG, Hedeker D, Peterson JL, Davis JM. "The Altman Self-Rating Mania Scale". Biol Psychiatry. 1997 Nov 15;42(10):948-55

45 Weintraub, D., Mamikonyan, E., Papay, K., Shea, J. A., Xie, S. X., & Siderowf, A. (2012). Questionnaire for impulsive-compulsive disorders in Parkinson's Disease–Rating Scale. Movement Disorders, 27(2), 242-247.

46 Atkinson, M. J., Sinha, A., Hass, S. L., Colman, S. S., Kumar, R. N., Brod, M., & Rowland, C. R. (2004). Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health and quality of life outcomes, 2(1), 12.

47 Herdman, M., Gudex, C., Lloyd, A., Janssen, M. F., Kind, P., Parkin, D., ... & Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research, 20(10), 1727-1736.

48 Keeley T, Al-Janabi H, Lorgelly P, Coast J. A qualitative assessment of the content validity of the ICECAP-A and EQ-5D-5L and their appropriateness for use in health research. PLoS One 2013;8(12):e85287.

49 Mitchell PM, Al-Janabi H, Byford S, Kuyken W, Richardson J, Iezzi A, et al. Assessing the validity of the ICECAP-A capability measure for adults with depression. BMC Psychiatry 2017 Feb 2;17(1):46.

50 Vergunst, F., Jenkinson, C., Burns, T., Anand, P., Gray, A., Rugkåsa, J., & Simon, J. (2017). Psychometric validation of a multi-dimensional capability instrument for outcome

measurement in mental health research (OxCAP-MH). Health and quality of life outcomes, 15(1), 250.

51 Simon, J., Anand, P., Gray, A., Rugkåsa, J., Yeeles, K., & Burns, T. (2013). Operationalising the capability approach for outcome measurement in mental health research. Social Science & Medicine, 98, 187-196.

52 Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: reliability, validity and sensitivity. The British Journal of Psychiatry, 133(5), 429-435.

53 Montgomery, S.A., Asberg, M. (1979). A new depression scale designed to be sensitive to change. The British Journal of Psychiatry (134) 382-389

54 Geddes JR, Gardiner A, Rendell J, Voysey M, Tunbridge E, Hinds C, et al. Comparative evaluation of quetiapine plus lamotrigine combination versus quetiapine monotherapy (and folic acid versus placebo) in bipolar depression (CEQUEL): a 2 x 2 factorial randomised trial. Lancet Psychiatry 2016 Jan;3(1):31-9.

55 Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IVand ICD-10. J clin psychiatry, 59(Suppl 20), 2233.

56 American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub.

57 Fava, M. (2003). Diagnosis and definition of treatment-resistant depression. Biological psychiatry, 53(8), 649-659.

58 Hidalgo-Mazzei, D., Berk, M., Cipriani, A., Cleare, A. J., Di Florio, A., Dietch, D. & Jones, I. (2019). Treatment-resistant and multi-therapy-resistant criteria for bipolar depression: consensus definition. The British Journal of Psychiatry, 214(1), 27-35.

59 Chisholm, D., Knapp, M. R. J., Knudsen, H. C., Amaddeo, F., Gaite, L. U. I. S., Van Wijngaarden, B. O. B., & EPSILON Study Group. (2000). Client socio-demographic and service receipt inventory–European version: development of an instrument for international research: EPSILON Study 5. The British Journal of Psychiatry, 177(S39), s28-s33.

60 Coulthard K, Patel D, Brizzolara C, Morriss R, Watson S. (2013). A feasibility study of expert patient and community mental health team led bipolar psychoeducation groups: implementing an evidence based practice. BMC Psychiatry (13) 301

61 Al-Janabi, H., Flynn, T. N., & Coast, J. (2012). Development of a self-report measure of capability wellbeing for adults: the ICECAP-A. Quality of Life Research, 21(1), 167-176.

62 H. Lahrmann, P. Cortelli, M. Hilz, C. J. Mathias, W. Struhal and M. Tassinari. EFNS guidelines on the diagnosis and management of orthostatic hypotension. European Journal of Neurology 2006, 13: 930–936

63 Geddes JR, Goodwin GM, Rendell J, Azorin JM, Cipriani A, Ostacher MJ, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 2010 Jan 30;375(9712):385-95.

64 Curtis, L. & Burns, A. (2017) Unit Costs of Health and Social Care 2017, Personal Social Services Research Unit, University of Kent, Canterbury.

65 Joint Formulary Committee. (2018) British National Formulary. (76 ed.) BMJ Group and Pharmaceutical Press, London

66 Tarricone, R. (2006). Cost-of-illness analysis: what room in health economics?. Health policy, 77(1), 51-63.

67 National Institute for Health and Clinical Excellence. The Guidelines Manual. 2009.

68 M.F. Drummond, B.J. O'Brien, G.L. Stoddart, G.W. TorranceMethods for the economic evaluation of health care programmes (2nd ed), Oxford Medical Publications, Oxford (1997)

69 EuroQoL—a new facility for the measurement of health-related quality of life Health Policy, 16 (1990), pp. 199-208

70 National Institute for Health and Clinical Excellence. Developing NICE guidelines: the manual. 2014.

71 Flynn, T. N., Huynh, E., Peters, T. J., Al-Janabi, H., Clemens, S., Moody, A., & Coast, J. (2015). Scoring the ICECAP-A capability instrument. Estimation of a UK general population tariff. Health Economics, 24(3), 258-269.

72 White, I. R., Royston, P., & Wood, A. M. (2011). Multiple imputation using chained equations: issues and guidance for practice. Statistics in medicine, 30(4), 377-399.

73 Little, R. J., & Rubin, D. B. (2002). Bayes and multiple imputation. Statistical analysis with missing data, 200-220.

74 Efron, B., & Tibshirani, R. J. (1994). An introduction to the bootstrap. CRC press.

75 Fenwick, E., & Byford, S. (2005). A guide to cost-effectiveness acceptability curves. The British Journal of Psychiatry, 187(2), 106-108.

76 Stinnett, A. A., & Mullahy, J. (1998). Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Medical decision making, 18(2_suppl), S68-S80.

18. APPENDICES

18.1. Appendix 1 - Amendment History

Amendment number	Protocol version no.	Protocol version date	Author(s) of changes	Details of changes made
SA6	6.0	23/07/2020	Prof. R. Hamish McAllister-Williams, Dr Thomas Chadwick, NCTU	- Protocol updated in response to COVID-19 pandemic to allow sites flexibility regarding flexibility of study tasks. - Updated wording regarding Pre-Randomisation inclusion criteria number 5 for clarification purposes. - Updated the timings so that Adverse Event reports are sent to sites to coincide with when prescriptions are due to be written. - updated wording in section .8.4.1 regarding the flexible dosing reports to provide additional clarification to sites regarding this process - Updated section 9.4 Assessment of Adverse Events so that the definitions in the protocol used to assess severity and causality are clearer. - clarification around the process re the staff qualitative interviews - Other minor administrative updates
SA4	5.0	29 Jan 2020	Prof. R. Hamish McAllister-Williams, NCTU	- Trial Summary amended to reflect correct data collection points regarding the Health Economics questionnaires as per the Schedule of Events. - Patient Flow Diagram on page 12 updated to make it consistent with the Schedule of Events. - Pre-Randomisation Inclusion Criteria number 5 has been updated to provide further clarification - Pre-Randomisation Exclusion Criteria number 5 and 10 and Randomisation Exclusion Criteria number 8 have been updated to provide further clarification - Schedule of Events updated regarding when the End of Study Information Sheet should be given out - In section 7.2.4 and 7.7.2 it previously outlined that the first BP measurement must be taken after a participant has been lying down for 5 minutes - this has been amended to sitting

				- Section 8.4.1 - the wording in the table at the end of this section has been clarified so that it is clear that these are recommendations - Clarification provided in Section 4 that the staff interviews will include a range of different staff types across participating sites that are open to recruitment. - Clarification of wording within section 13.2 - Minor administrative changes
N/A	4.0	10/12/2019	NCTU	Updated sponsor name and logo referenced throughout in light of recent Change in Trust name from Northumberland Tyne and Wear NHS Foundation Trust to Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust
N/A	3.0	31 Jul 2019	Prof. R. Hamish McAllister-Williams, Dr Thomas Chadwick, NCTU	Updated in line with feedback from regulatory reviews
N/A	2.0	13 Jun 2019		Submitted for regulatory review but not approved.
N/A	1.0	29 Nov 2018		N/A – Original version. Not submitted for regulatory review.